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Değerli Bilim İnsanları,

Dergimizin 2025 yılı Eylül sayısını sizlerin beğeninize sunmanın gururunu yaşıyoruz.

Bu dopdolu sayımızda 24 orijinal makale, 2 olgu sunumu ve 1 adet derleme bulunmaktadır. Neonatoloji alanında 1, obstetri-perinatoloji alanında 9, genel jinekolojiden 12, jinekolojik onkoloji 1 ve reprodüktif endokrinoloji- infertilite alanlarından 2 orjinal makale yayınlanmıştır. İki adet ilginç olgu sunumunu ve gebelerde periodontal hastalıklar ile ilgili 1 adet derlemeyi de bu güzel sayımıza ekledik.

Hepinizin güzel bir tatil dönemi geçirdiğini umarak yeni akademik yılın başladığı bu güzel sonbahar aylarında bilimsel çalışmalarınızı aynı şevk ve heyecanla bekliyoruz...

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Prof. Dr. Özlem MORALOĞLU TEKİN
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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Effect of prenatal magnesium sulphate on hearing function in premature newborns

Prematüre yenidoğanlarda doğum öncesi magnezyum sülfatın işitme fonksiyonu üzerine etkisi

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ABSTRACT

Aim: The study aimed to evaluate the potential neuroprotective effects of antenatal magnesium sulfate (MgSO4) on sensorineural hearing and auditory nerve development in premature newborns.

Methods: This retrospective study included premature newborns (<37 weeks) born between November 1, 2022, and December 31, 2023, at Etlik City Hospital. Newborns were divided into two groups: those exposed to antenatal MgSO4 (study group, n=40) and those unexposed (control group, n=126). Antenatal MgSO4 was administered at 2 grams/hour for at least 8 hours after a 6-gram loading dose. Hearing screening was conducted using auditory brainstem response (ABR) tests within the first month after birth. Maternal and neonatal characteristics, including gestational age, birthweight, and APGAR scores, were analyzed. Statistical comparisons between groups were performed using appropriate tests, with a significance level of $p<0.05$.

Results: The failure rate in hearing screening tests did not significantly differ between the MgSO4 group (10%) and the control group (6.3%) (p=0.437). However, the MgSO4 group had lower gestational age at birth (median: 30.0 vs. 34.0 weeks, $p<0.001$), lower birthweight (median: 1424 vs. 2325 grams, $p<0.001$), and higher rates of APGAR scores below 7 at both the 1st and 5th minutes. Placental abruption, retinopathy of prematurity, and bronchopulmonary dysplasia were associated with hearing abnormalities in the overall cohort.

Conclusion: Antenatal MgSO4 administration did not demonstrate a significant protective effect against hearing impairment in premature newborns. Larger prospective studies are warranted to clarify MgSO4's role in auditory neuroprotection.

Keywords: Magnesium sulphate (MgSO4), antenatal neuroprotection, premature newborn, sensorineural hearing loss

ÖZ

Amaç: Bu çalışma, antenatal magnezyum sülfatın (MgSO4) prematüre yenidoğanlarda sensorinöral işitme ve işitsel sinir gelişimi üzerindeki potansiyel nöroprotektif etkilerini değerlendirmeyi amaçlamaktadır.

Yöntem: Retrospektif olarak planlanan bu çalışmaya, 1 Kasım 2022 - 31 Aralık 2023 tarihleri arasında Etlik Şehir Hastanesi'nde doğan prematüre (<37 hafta) yenidoğanlar dahil edilmiştir. Yenidoğanlar, antenatal MgSO4 alan (çalışma grubu, n=40) ve almayan (kontrol grubu, n=126) olmak üzere iki gruba ayrılmıştır. Antenatal MgSO4, 6 gramlık yükleme dozunun ardından en az 8 saat süreyle 2 gram/saat hızında uygulanmıştır. İşitme taramaları, doğumdan sonraki ilk ay içerisinde odyolojik beyin sapı yanıtı (ABR) testleri ile gerçekleştirilmiştir. Gestasyonel hafta, doğum ağırlığı ve APGAR skorları gibi maternal ve neonatal özellikler analiz edilmiştir. Gruplar arasındaki istatistiksel karşılaştırmalar uygun testlerle yapılmış ve $p<0,05$ anlamlı kabul edilmiştir.

Bulgular: İşitme tarama testlerinde başarısızlık oranı, MgSO4 grubu (%10) ile kontrol grubu (%6,3) arasında anlamlı bir fark göstermemiştir (p=0,437). Ancak MgSO4 grubunda daha düşük gestasyonel hafta (ortanca: 30,0 hafta vs. 34,0 hafta, $p<0,001$), daha düşük doğum ağırlığı (ortanca: 1424 gram vs. 2325gram, $p<0,001$) ve 1. ve 5. dakika APGAR skorlarının 7'nin altında olma oranları daha yüksektir. Total hasta grubunda işitme anomalisi ile plasental dekolman, prematüre retinopatisi ve bronkopulmoner displazi arasında ilişki bulunmuştur.

Sonuç: Antenatal MgSO4 uygulaması, prematüre yenidoğanlarda işitme bozukluklarına karşı anlamlı bir koruyucu etki göstermemiştir. MgSO4'ün işitsel nöroproteksiyon üzerindeki rolünü netleştirmek için daha geniş kapsamlı prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Magnezyum sülfat (MgSO4), antenatal nöroproteksiyon, prematüre yenidoğan, sensorinöral işitme kaybı

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INTRODUCTION

In the last fifty years, the development of evidence-based care practices and interventions has significantly improved mortality outcomes for premature infants. Specifically, the use of antenatal corticosteroid applications and neonatal surfactant replacement has greatly reduced early deaths due to respiratory failure in very preterm (<32 weeks of gestation) newborns. However, significant long-term neurological morbidities have been observed in surviving infants. Developing, evaluating, and implementing strategies to reduce the frequency and severity of neurological sequelae is a priority in perinatal care (1-4).

The disease burden imposed by neurosensory disorders and impairments on surviving premature infants is considerable. Major morbidities such as cerebral palsy, blindness, deafness, and developmental delays are observed. Furthermore, school-aged children exhibit cognitive deficits, including academic problems, executive dysfunction, and behavioral disorders such as attention deficit hyperactivity disorder (ADHD), with increasing rates (5–8).

Today, magnesium sulfate (MgSO4) is widely used in obstetric care for various indications to improve obstetric outcomes. These include reducing the risk of eclampsia and its use as a tocolytic agent. However, its efficacy as a tocolytic agent is still debated (9). The current view is that MgSO4 may be neuroprotective for the immature fetal central nervous system and may reduce the incidence of major neurological morbidities, particularly cerebral palsy (CP), in premature newborns (10). Based on current research, magnesium has been extensively studied for its neuroprotective effects, and guidelines for antenatal MgSO4 administration in preterm births have been established. MgSO4 infusions are recommended to protect the fetal central nervous system in premature infants and to reduce preterm birth rates in patients presenting with preterm labor threats (9).

Despite reductions in mortality rates associated with prematurity, the incidence of sensorineural hearing loss remains high, ranging from 2% to 64% (11). Hearing loss, which affects speech and language development, is a significant disability closely linked to the newborn's social and physical development and has a substantial impact on quality of life. Congenital hearing loss is a universal health issue and is one of the health measures used to determine health-related quality of life (12). Early diagnosis and appropriate treatment regimens can mitigate adverse outcomes. Therefore, neonatal hearing screening programs have been widely initiated, and hearing screening within the first month of life is recommended for all infants (13).

There is a lack of evidence-based data regarding the effectiveness of MgSO4 in preventing hearing loss in premature infants. Previous studies evaluating magnesium for neuroprotection primarily focused on CP as the primary outcome, but there is insufficient data on cochlear function (9). Some studies suggest that magnesium may have a beneficial effect on noise-induced hearing loss in adults (14). However, the mechanisms of noise-induced hearing loss and congenital hearing loss are different. Considering the widespread use of MgSO4 in obstetric care, this study aims to evaluate the potential neuroprotective effect of antenatal MgSO4 on auditory nerve development and sensorineural hearing in premature newborns.

METHODS

Our study included patients who delivered between November 1, 2022, and December 31, 2023, at Etlik City Hospital's Obstetrics and Gynecology Department, with follow-up and treatment completed at our center, including postnatal neonatal follow-ups. The medical records of the study patients were retrospectively reviewed. The study was approved by the local ethics committee (approval number: AEŞH-BADEK-2024-087).

Newborns born to mothers who received antenatal MgSO4 for various indications at least eight hours before delivery were included in the study group. Newborns who did not receive MgSO4 formed the control group. Those with fetal disease or maternal systemic conditions (Body Mass Index (BMI)>30, history of chronic mental or physical illness, severe renal, hepatic, gastrointestinal, acute/chronic inflammatory disease, hyperthyroidism, hypothyroidism, hypertension, type 1/2 diabetes mellitus, polycystic ovary syndrome (PCOS) history, malignancy history, smoking, or alcohol use) were excluded from the study.

Antenatal MgSO4 was administered intravenously at a dose of 2 grams/hour continuously. The infusion duration was at least 8 hours, following a loading dose of 6 grams, as recommended. The indications for MgSO4 included neuroprotection. When indicated, antenatal corticosteroids were administered in two intramuscular doses of 12 mg betamethasone. In our study, patients who received two doses of betamethasone were considered for standardization purposes.

The primary outcome measure was the failure rate in newborn hearing screening. Auditory brainstem response (ABR) allows for the neurophysiological evaluation of brainstem maturation and the auditory pathway in newborns. The effect of antenatal MgSO4 infusion was the main variable.

Since all newborns were premature and had risk factors for hearing loss, they were subjected to hearing screening within the first

month after birth. The results of the hearing screening tests were evaluated, and comparisons were made between the study and control groups. Hearing tests were performed using the Madsen Accuscreen (Otometrics, Denmark). The tests consisted of a click stimulus at up to 30 dB, using disposable hydrogel electrodes, and the device standard was EN-60645-7 type 2.

According to the recommended algorithm for newborn hearing screening, newborns were classified as "passed" if the screening test produced a response in both ears at the 30 dB-NHL stimulus level, and "failed" if it did not.

Maternal characteristics that could affect neonatal outcomes, such as maternal age, parity, prelabor rupture of membranes, amniotic fluid volume, mode of delivery, gestational age at birth, birth weight, placental abruption, and APGAR scores, as well as neonatal characteristics, were also recorded. Additionally, neonatal parameters evaluated within the first 28 days, such as the need for mechanical ventilation, neonatal sepsis, intraventricular hemorrhage, respiratory distress syndrome (RDS), retinopathy of prematurity, necrotizing enterocolitis, and bronchopulmonary dysplasia, were analyzed as composite outcomes. Pathological electroencephalography (EEG) and visual evoked potentials were also analyzed.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY). Continuous variables were presented as median and interquartile range (IQR), and categorical variables were presented as frequencies and percentages. The normality of continuous variables was assessed using the Shapiro-Wilk test. For comparisons between groups, the Mann-Whitney U test was used for continuous variables that did not follow a normal distribution, while the Student's t-test was applied for normally distributed continuous variables. For categorical variables, the chi-square test or Fisher's exact test, where appropriate, was used. A p-value of less than 0.05 was considered statistically significant.

RESULTS

During the study period, 166 pregnant patients were included. Among the 166 newborns, 40 (24%) received MgSO4 for neuroprotective purposes, while 126 newborns (75%) did not receive MgSO4.

The median maternal age at birth was similar between the study and control groups (median values were 27.5 and 28, respectively, p = 0.35). Body mass index, parity, and mode of delivery were also found to be similar between the two groups (Table 1).

Table 1. Comparison of maternal, neonatal and birth characteristics between patients receiving neuroprotective magnesium ınfusion and control groups

Variables	Neuroprotection Group N:40	Control Group N:126	P Value
Maternal age in years, median (IQR)	27.5 (24.0, 30.0)	28.0 (24.0, 33.0)	0.350
Maternal body mass index at booking in kg/m2, median (IQR)	26.0 (24.0, 31.0)	28.0 (25.0, 31.0)	0.436
Nulliparity, n(%)	19 (47.5)	53 (42.1)	0.546
Oligohydramnios, n(%)	19 (47.5)	28 (22.2)	**0.002**
Mode of delivery, n(%)			0.619
Vaginal	17 (42.5)	48 (38.1)	
C/S	23 (57.5)	78 (61.9)	
Time period until birth in days, median (IQR)	2.50 (0.75, 5.25)	0.00 (0.00, 1.00)	**<0.001**
Gestational age at birth in weeks, median (IQR)	30.0 (27.5, 31.3)	34.0 (33.0, 35.0)	**<0.001**
Birthweight in grams, median (IQR)	1424 (948, 1845)	2325 (1980, 2633)	**<0.001**
Neonatal Gender, n(%)			0.829
Male	23 (57.5)	70 (55.6)	
Female	17 (42.5)	56 (44.4)	
APGAR score <7 at 1th minute, n(%)	17 (43.6)	15 (12.1)	**<0.001**
APGAR score <7 at 5th minutes, n(%)	9 (23.1)	6 (4.8)	**<0.001**
Neonatal abnormal hearing test, n(%)	4 (10.0)	8 (6.3)	0.437

p-value of less than 0.05 was considered statistically significant
C/S: Cesarean section, IQR: Interquartile range

Table 2. Comparison of maternal and neonatal outcomes between hearing abnormality and control groups

Variables	Hearing Abnormality Group N:12	Control Group N:154	P Value
Placental abruption, n (%)	2 (16.7)	3 (1.9)	**0.004**
Gestational age at birth in weeks, median (IQR)	30.5 (28.8, 31.0)	34.0 (32.0, 35.0)	**<0.001**
Birthweight in grams, median (IQR)	1660 (1251, 1903)	2230 (1768, 2583)	**0.006**
APGAR score <7 at 1th minutes, n (%)	4 (33.3)	28 (18.5)	0.214
APGAR score <7 at 5th minutes, n (%)	2 (16.7)	13 (8.6)	0.353
Neonatal Outcomes, n (%)			
EEG patology	2 (16.7)	4 (2.6)	**0.012**
Retinopathy of prematurity	7 (58.3)	34 (22.1)	**0.005**
Resuscitation requirement	4 (33.3)	24 (15.6)	0.114
Respiratory distress syndrome	2 (16.7)	26 (16.9)	0.985
Surfactant requirements	3 (25.0)	23 (14.9)	0.355
Cardiac inotrope requirement	2 (16.7)	10 (6.5)	0.190
Sepsis	3 (25.0)	18 (11.7)	0.192
Intraventricular haemorrhage	0 (0.0)	8 (5.2)	0.418
Necrotising enterocolitis	0 (0.0)	3 (1.9)	0.626
Pulmonary Hypoplasia	0 (0.0)	3 (1.9)	0.626
Bronchoulmonary Dysplasia	2 (16.7)	6 (3.9)	**0.049**

The neuroprotection group had significantly higher rates of oligohydramnios (47.5% vs. 22.2%, p = 0.002). The time period until birth was also longer in the neuroprotection group (median: 2.50 days, IQR: 0.75-5.25 vs. 0.00 days, IQR: 0.00-1.00, p < 0.001). Additionally, the neuroprotection group had a significantly lower gestational age at birth (median: 30.0 weeks vs. 34.0 weeks, p < 0.001) and lower birthweight (median: 1424 grams vs. 2325 grams, p < 0.001). APGAR scores below 7 at both the 1st and 5th minutes were more common in the neuroprotection group (1st minute: 43.6% vs. 12.1%, p < 0.001; 5th minute: 23.1% vs. 4.8%, p < 0.001). However, no significant differences were observed in abnormal hearing test results (p = 0.437) (Table 1).

Placental abruption was significantly more common in the hearing abnormality group compared to the control group (16.7% vs. 1.9%, p = 0.004). Additionally, gestational age at birth was lower in the hearing abnormality group (median: 30.5 weeks, IQR: 28.8-31.0 vs. 34.0 weeks, IQR: 32.0-35.0, p < 0.001) as well as birthweight (median: 1660 grams, IQR: 1251-1903 vs. 2230 grams, IQR: 1768-2583, p = 0.006). There were no statistically significant differences in APGAR scores at the 1st or 5th minute between the two groups (Table 2).

Regarding neonatal outcomes, EEG pathology was significantly more frequent in the hearing abnormality group (16.7% vs. 2.6%, p = 0.012), as well as retinopathy of prematurity (58.3% vs. 22.1%, p = 0.005), and bronchopulmonary dysplasia (16.7% vs. 3.9%, p = 0.049). Other neonatal outcomes, such as resuscitation requirement, respiratory distress syndrome, and sepsis, did not show significant differences between the groups (Table 2).

DISCUSSION

The prevention of neurological and developmental disorders in premature newborns remains a challenging health issue today. All reported studies show improvement with the optimal organization of antenatal and postnatal care (15).

The use of MgSO4 is primarily recommended for eclampsia prophylaxis and, more recently, for the protection of the fetal central nervous system in preterm births before 32 weeks (9). The purpose of the present study was to evaluate whether MgSO4 has a neuroprotective effect on hearing in premature newborns. Our findings indicate that the failure rate in the hearing screening test

did not significantly differ between the group of newborns exposed to antenatal MgSO4 and those who were not.

Magnesium is an essential element for many physiological processes in the body. In this context, magnesium contributes to cochlear physiology and plays a role in the hearing process. Despite its known neuroprotective effects and protective action against CP, data on magnesium's effect on sensorineural hearing are limited. In a study with guinea pigs, a negative correlation was observed between cochlear magnesium levels and hearing loss. It was shown that magnesium has a regulatory function in the inner ear and prevents the formation of reactive oxygen species after noise exposure (16,17). Moreover, there is evidence of cellular damage related to oxidative stress associated with magnesium deficiency (18). Additionally, protective effects of oral magnesium supplementation on acoustic trauma-related hearing loss have been demonstrated in adults (14). Most of these studies were conducted on animals or adults, specifically evaluating noise-induced cochlear damage. This evidence led the present study to evaluate the potential protective effects of magnesium on sensorineural hearing in premature newborns. Premature newborns were specifically assessed in this population due to their higher incidence of hearing loss, which is associated with delayed neurodevelopment. Although several mechanisms can be proposed for the development of hearing loss in premature newborns, prematurity alone is a well-established risk factor (19). This is because fetal audiological development primarily occurs between the 20th and 33rd weeks of gestation.

In a previous study examining risk factors for hearing loss in preterm newborns, it was suggested that the etiology of hearing loss is multifactorial rather than due to a single factor (20). For this reason, clinical factors were separately evaluated in both groups in this study. Comparisons between the groups revealed that newborns in the study group who received antenatal MgSO4 had significantly lower birth weights and lower APGAR scores at the first and fifth minutes, which may be related to earlier gestational ages at birth.

In a study conducted by Crowther et al. with 1,047 participants, hearing loss was not evaluated separately but was instead considered a component of moderate neurological impairment. The authors did not report a significant difference in sensory or neural impairments between the patient groups receiving magnesium and those who did not (21).

Antenatal corticosteroid applications have been reported to reduce the risk of hearing loss (22). Most studies evaluating the neuroprotective effects of magnesium note that participants also received corticosteroids, as was the case in the present study. In another recent study evaluating the effects of antenatal steroid administration solely on hearing function in newborns, no association was found between corticosteroids and hearing screening results (23). In a further study, repeated doses of antenatal steroids, rather than a single dose, did not provide benefits according to newborn hearing test evaluations (24). In our study population, patients who received two doses of betamethasone were evaluated for standardization of newborn outcomes.

Although this study includes all premature newborns (<37 weeks) over a one-year period, the study population is relatively small, and the retrospective nature of the study is another limitation. Additionally, the difference in gestational age between the groups with and without MgSO4 administration is a limitation, as the target population for antenatal neuroprotective interventions is primarily those born before 32 weeks. However, despite the gestational age difference, the similar hearing test results in the neuroprotective MgSO4 group are promising in terms of its potential contribution to sensorineural development. We believe that large-scale studies designed with different methodological approaches to eliminate gestational age differences will provide more objective evidence.

Magnesium sulfate has demonstrated sustained beneficial effects even at lower total doses in previous studies; however, current evidence remains insufficient to establish the minimum effective dose or the ideal administration regimen. There is a lack of comprehensive data on optimal maternal loading and maintenance doses necessary to maximize neonatal benefits while minimizing risks. Given the possibility that magnesium sulfate may exert both neuroprotective and potentially harmful effects on the fetus depending on dosage and exposure, further research in this area is essential (25). Furthermore, in our study, all patients who met the inclusion criteria between the specified study dates were included in the study and no power analysis was performed when determining the sample size. This is considered as a limitation of the study.

CONCLUSION

Our findings do not demonstrate a clear and definitive benefit of antenatal MgSO4 infusion in terms of hearing impairment in premature newborns. To reach a definitive conclusion regarding the use of MgSO4 as a neuroprotective intervention against hearing impairment in premature newborns, the results need to be supported by larger-scale, carefully designed studies.

Ethics Committee Approval: The study was approved by the local ethics committee (approval number: AEŞH-BADEK-2024-087).

Conflict of Interest: There is no evidence of any potential conflict of interest relevant to this article.

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Leukocyte subtype variations in preterm births: insights from robson group 10 using machine learning and conventional analysis

Preterm doğumlarda lökosit alt tipi varyasyonları: Robson grup 10 üzerine makine öğrenimi ve geleneksel analiz yaklaşımıyla öngörüler

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ABSTRACT

Aim: The aim of this study was to investigate the differences in leukocyte subtypes between preterm births classified as Robson Group 10 and term births, and to focus on how these hematological changes can be evaluated using both conventional statistical methods and machine learning models such as SHAP analysis.

Materials and Methods: A retrospective case-control study was conducted at Ankara Etlik City Hospital between May and December 2023. Data obtained from 2,662 patients, including preterm births (Robson Group 10) and term pregnancies (control group), were analyzed. Hematological parameters such as white blood cells, neutrophils, monocytes, and eosinophils were compared between groups. Conventional statistical tests, including the Mann-Whitney U test and logistic regression analyses, were applied. In addition, machine learning models such as XGBoost and SHAP analysis were used to identify individual variations in leukocyte subtypes.

Results: In Robson Group 10, neutrophil and total WBC levels were significantly higher compared to the control group, whereas monocyte and eosinophil levels were significantly lower. Machine learning analysis revealed that higher counts of immature granulocytes were predictive for Robson Group 10, while higher monocyte counts were predictive for the control group.

Conclusion: Preterm births in Robson Group 10 exhibit distinct hematological profiles, including notable inflammatory markers such as increased neutrophils and immature granulocytes. The combined use of conventional statistics and machine learning provides valuable insights into individual variations and suggests a more personalized approach in the assessment of preterm birth risks. Further studies with larger cohorts are warranted to validate these findings.

Keywords: Preterm birth, leukocyte subtypes, Robson classification, machine learning, inflammatory markers

ÖZ

Amaç: Bu çalışmanın amacı, Robson Grup 10 olarak sınıflandırılan erken doğumlar ile term doğumlar arasındaki lökosit alt tiplerindeki farklılıkları araştırmak ve bu hematolojik değişikliklerin hem geleneksel istatistiksel yöntemler hem de SHAP analizi gibi makine öğrenimi modelleri kullanılarak nasıl değerlendirildiğine odaklanmaktır.

Gereç ve Yöntemler: Mayıs-Aralık 2023 tarihleri arasında Ankara Etlik Şehir Hastanesi'nde retrospektif bir vaka-kontrol çalışması yürütülmüştür. Preterm doğumlar (Robson Grup 10) ve term gebelikler (kontrol grubu) dahil olmak üzere 2662 hastadan elde edilen veriler analiz edilmiştir. Beyaz kan hücreleri, nötrofiller, monositler ve eozinofiller gibi hematolojik parametreler gruplar arasında karşılaştırılmıştır. Mann-Whitney U ve lojistik regresyon analizleri dahil olmak üzere geleneksel istatistiksel testler kullanılmıştır. Ayrıca, lökosit alt tiplerindeki bireysel varyasyonları belirlemek için XGBoost ve SHAP analizi gibi makine öğrenimi modelleri kullanılmıştır.

Bulgular: Robson Grup 10'da nötrofil ve toplam WBC seviyeleri kontrol grubuna kıyasla anlamlı derecede yüksek, monosit ve eozinofil seviyeleri ise anlamlı derecede düşük bulunmuştur. Makine öğrenimi analizi, daha yüksek olgunlaşmamış granülosit sayılarının Robson Grup 10 için öngörücü olduğunu, daha yüksek monosit sayılarının ise kontrol grubu için öngörücü olduğunu ortaya koymuştur.

Sonuç: Robson Grup 10'daki erken doğumlar, artmış nötrofiller ve olgunlaşmamış granülositler gibi dikkate değer enflamatuar belirteçlerle birlikte farklı hematolojik profiller sergilemektedir. Geleneksel istatistiklerin ve makine öğreniminin birlikte kullanımı, bireysel varyasyonlara ilişkin değerli bilgiler sunmakta ve erken doğum risklerinin değerlendirilmesinde daha kişiselleştirilmiş bir yaklaşım önermektedir. Bu bulguları iyileştirmek için daha büyük kohortlarla daha fazla çalışma yapılması gerekmektedir.

Anahtar Kelimeler: Preterm doğum, lökosit alt tipleri, robson sınıflandırması, makine öğrenmesi, inflamatuar belirteçler

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INTRODUCTION

Preterm births are defined as births that occur at a gestational age of less than 37 weeks and are classified in group 10 according to the Robson classification [1,2]. Preterm births are one of the main causes of perinatal morbidity and mortality. While the preterm birth rate in the USA is 12-13%, the rates reported in Europe and other industrialized countries are generally 5-9% [3,4].The development of preterm birth is a result of preterm labor due to many primary and associated causes. One possible cause for the development of preterm labor is impaired maternal-fetal tolerance, which can trigger maternal inflammatory responses and subsequently lead to the onset of preterm labor. Accordingly, the relationship between white blood cells (WBCs) and their subtypes (neutrophils, lymphocytes, basophils, monocytes and immature granulocytes), which are biological markers of inflammation, and preterm labor is of clinical importance.

The Robson group 10 is a group that includes preterm birth and has a high rate of cesarean sections. However, there are few studies on the subtypes of white blood cells in this group. White blood cells have been shown in the literature to be associated with inflammation, infection and immune responses, but further studies are needed on the impact of white blood cell subtypes on clinical model outcomes, particularly in Robson group 10.

The aim of this study was to investigate how the subtypes of white blood cells (neutrophils, lymphocytes, basophils, monocytes, immature granulocytes, etc.) differ between preterm births in the Robson group 10 and term pregnancies in the control group. In addition, it is also evaluate how these differences are predicted at the individual patient level using the machine learning model and SHAP analysis and what differences they show using conventional statistical methods.

MATERIAL-METHODS

Our study was conducted as a single-center retrospective case-control study at Ankara Etlik City Hospital between May and December 2023, with approval from the Ethics Committee (AESH-BADEK-2024-895 numbered approval, dated 02.10.2024). Informed consent was obtained from all patients prior to the study.

Patients included in the study were those who were followed up at the Obstetrics and Gynecology Clinic of Ankara Etlik City Hospital, continued their follow-up in our clinic, and delivered at our center. Between May and December 2023, all patients meeting the predefined inclusion and exclusion criteria, resulting in a convenience sample determined by the available patient population during the study period. A total of 2662 patients aged between 18-54 years and with gestational ages between 28-42 weeks were included in the study.

Exclusion criteria: Patients complicated by hypertensive disorders of pregnancy, fetuses with fetal anomalies, patients with maternal infection findings, patients under 18 years of age, those whose delivery records could not be accessed, and those who did not meet the inclusion criteria were excluded from the study.

Patients included in Robson Group 10 consisted of those who experienced spontaneous preterm labor before the 36th gestational week. The control group was composed of patients who delivered after the 36th gestational week.

Demographic information, labor records, and neonatal data of the patients were obtained from the electronic health records of our hospital. Patient data were reviewed retrospectively. The demographic variables evaluated in the study included the patients' age, parity, mode of delivery (Cesarean section, normal vaginal delivery, vacuum-forceps assisted vaginal delivery), Robson group, gestational age at delivery, and newborn weight. Complete blood count (CBC) results collected during antenatal visits between 28-42 gestational weeks, in accordance with guidelines, were used in the study. CBC was performed upon hospital admission at the gestational week of delivery. The CBC parameters evaluated in the study included white blood cell count (WBC), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet count (PLT), neutrophil count (NEU), lymphocyte count (LYM), monocyte count (MON), eosinophil count (EO), basophil count (BA), and immature granulocyte count (IG).

Patients were divided into 10 groups based on the Robson classification, following the guidelines. The Robson groups are shown in Supplementary Table 1. Patients with singleton pregnancies, cephalic presentation, and gestational ages less than 36 weeks (including those with prior Cesarean sections) were classified as Robson Group 10. The remaining patients were considered the control group.

Statistical Analyses

Statistical analyses were conducted using the SPSS software (IBM SPSS Statistics 29). Frequency tables and descriptive statistics were used to interpret the findings. Parametric methods were applied for measurement values that followed a normal distribution. The "Student's t-test" was used to compare measurement values between two independent groups for parametric variables. For

measurement values that did not follow a normal distribution, non-parametric methods were employed, and the "Mann-Whitney U test" was used to compare measurement values between two independent groups. Results were reported in tables with median values and interquartile ranges (25th and 75th percentiles). A binary logistic regression analysis (enter LR model) was used to identify factors influencing disease status. A p-value of less than 0.05 was considered statistically significant.

Machine Learning Analyses:

The performance metrics of machine learning algorithms were compared using Python. The algorithms used include Random Forest, Logistic Regression, XGBoost, K-Nearest Neighbors (KNN) and Support Vector Machines (SVM). Their performances were evaluated using metrics such as AUC (Area Under the Curve), Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV).

SHAP (Shapley Additive Explanations) Analysis:

To enhance the interpretability of the model outputs and to determine the impact of each feature on the model, a SHAP analysis was performed. Since XGBoost showed the best performance, the SHAP analysis was conducted using this model. The SHAP analysis visually demonstrated the contribution of each variable to the model output, highlighting which features had the most significant impact on predictions. The SHAP values were presented in graphical form, showcasing the importance of each feature in the model. This analysis was conducted using Python, adhering to standard methodologies and libraries for SHAP value calculations.

RESULTS

In Table 1, we compared the maternal and neonatal outcomes of the Robson 10 group with those of the control group (other Robson groups). Gestational age was significantly lower in the Robson 10 group compared to the control group (median: 33.0 vs. 37.0 weeks, p<0.001). Maternal age was also significantly higher in the Robson 10 group (median: 28.0 vs. 27.0 years, p<0.001). There was no significant difference in nulliparity between the two groups (30.7% vs. 31.7%, p=0.828). Mode of delivery was significantly different, with a higher rate of cesarean sections in the Robson 10 group (66.1% vs. 45.7%, p<0.001), and a significantly lower rate of vaginal birth (33.9% vs. 53.4%, p<0.001). Live birth rates were slightly lower in the Robson 10 group compared to the control group (97.5% vs. 99.8%, p<0.001). Neonatal birth weight was significantly lower in the Robson 10 group (median: 2290g vs. 3190g, p<0.001), while neonatal gender distribution showed no significant differences between the groups (p = 0.915).

In the comparison of hematological parameters between the Robson 10 group and the control group, several significant differences were observed (Table 2). The white blood cell count (WBC) was notably

Table 1. Demographic data and neonatal outcomes of Robson 10 group and control group

Maternal and fetal characteristic	Robson 10 group N=357	Control group N=2305	P value
Gestational age, median (IQR)	33.0 (31.0, 35.0)	37.0 (33.0, 39.0)	**<0.001**
Maternal age, median (IQR)	28.0 (23.0, 33.0)	27.0 (23.0, 31.0)	**<0.001**
Nulliparity, n (%)	35 (30.7)	267 (31.7)	0.828
Mode of delivery, n (%)			**<0.001**
Vaginal birth	121 (33.9)	1231 (53.4)	
C-section	236 (66.1)	1054 (45.7)	
Operative vaginal birth	0	20 (0.9)	
Live birth rate, n (%)	348 (97.5)	2300 (99.8)	**<0.001**
Neonatal birth weight, median (IQR)	2290 (1800, 2690)	3190 (2890, 3470)	**<0.001**
Gestational age at birth, median (IQR)	34.0 (32.0, 35.0)	38.0 (38.0, 39.0)	**<0.001**
Neonatal gender, n (%)			0.915
Male	184 (51.5)	1195 (51.8)	
Female	173 (48.5)	1110 (48.2)	

Data are given as n (%), median (interquartile range) or n/N (%).
p<0.05 is considered statistically significant

Table 2. Comparison of hematological parameters for Robson-10 group and control group

Median (25th, 75th percentile)	Robson-10 group	Control group	P value
WBC ($10^3/mm^3$)	11.5 (9.35, 13.50)	10.4 (8.82,12.00)	<0.001
RBC	4.19 (3.89, 4.49)	4.20 (3.93, 4.47)	0.648
Hemoglobin (g/dL)	11.7 (10.9, 12.8)	11.8 (10.8, 12.7))	0.315
Hematocrit (%)	36.3 (34.2, 39.1)	36.6 (34.3, 38.8)	0.869
MCV (fL)	88.0 (83.4, 92.5)	87.9 (83.5, 91.8)	0.714
MCH (pg)	28.8 (26.3, 30.4)	28.3 (26.2, 30.0)	0.051
MCHC (g/dL)	32.3 (31.5, 33.1)	32.0 (31.1, 32.9)	<0.001
Platelet ($10^3/mm^3$)	245 (204, 293)	241 (199, 285)	0.487
Neutrophil ($10^3/mm^3$)	8.40 (6.61, 10.8)	7.42 (6.19, 8.93)	<0.001
Lymphocyte ($10^3/mm^3$)	1.90 (1.48, 2.38)	1.97 (1.64, 2.38)	0.006
Monocyte ($10^3/mm^3$)	0.640 (0.490, 0.810)	0.670 (0.560, 0.820)	<0.001
Eosinophil ($10^3/mm^3$)	0.050 (0.020, 0.110)	0.070 (0.040, 0.110)	<0.001
Basophil ($10^3/mm^3$)	0.030 (0.020, 0.050)	0.030 (0.020, 0.040)	0.466
IG ($10^3/mm^3$)	0.080 (0.050, 0.140)	0.070 (0.050, 0.120)	0.018

WBC: White blood cell; RBC: Red blood cell, MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; IG: Immature Granulocyte

higher in the Robson 10 group (median: 11.5, IQR: 9.35-13.50) compared to the control group (median: 10.4, IQR: 8.82-12.00), with a statistically significant p value of <0.001. Additionally, the mean corpuscular hemoglobin concentration (MCHC) was elevated in the Robson 10 group (median: 32.3, IQR: 31.5-33.1) compared to the control group (median: 32.0, IQR: 31.1-32.9), with p<0.001. Neutrophil counts were higher in the Robson 10 group (median: 8.40, IQR: 6.61-10.8) compared to the control group (median: 7.42, IQR: 6.19-8.93), also with p<0.001. Conversely, the lymphocyte count was slightly lower in the Robson 10 group (median: 1.90, IQR: 1.48-2.38) than in the control group (median: 1.97, IQR: 1.64-2.38), with a p value of 0.006. Monocyte counts were lower in the Robson 10 group (median: 0.640, IQR: 0.490-0.810) than in the control group (median: 0.670, IQR: 0.560-0.820), with p<0.001. Additionally, eosinophil counts were significantly lower in the Robson 10 group (median: 0.050, IQR: 0.020-0.110) compared to the control group (median: 0.070, IQR: 0.040-0.110), p<0.001. Finally, the immature granulocyte (IG) count was higher in the Robson 10 group (median: 0.080, IQR: 0.050-0.140) than in the control group (median: 0.070, IQR: 0.050-0.120), with a p value of 0.018.

Table 3 shows the results of both univariable and multivariable logistic regression analyses of hematological variables for the Robson-10 group. In the univariable analysis, white blood cell count (WBC) and neutrophil count both had significant associations with the Robson-10 group, with odds ratios (OR) of 1.125 (95% CI: 1.085–1.166, p<0.001) and 1.178 (95% CI: 1.131–1.227, p<0.001), respectively. Similarly, monocytic count (OR: 0.345, 95% CI: 0.205–0.582, p<0.001) and eosinophils (OR: 0.183, 95% CI: 0.041–0.827, p=0.027) were inversely associated with the Robson-10 group. Immature granulocytes (IG) were strongly associated with the group, with an OR of 4.204 (95% CI: 2.083–8.487, p<0.001). However, after adjustment in the multivariable analysis, only monocyte count and IG remained significant. Monocytes showed a strong negative association with the Robson-10 group (adjusted OR: 0.157, 95% CI: 0.084–0.296, p<0.001), while IG remained positively associated (adjusted OR: 3.405, 95% CI: 1.474–7.865, p=0.004). Other variables, including WBC and neutrophils, lost significance after adjustment.

The performance of machine learning models in predicting clinical outcomes was evaluated based on the test sets, and the results are summarized in Figure 1. The models compared include Random Forest, Logistic Regression, XGBoost, KNN (K-Nearest Neighbors), and SVM (Support Vector Machines).

Table 3. Results of univariable and multivariable logistic regression analysis of hematological variables for the Robson-10 group

	Univariable			Multivariable		
	B	OR (95% CI)	P value	aB	aOR (95% CI)	P value
WBC	0.118	1.125 (1.085 – 1.166)	**<0.001**	0.002	1.002 (0.804 – 1.249)	0.985
Neutrophil	0.164	1.178 (1.131 – 1.227)	**<0.001**	0.190	1.209 (0.964 – 1.515)	0.100
Lymphocyte	-.0251	0.778 (0.645 – 0.938)	**0.009**	-0.005	0.995 (0.730 – 1.355)	0.973
Monocyte	-1.064	0.345 (0.205 – 0.582)	**<0.001**	-1.850	0.157 (0.084 – 0.296)	**<0.001**
Eosinophil	-1.696	0.183 (0.041 – 0.827)	**0.027**	-0.538	0.584 (0.131 – 2.602)	0.480
IG	1.436	4.204 (2.083 – 8.487)	**<0.001**	1.225	3.405 (1.474 – 7.865)	**0.004**

OR: odds ratio; CI: Confidence interval; aOR: Adjusted odds ratio

Table 4. Comparison of maternal hematological variables in fetuses with a birth weight above and below 2500 g

	Birth weight < 2500 g	Birth weight ≥ 2500 g	P value
WBC (10^3/mm^3)	11.9 (9.41, 14.50)	10.9 (9.20, 12.40)	0.002
Neutrophil (10^3/mm^3)	9.07 (6.78, 11.60)	8.04 (6.49, 9.60)	<0.001
Lymphocyte (10^3/mm^3)	1.90 (1.38, 2.39)	1.95 (1.56, 2.38)	0.138
Monocyte (10^3/mm^3)	0.630 (0.425, 0.820)	0.680 (0.550, 0.798)	0.020
Eosinophil (10^3/mm^3)	0.040 (0.010, 0.110)	0.060 (0.030, 0.100)	0.063
IG (10^3/mm^3)	0.080 (0.050, 0.140)	0.080 (0.060, 0.147)	0.682

AUC (Area Under the Curve): The highest AUC was observed in the XGBoost model (0.945), followed by Random Forest (0.876) and SVM (0.678). The Logistic Regression model had the lowest AUC (0.621).

Sensitivity: The XGBoost model also had the highest sensitivity (0.875), while Logistic Regression had the lowest sensitivity (0.290).

Specificity: All models performed consistently high in terms of specificity, with values ranging from 0.895 to 0.899.

PPV (Positive Predictive Value): The XGBoost model again had the highest PPV (0.888), followed closely by Random Forest (0.851) and KNN (0.857).

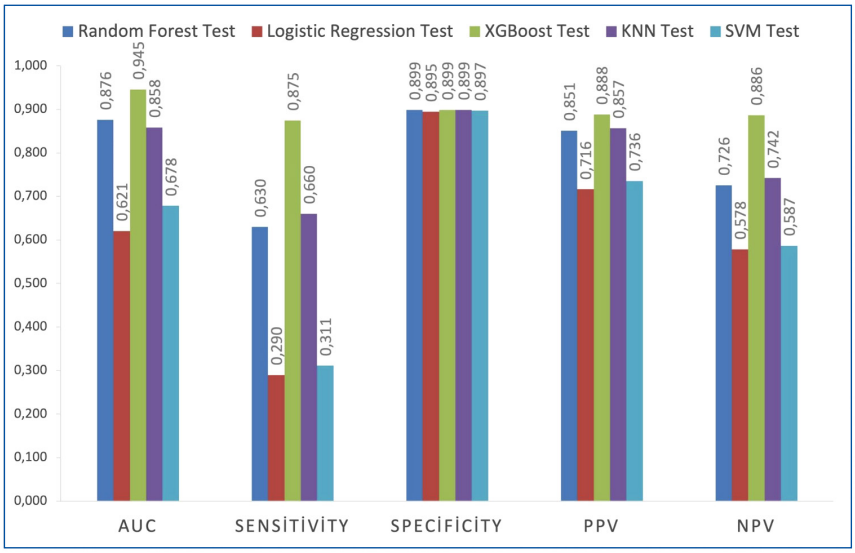

Figure 1. Comparison of Machine Learning Model Performance for Predictive Analysis of Clinical Outcomes.

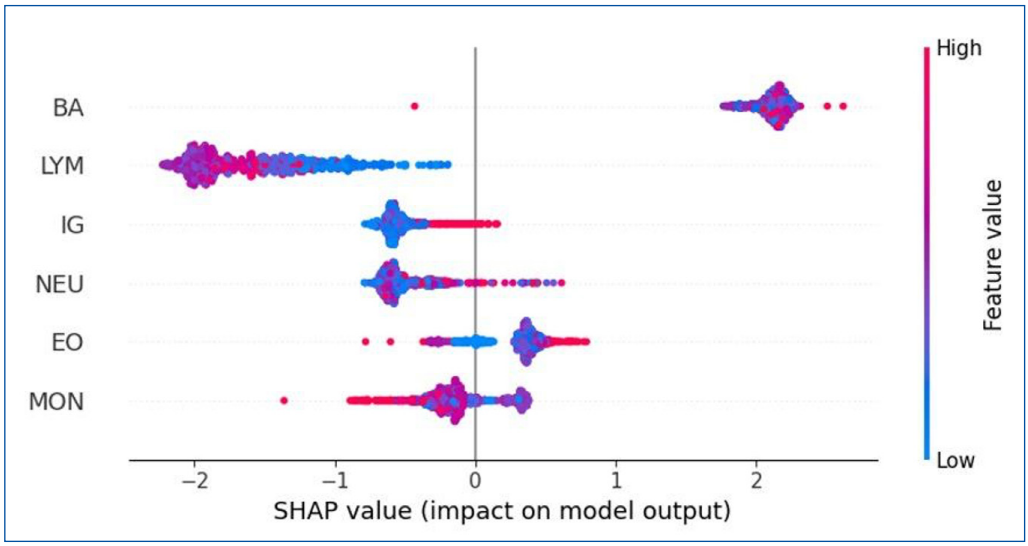

Figure 2. SHAP Analysis of White Blood Cell Subtypes in Predicting Clinical Outcomes.

NPV (Negative Predictive Value): The XGBoost model had the highest NPV (0.886), followed by KNN (0.742), while the lowest NPV was observed in Logistic Regression (0.578).

Figure 2 evaluates the effects of white blood cell subtypes between Robson Group 10 and the control group using SHAP analysis. SHAP analysis demonstrates how white blood cell parameters contribute to the model output in the machine learning model. Immature granulocytes (IG) and neutrophils (NEU) at high levels (red) showed positive SHAP values, indicating an increased likelihood of being classified into Robson Group 10. Lymphocytes (LYM), on the other hand, were associated with positive SHAP values at low levels (blue), suggesting a higher likelihood of being included in Robson Group 10. However, high monocyte levels (red) were generally associated with negative or neutral SHAP values, indicating that high monocyte levels may increase the likelihood of remaining in the control group.

Table 4 compares maternal haematological variables in fetuses with birth weight above and below 2500 g. There is a significant difference in white blood cell count (WBC), with mothers of fetuses weighing less than 2500 g having higher WBC counts (median: 11.9, IQR: 9.41-14.50) compared to mothers of fetuses weighing 2500 g or more (median: 10.9, IQR: 9.20-12.40), p=0.002. Similarly, neutrophil counts were significantly higher in the <2500 g group (median: 9.07, IQR: 6.78-11.60) compared to the ≥2500 g group (median: 8.04, IQR: 6.49-9.60), p<0.001. Monocyte levels also showed a significant difference, with higher values in the ≥2500 g group (median: 0.680, IQR: 0.550-0.798) compared to the <2500 g group (median: 0.630, IQR: 0.425-0.820), p = 0.020. No significant differences were observed in lymphocyte counts (p=0.138), eosinophil counts (p=0.063), or immature granulocyte (IG) levels (p=0.682).

DISCUSSION

The Robson 10 group consists of patients with preterm births by definition. The causes of preterm births in this group vary. Various conditions such as severe pre-eclampsia, fetal growth retardation with Doppler abnormalities, preterm premature rupture of membranes and placental abruption can be the cause of preterm birth [1,5,6]. However, most etiologic causes include maternal inflammatory reactions. In addition, maternal hematologic adaptations induced by pregnancy also differ in the assessment of hematologic parameters from non-pregnant women. The aim of this study was to show what differences preterm births show in the hematologic environment within the physiologic changes of the hematologic system that occur during pregnancy.

In a study investigating hematological-physiological changes during pregnancy, 24,318 pregnant women were evaluated and the distribution of leukocytes and subtypes by week of pregnancy was examined. The study showed that the total number of white blood cells and the number of neutrophils increased with the week of pregnancy. Although the number of monocytes increased with the week of pregnancy, this increase was not statistically significant, while a decrease was observed in the number of eosinophils, although this was not statistically significant[7]. Another study showed that the total number of leukocytes increased continuously with pregnancy between 8-40 weeks of gestation[8] and that the main reason for this was an increase in neutrophils [9–11]. Luppi et al. found that pregnancy is characterized by an increased proportion of granulocytes and a decrease in lymphocytes, while monocytes remain constant throughout pregnancy, but there is a progressive upregulation of the surface markers CD11a, CD54 and CD64. Monocytes also showed higher production of interleukin (IL)-12 and IL-1beta compared to the non-pregnant state, and granulocytes

were shown to have a greater potential to synthesize IL-8 [11]. Although Dockree et al. have shown that the absolute difference in the number of circulating monocytes during pregnancy is small, it is thought that monsitosis occurs during pregnancy, which prevents fetal allograft rejection [12] and provides an important protective mechanism for the developing fetus by altering the maternal innate immune response.

In our study, it was observed that leukocyte and neutrophil counts increased in the Robson 10 group patients who delivered at preterm, consistent with the literature. Although the week of gestation at which the complete blood count was performed was more advanced in the control group, neutrophil and total white blood cell counts were higher in the Robson 10 group than in the control group. On the other hand, monocyte and eosinophil counts were lower in the Robson 10 group. The differences were statistically significant. We hypothesize that neutrophilia and leukocytosis are caused by the inflammatory milieu created by or causing preterm labor. This hypothesis is supported by the statistically significantly high number of immature granulocytes in the Robson 10 group. However, it is noteworthy that the monocyte and eosinophil counts were lower in the Robson 10 group. The fact that hemodilution varies depending on the gestational week and etiologic reasons in the preterm laboured patients included in our study has a confounding effect on our results. However, considering the role of monocytes in the prevention of fetal allograft rejection demonstrated by Oberbarnscheidt et al. we consider the low number of monocytes in the Robson 10 group to be a remarkable result.

Almost all studies in the literature were conducted using conventional statistical methods. The data we analyzed in our study were analyzed using conventional statistical methods. Conventional statistical tests (e.g. t-test and Mann-Whitney U-test) focus on mean and median values. However, these methods may miss variations at the individual patient level. For example, monocyte levels may have varied at the individual level even if they did not differ significantly between means. Developments in the field of artificial intelligence and its applications in medicine have opened up new perspectives. In this context, machine learning algorithms offer the possibility to perform more detailed analysis at the individual level [13]. We believe that methods such as SHAP analysis, which we used in our study, offer a new perspective to show how leukocyte subtypes influence preterm births. The findings obtained with the machine learning algorithms show that when the monocyte count is high, the algorithm predicts the control group, while the high immature granulocyte count predicts the Robson 10 group. However, it is noteworthy that elevated levels of immature granulocytes are not always included in the Robson 10 group, and we have shown that they can also predict the control group. Another noteworthy aspect is the role of lymphocyte count in the prediction model. Both high and low lymphocyte counts predict the control group. However, low lymphocyte counts are less important for predicting the control group.

Conventional methods are very powerful in detecting differences on a group basis. However, when combined with machine learning methods, they can also help uncover nuances at the individual patient level. Through this combination, clinical decision making can become more personalized. In this context, our study provides a different perspective on leukocytes and subtypes in the Robson 10 group.

However, we have limitations. Our main limitation is that we did not create etiological subgroups in the Robson 10 group. Another limitation is that the week of gestation at which the CBCs of the patients included in the study were performed differed between the control group and the Robson 10 group. This is due to the fact that our data were obtained retrospectively from patient records. However, the large number of patients included in the study and the use of conventional statistical methods and machine learning algorithms make our study powerful.

Further studies in which the problems of randomization are eliminated and the number of patients is increased due to the nature of machine learning will provide a better understanding of the changes in the immunological system.

In this study, we demonstrated that preterm births in the Robson 10 group exhibit notable hematological differences compared to term deliveries, particularly with respect to leukocyte subtypes. Increased levels of neutrophils and leukocytes in the Robson 10 group suggest an inflammatory response associated with preterm labor. However, lower monocyte and eosinophil counts in this group are intriguing, potentially reflecting different immune mechanisms. The application of both conventional statistical methods and machine learning algorithms, such as SHAP analysis, provides valuable insights into individual variations, highlighting the potential of personalized approaches in clinical decision-making. Future studies with improved randomization and larger patient cohorts could further elucidate the immunological changes associated with preterm birth.

Ethics Committee Approval: Our study has been approved by the Etlik City Hospital Ethics Committee (approval numbered AESH-BADEK-2024-895, dated 02.10.2024)..

Conflict of Interest: The authors declare that they have no known financial interests or personal relationships with any companies or organizations that could influence the work reported in this manuscript.

Informed Consent: Informed consent was obtained from all patients prior to the study.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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The Utility of the Systemic Immune-Inflammation Index (SII) and the Systemic Immune-Response Index (SIRI) in predicting pregnancy-related cerebral venous sinus thrombosis: An experience from a tertiary center

Sistemik İmmün-İnflamasyon İndeksi (SII) ve Sistemik İnflamatuar-Yanıt İndeksi'nin (SIRI) gebelikle ilişkili serebral venöz sinüs trombozunu öngörme etkisi: Üçüncü basamak merkez deneyimi

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ABSTRACT

Aim: Our aim in this study was to investigate the difference of systemic immune inflammatory index (SII) and systemic inflammatory response index (SIRI) indices between pregnancy-related cerebral venous sinus thrombosis (CVST) patients and healthy pregnant and postpartum women and to evaluate the association between these indices and disease severity and prognosis in the CVST group.

Materials and Methods: This retrospective study included 21 patients with CVST and 80 healthy pregnant and postpartum patients as the control group. We looked at whether there was a statistical difference in demographic and clinical characteristics and laboratory results between the groups. Then we compared the SII and SIRI values, whose prognostic value has been studied as new inflammatory indices in many subjects.

Results: Neutrophil, monocyte, lymphocyte and platelet counts were similar between the groups. SII and SIRI were significantly higher in the CVST group (p:0.006, p:0.043; respectively). It was found that the SII and SIRI indices were higher in the group with severe disease and the poor prognosis, but the results were not statistically significant.

Conclusion: These results showed us that the SII and SIRI indices can be used as a supporting factor for the diagnosis in patients with suspected CVST. Studies with more patients may help to demonstrate the impact of SII and SIRI indices on disease severity and prognosis.

Keywords: Cerebral venous sinus thrombosis, pregnancy, systemic inflammatory response index, systemic immune inflammation index, thrombo-inflammatory markers

ÖZ

Amaç: Gebelikle ilişkili serebral venöz sinüs trombozu (SVST) hastaları ile sağlıklı gebe ve doğum sonrası kadınlar arasında sistemik immün inflamasyon indeksi (SII) ve sistemik inflamatuar yanıt indeksi (SIRI) arasındaki farkı araştırmak ve bu indeksler ile hastalık şiddeti ve prognoz arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntemler: Bu retrospektif çalışmaya 21 SVST hastası ve kontrol grubu olarak 80 sağlıklı gebe ve postpartum hasta dahil edildi. Grupların demografik ve klinik özellikleri, laboratuvar sonuçları, SII ve SIRI indeksleri karşılaştırıldı. SVST grubunda SII ve SIRI indekslerinin hastalığın şiddeti ve prognozu ile ilişkisi araştırıldı.

Bulgular: Gruplar arasında nötrofil, monosit, lenfosit ve trombosit sayıları benzerdi. SII ve SIRI değerleri SVST grubunda daha yüksekti ve fark istatistiksel olarak anlamlı olarak anlamlıydı (sırasıyla; p:0,006, p:0,043). Şiddetli hastalık ve kötü prognozlu grupta SII ve SIRI indekslerinin daha yüksek olduğu görüldü ancak sonuçlar istatistiksel olarak anlamlı değildi.

Sonuç: SVST için klinik şüphe olan hastalarda tanıyı destekleyici bir faktör olarak SII ve SIRI değerleri kullanılabilir. Daha fazla hasta sayılı çalışmalar SII ve SIRI indekslerinin hastalık şiddeti ve prognozundaki etkisini göstermeye yardımcı olabilir.

Anahtar Kelimeler: Serebral venöz sinüs trombozu, gebelik, sistemik inflamatuar yanıt indeksi, sistemik immün inflamasyon indeksi, trombo-inflamatuar belirteçler

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INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is a rare subtype of stroke that accounts for 0.5-1% of all strokes (1). In the general population, the incidence of CVST is on average three times higher in women than in men (2,3).This gender difference has been associated with sex-specific risk factors such as oral contraceptive use, pregnancy, puerperium, or hormone replacement therapy (4). In a prospective international study of crebral vein and dural sinus thrombosis (ISCVT), 20% of patients presented during pregnancy and the puerperium (5). CVST accounts for approximately 2% of pregnancy-related strokes and occurs in up to 0.01% of all pregnancies (6). Pregnancy-related CVST occurs more frequently in the third trimester or in the puerperium (7). Studies have been performed to determine various risk scores to predict the prognosis of patients with cerebral venous and dural sinus thrombosis (8,9).

It is well known that changes in cellular content in peripheral blood are indicative of the inflammatory response in various diseases (10,11). In addition, systemic inflammatory response index (SIRI) and systemic immune inflammation index (SII) have been studied as more complicated inflammatory markers in various diseases and cancers (12-15). Although the effects of inflammation on CVST have not been fully elucidated, conditions such as infections, coagulation factor deficiency, and systemic autoimmune diseases, which are risk factors for CVST, are associated with inflammatory responses (16). This suggests that inflammation plays a role in the etiopathogenesis of CVST (16). The role of inflammation has been confirmed by studies showing markedly elevated inflammatory markers in serum and cerebrospinal fluid (CSF) in CVST (17,18). The SII, based on peripheral lymphocyte, neutrophil, and platelet counts, and the SIRI, based on peripheral lymphocyte, neutrophil, and monocyte, are the new inflammatory indices that reflect in detail the patient's immune and inflammatory state. The role of inflammation in the prognosis of CVST has been proven in a small number of studies. The systemic immune inflammation index was first investigated in CVST patients in a 2020 study by Li et al (17). Although pregnancy and puerperium are known risk factors for CVST, publications on this group of patients are limited to small series (3). Our aim in this study was to investigate the difference of SII and SIRI indices between pregnancy-related CVST patients and healthy pregnant and postpartum women and to evaluate the association between these indices and disease severity and prognosis in the CVST group.

MATERIAL AND METHODS

Study population

We conducted this retrospective cohort study between September 2019 and June 2021 in the Maternal-Fetal Medicine Department of Ankara City Hospital. The study was approved by the Ethics Committee of Ankara City Hospital (Date: No.:E2-21-624). Study was carried out in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all the participants.

A total of 21 patients with CVST and 80 healthy pregnant and postpartum patients at the same gestational week were included as the control group. Primarily, all patients who were diagnosed with CVST in our hospital between September 2019 and November 2022 or who were referred to our hospital with this diagnosis during prenatal care or the postpartum period were identified. The inclusion criteria were as follows: (1) presence of clinical signs such as headache, visual disturbances, seizures, focal neurological deficits, consciousness disorders, (2) presence of cerebral sinus filling defect on magnetic resonance venography (MRV), (3) acute and subacute patients (less than thirty days from the onset of symptoms). The exclusion criteria were as follows: (1) patients with insufficient clinical data and (2) chronic patients.

Demographic characteristics of the CVST group such as age, presence of known disease, smoking, family history, and disease-related outcomes such as time of onset of symptoms, gestational age or duration of postpartum, current symptoms, laboratory results at admission, presence of preeclampsia, autoimmune disease, or thrombophilia, and imaging findings (location of clot and cerebral infarction or hemorrhage) were extracted. Healthy pregnant and postpartum patients whose gestational age matched that of the CVST group were identified, and a control group was formed with four control subjects for each patient. Disability was graded according to the modified Rankin Scale (mRS, 0=complete recovery, 6=dead)(5).

In this study, we first performed a descriptive analysis of the CVST group, which consisted of 21 pregnant and postpartum patients we cared for in our hospital. Then, we looked at whether there was a statistical difference in demographic and clinical characteristics and laboratory results between the study and control group and we compared the SII (neutrophilXplatelet/lymphocyte) and SIRI (neutrophilXmonocyte/lymphocyte) values, whose prognostic value has been studied as new inflammatory indices in many subjects (control group, n:80). Furthermore, we analyzed these inflammatory markers within the CVST group and evaluated whether they had an impact on predicting the severity or prognosis of the disease.

Statistical Analysis

All statistical analyzes were performed using SPSS 26 (IBM Inc, Chicago, IL, USA). First, the Shapiro-Wilk test was used to determine

whether the data were normally distributed or not. Because the data were not normally distributed, median and interquartile range values were used to represent related variables, and the Mann-Whitney U test was performed to compare median values between groups. Categorical variables were presented as numbers and percentages. Next, a receiver operating characteristic curve analysis (ROC) was performed to determine the optimal cut-off values for SII and SIRI for predicting pregnancy-related CVST. Then, a ROC analysis was performed to determine the optimal cut-off values for SII and SIRI for predicting adverse outcomes in the study group. The Youden index was used to select appropriate cut-off values for SII and SIRI. P values <0.05 was assumed as statistically significant.

RESULTS

A total of 101 patients were included in this study (n:21 patients in the CVST group and n:80 cases in the control group). The baseline data of the study group are shown in Table 1. Of the 21 patients in the cohort, 18 (85.7%) were pregnant, 3 (14.3%) were postpartum, 3 (14.3%) were suffering in the first trimester, 5 (23.8%) in the second trimester, and 10 (47.6%) in the third trimester. All pregnant patients had a live birth, one of them at 23 weeks' gestation with an Apgar score of 2 at 5 minutes. 4 other patients had a preterm delivery due to preeclampsia and fetal indications.

The most common symptoms were headache (76%) and paresthesias (28.6%). Other less common signs and symptoms were seizures (14.3%), motor weakness (14.3%), dysarthria/aphasia (9.5%), mental status disorders (14.3%), and visual disturbances (4.8%). The diagnosis was confirmed by MR venography in patients who had symptoms and were suspected of having CVST. Thrombi were most commonly located in the transverse sinuses (76.2%) and superior sagittal sinuses (52.4%). Concomitant thrombophilia was found in 81% of patients. Two of the patients who developed CVST had rheumatologic disease and two others had active infection (Covid-19). Two of the patients who developed CVST in the postpartum period delivered after a diagnosis of preeclampsia. In addition, preeclampsia developed in the later weeks of pregnancy in two of the patients who were diagnosed with CVST in the second trimester.

Anticoagulant therapy was initiated in all patients. In addition to anticoagulant treatment, antiepileptic treatment was required in 5 patients, hypertonic solution in 4 patients, and steroid use in

Table 1. Baseline characteristics of pregnancy-related CVST patients

	n:21 (100%)		n:21 (100%)
Pregnant	18(85.7%)	**Clot Location**	
First trimester	3(14.3%)	**Süperior sagital sinus**	11(52.4%)
Second trimester	5(23.8%)	**Sigmoid sinus**	8(38.1%)
Third trimester	10(47.6%)	**Straight sinus**	2(9.5%)
Postpartum	3(14.3%)	**Transverse sinus**	16(76.2%)
Signs and symptoms		**One sinus**	9(42.9%)
Headaches	16(76.2%)	**Two sinus**	8(38.1%)
Paresthesias	6(28.6%)	**More than two**	4(19.0%)
Seizure	3(14.3%)	**Intracranial complications**	
Motor weakness	3(14.3%)	**Intracranial hemorrhage**	1(4.8%)
Visual disturbance	1(4.8%)	**Cerebral infarction**	6(28.6%)
Mental status disorder	3(14.3%)	**Treatment**	
Dysarthria/aphasia	2(9.5%)	**Anticoagulant**	21(100%)
Coma	1(4.8%)	**Antiepileptic**	5(23.8%)
Thrombophilia	17(81.0%)	**Hipertonic solution**	4(19.0%)
Preeclampsia	3(14.3%)	**Steroid**	2(9.5%)
Infection (Covid-19)	2(9.5%)		
mRS score on admission		**Outcome at 3 months**	
1-2	14(66.7%)	**Complete recovery (mRS 0-1)**	17(81.0%)
3-4	5(23.8%)	**Disability (mRS 2-5)**	3(14.3%)
5	2(9.5%)	**Hospital mortality (mRS 6).**	1(4.8%)

Data are given %. mRS, modified Rankin Scale.

Table 2. Comparison of demographic and clinical characteristics between the study and control groups

	Control (n = 80)		CVST (n = 21)		
	Median	Interquartile Range	Median	Interquartile Range	p-Value
Age, years	28	6	26	13	0.671
Gravity	2.0	1	2.0	2	0.277
Parity	0.0	1	1.0	2	0.219
Miscarriage	0.0	0	0.0	0	0.843
Birth weight (g)	3400	540	2780	1690	**<.0.001**
Apgar score at first minute	8.0	1	7	1	0.301
Apgar score at fifth minute	9.0	0	9	1	0.302
Hemoglobin (g/dL)	11.8	1.5	12.2	2.9	0.471
White blood cell (10^9/L)	9760	2490	10510	4930	0.688
Neutrophil (10^9/L)	7310	2590	8650	3125	0.098
Monocyte (10^9/L)	480	240	520	265	0.552
Lymphocyte (10^9/L)	1790	730	1860	710	0.525
Platelet (10^9/L)	249000	76000	271000	119000	0.100

p value < 0,05 was considered statistically significant. g, gram; dL, deciliter; L, liter.

Table 3. SII and SIRI for predicting CVST

	Cut-off	AUC	95%CI	p-Value	Sensitivity(%)	Specificity(%)
SII	1251.55	0.695	0.557-0.832	0.006	61.9	78.0
SIRI	2.109	0.644	0.504-0.784	0.043	66.7	63.7

AUC, Area under the curve; CI, confidence interval; SII, systemic immun inflammation index; SIRI, systemic immun inflammatory index

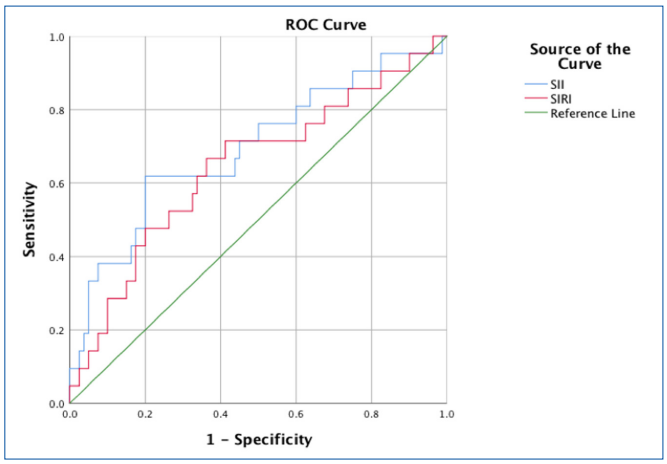

Figure 1. ROC curve of SII and SIRI for predicting the presence of CVST.
CVST, cerebral venous sinus thrombosis; ROC, receiver operating curve; SII, systemic immune inflammation index; SIRI, systemic immune response index.

2 patients. Four patients that presented coma or mental status disorder at the time of admission. Mortality was observed in 1 patient (4.8%), disability (mRS 2-5) was observed in 3 patients (14,3%) after treatment.

Comparison of demographic and clinical characteristics between the study and control groups were shown in Table 2. No statistically significant difference was found between the two group, except for birth weight. Neutrophil, monocyte, lymphocyte and platelet counts were similar between the groups.

After descriptive analysis of the CVST group, we evaluated the ability to discriminate between the patient and healthy groups of SII and SIRI values using the AUC on the ROC curve. SII and SIRI were significantly higher in the CVST group. The discriminatory power of SII based on the area under the ROC curve was 0.695 (95% confidence interval [CI]: 0.557-0.832, p< 0.05) for CVST, and at a cut-off value of 1251.55. The discriminatory power of the SIRI value using the area under the ROC curve was 0.644 (95% CI: 0.504 - 0.784, p< 0.05) for CVST, and using a cut-off value of 2.109. The sensitivity and specificity of predicting CVST using SII was 61.9% and 78.0%, wheras using SIRI was 66.7% and 63.7%, as shown in (Figure 1) (Table 3).

The ability of SII and SIRI scores to discriminate disease severity and prognosis within the CVST group was also assessed. Those who had an mRS score of 0-1 at diagnosis were classified as having mild disease, while those with a score of 2 or more were considered to have severe disease. It was found that the SII and SIRI indices were higher in the group with severe disease, but the results were not

Table 4. SII and SIRI for assessing disease severity in the CVST group

	Cut-off	AUC	95%CI	p-Value	Sensitivity(%)	Specificity(%)
SII	1174.04	0.731	0.511-0.951	0.082	76.9	62.5
SIRI	2.169	0.635	0.386-0.883	0.311	69.2	62.5

AUC, Area under the curve; CI, confidence interval; SII, systemic immun inflammation index; SIRI, systemic immun inflammatory index

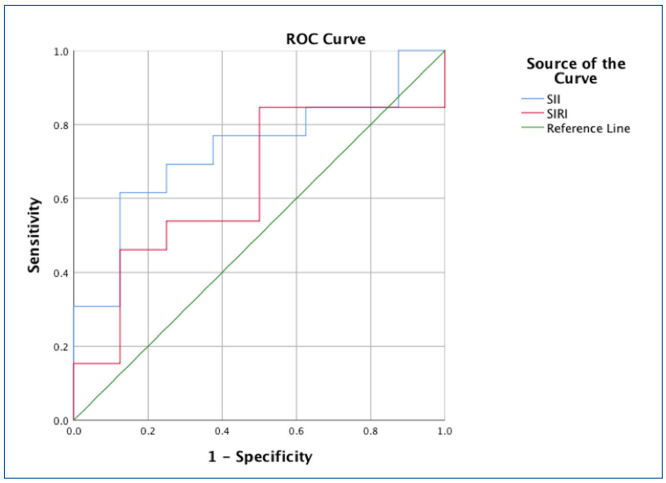

Figure 2. ROC curve of SII and SIRI in assessing disease severity in the CVST group.

CVST, cerebral venous sinus thrombosis; ROC, receiver operating curve; SII, systemic immune inflammation index; SIRI, systemic immune response index.

statistically significant. The discriminating power of the SII and SIRI based on the area under the ROC curve was 0.731 (95% confidence interval [CI]: 0.511 - 0.951, p>0.05) and 0.635 (95% CI: 0.386 - 0.883, p>0.05) for severe disease. When SII is used to estimate the severity of the disease, if the cut-off value is accepted as 1174.04, the sensitivity was 76.9% and the specificity was 62.5%, when we use SIRI and accepted cut-off value of 2.169, the sensitivity was 69.2% and the specificity was 62.5%, as shown in (Figure 2) (Table 4).

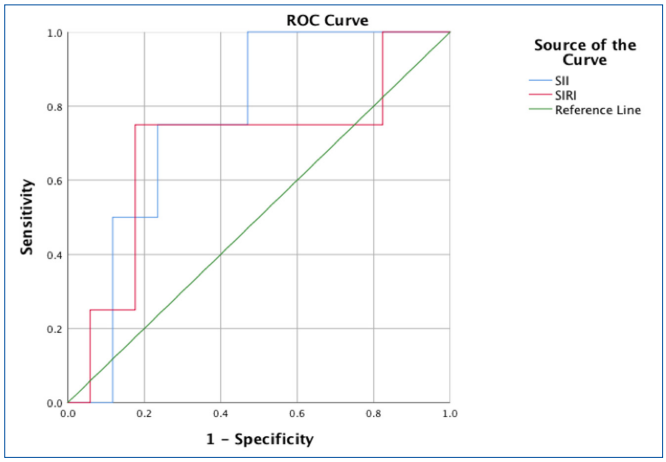

Figure 3. ROC curve of SII and SIRI in assessing prognosis in the CVST group.

CVST, cerebral venous sinus thrombosis; ROC, receiver operating curve; SII, systemic immune inflammation index; SIRI, systemic immune response index.

The mRS scores at the third month of treatment were used to assess prognosis. Those with an mRS score of 0-1 were classified as having a good prognosis, and those with an mRS score of 2 or more were classified as having a poor prognosis. It was found that the SII and SIRI indices were higher in the poor prognosis group, but the results were not statistically significant. The discriminatory power of the SII and SIRI using the area under the ROC curve was 0.765 (95% confidence interval [CI]: 0.548 - 0.981, p>0.05) and 0.691 (95% CI: 0.366 - 0.1000, p>0.05) for poor prognosis. When SII is used to estimate poor prognosis, if the cut-off value is accepted as 1577.07, the sensitivity was 75.0% and the specificity was 71.6%, when we use SIRI and accepted cut-off value of 2.684, the sensitivity was 75.0% and the specificity was 71.6%, as shown in (Figure 3) (Table 5).

DISCUSSION

CVST can be life-threatening, and morbidity and mortality increase significantly, especially when diagnosis and treatment are delayed. Prompt diagnosis and treatment is one of the most important factors that reduce morbidity and mortality and improve outcomes. Due to the difficulty in diagnosis and the importance of early diagnosis and treatment, cost-effective and easily accessible methods are becoming increasingly important.

In our study, we basically investigated whether there was a difference between SII and SIRI indices between pregnancy-related CVST patients and healthy pregnant and postpartum women. Our main finding was that SII and SIRI scores were significantly higher in the CVST group at the time of hospital admission. We also examined the effect of SII and SIRI indices in predicting the severity of the disease and prognosis in the group with CVST patients, and

Table 5. SII and SIRI for assessing prognosis in the CVST group

	Cut-off	AUC	95%CI	P value	Sensitivity(%)	Specificity(%)
SII	1577.07	0.765	0.548-0.981	0.107	75.0	71.6
SIRI	2.684	0.691	0.366-0.1000	0.244	75.0	71.6

AUC, Area under the curve; CI, confidence interval; SII, systemic immun inflammation index; SIRI, systemic immun inflammatory index

although the scores were higher in patients with severe and poor prognosis, we could not obtain a statistically significant result.

CVST is a rare form of stroke, and diagnosis can be challenging due to nonspecific findings (3). Although the etiopathogenesis of CVST is not fully understood, it is thought that the disease is multifactorial and thrombo-inflammatory processes play the most important role (18). In addition to draining blood, the cerebral sinuses are essential for CSF transport. Occlusion of the cerebral sinuses blocks CSF transport, resulting in intracranial hypertension. In the second mechanism, occlusion of a cortical vessel blocks blood flow from brain tissue, resulting in increased vasculer pressure and disruption of the blood-brain barrier (19). This process can lead to brain tissue damage. Headache is the most common symptom, but it does not occur in a minority of patients, while almost half of them experience seizures in the acute phase. Patients may present with various combinations of symptoms (20). Bentley et al. reported that most patients are misdiagnosed and that in 40% of patients admitted to the hospital, the diagnosis is delayed for days (21). Patients with pregnancy-related CVST are more likely to have a delayed or missed diagnosis than other CVST patients. Symptoms and signs of preeclampsia and eclampsia, as well as headache used are magnetic resonance imaging (MRI) with MR-venography, computed tomography (CT)-venography, and catheter angiography, but MRI with MR-venography being the most commonly preferred method (7). Moreover, MRI is not always positive for the diagnosis of CVST in the acute phase. For this reason, new parameters that facilitate diagnosis are gaining importance.

Inflammation, infection, hypercoagulability, and stasis are well-defined risk factors in the etiopathogenesis of CVST (22,23). Although the mechanism of CVST is still not fully understood, previous evidence suggests that it is a multifactorial disease in which thromboinflammatory processes play an important role (24).

Many thrombotic and inflammatory markers have been studied in assessing disease severity and predicting prognosis in patients (18). In a 2014 study, it was shown that high D-dimer levels can be an important biomarker for CVST, while the positive predictive value of an elevated D-dimer-fibrinogen combination is even higher (25). Neutrophil-to-lymphocyte ratio (NLR) has been identified as an important inflammatory marker in cerebral arterial ischemia, but its role in CVST is not clear. Although there are conflicting results in the literature, a 2022 review by Ding et al. found that NLR is significantly elevated in patients with CVST (26). In addition to the known inflammatory effect of neutrophils; it has also been shown in studies that it is a tissue factor that provokes thrombus formation (27). In another recent study, high NLR and platelet-to-lymphocyte ratio (PLR) levels were found to be associated with the presence of CVST (28). In previous studies, SII has been shown to be more reliable than other leukocyte-based indicators of inflammation, including PLR and lymphocyte-to-monocyte ratio (LMR) (28). SIRI has also received more attention after some studies showed that it is able to predict the progression of diseases such as cancer, cardiovascular disease, and ischemic stroke (29-31). Moreover, the association between high SIRI levels and mortality in stroke patients has been previously demonstrated (32). All these studies show us that biomarkers indicating thromboinflammatory state and their combinations occupy an important place in the diagnosis of CVST.

Our results show that SII and SIRI indices, which are easily accessible and can be combined with some thromboinflammatory parameters, can be used to predict pregnancy-related CVST. But, of course, these indices alone cannot be used to tell whether CVST is present or not. They can be used as a diagnostic aid in patients with clinical suspicion. The small number of CVST patients may be the reason why we could not obtain statistically significant results in terms of disease severity and prognosis, and this relationship can be demonstrated by studies with a larger number of patients.

Informed Consent: Written informed consent was obtained from all the participants.

Author Contributions: EB: Manuscript writing, Data collection, Literature search. AT: Project development, Reviewing, Editing, Data analysis. NF: Data collection, Literature search. ZA: Data collection, Data analysis, Literature search. HŞ: Patient selection, Data collection. ÖK: Data analysis, Literature search, Reviewing. NNÖ: Patient selection, Reviewing, Editing. DŞ: Project development, Visualization, Reviewing, Editing

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Maternal "Near Miss" ve maternal mortalite olgularında risk faktörlerinin saptanması, tedavi prognozu ve perinatal sonuçların incelenmesi

Analysis of risk factors, treatment prognosis and perinatal outcomes in maternal "Near Miss" cases

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ÖZ

Amaç: Anne ölümü, sağlık sistemlerinin gelişmişliğinin önemli bir göstergesidir. Maternal near-miss, sağlık hizmeti kalitesini belirlemede maternal mortaliteden daha etkilidir. Bu çalışmanın amacı, kliniğimize başvuran gebeler arasında anne ölümünü veya ölümden dönme vakalarını belirlemek ve bu durumlara yol açan sebepleri tespit etmektir.

Gereç ve Yöntemler: Retrospektif ve gözlemsel tipte olan bu araştırmada, Şehit Prof. Dr. İlhan Varank Sancaktepe Eğitim ve Araştırma Hastanesi'nde 1 Şubat 2018 - 1 Eylül 2023 tarihleri arasında antenatal takip, doğum veya doğum sonrası 42 gün içinde başvuran 95 hastanın dosyaları incelenmiştir. DSÖ tarafından tanımlanan near-miss kriterlerine uyan hastalar ve maternal mortalite ile sonuçlanan hastalar çalışmaya dahil edilmiştir.

Bulgular: En sık görülen tanının %50,5 ile COVID-19 olduğu belirlenmiş olup, bunu sırasıyla eklampsi ve uterin kanama (%9,5), preeklampsi (%7,4) ve plasenta previa (%6,3) takip etmektedir. Katılımcıların %27,6'sı yaşamını sürdürmüş, %72,4'ü yaşamını yitirmiştir. COVID-19 tanısı alan hastalarda Maternal Severity Skoru, İndeksi, hastanede ve yoğun bakımda kalış süreleri, COVID-19 olmayanlara göre anlamlı şekilde daha yüksek bulunmuştur. Eklampsi vakalarında hastanede ve yoğun bakımda kalış süreleri ile maternal mortalite oranları, diğer vakalara kıyasla anlamlı olarak yüksek seyretmiştir. Kardiyovasküler ve respiratuar disfonksiyonun varlığı, maternal ölüm riskini güçlü biçimde arttırmıştır.

Sonuç: Anne ölümlerini önlemede erken tanı ve müdahale önemlidir. Hızlı ve doğru tanı ile gerekli müdahalelerin ivedilikle yapılması, anne kayıplarını önleyebilir. Daha fazla araştırma yapılması gerektiği sonucuna varılmıştır.

Anahtar Kelimeler: Maternal mortalite, maternal morbidite, near-miss

ABSTRACT

Aim: Maternal mortality is a crucial indicator of healthcare system development. Maternal near-miss cases are more effective than mortality alone in assessing healthcare quality. This study aims to identify maternal deaths or near-miss cases among pregnant women admitted to our clinic and to determine the contributing factors.

Materials and Methods: This retrospective, observational study examined the records of 95 patients who presented for antenatal care, delivery, or within 42 days postpartum at Şehit Prof. Dr. İlhan Varank Sancaktepe Training and Research Hospital between February 1, 2018, and September 1, 2023. Patients meeting the WHO-defined near-miss criteria and maternal mortality were included in the study.

Results: COVID-19 was identified as the most common diagnosis at 50.5%, followed by eclampsia and uterine bleeding (9.5%), preeclampsia (7.4%), and placenta previa (6.3%). Of the participants, 27.6% survived, while 72.4% died. Maternal Severity Score, Index, and hospital and ICU stays were significantly higher for COVID-19 patients than for non-COVID-19 patients. Eclampsia cases showed significantly longer hospital and ICU stays and higher mortality rates than other cases. The presence of cardiovascular and respiratory dysfunction substantially increased the risk of maternal mortality.

Conclusion: Early diagnosis and intervention are essential for preventing maternal deaths. Prompt and accurate diagnosis, along with necessary interventions, may prevent maternal losses. Further research is warranted.

Keywords: Maternal mortality, maternal morbidity, near-miss

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GİRİŞ

Maternal ve fetal ölüm, dünya genelinde gelişmişlik düzeyini gösteren en önemli bulgular arasında yer almaktadır. Ülkelerde topluma sunulan sağlık hizmetleri arasında doğum hizmetlerinin kalitesini değerlendirmekte bazı parametreler göz önünde bulundurulmaktadır. Bu parametreler arasında maternal mortalite ve maternal morbidite yer almaktadır. Maternal mortalitenin tek başına kullanılması yeterli olmayıp maternal morbidite/mortalite oranının daha anlamlı olduğu ortaya konmuştur (1). Maternal near-miss kavramı ise maternal mortaliteden daha yüksek oranda sağlık hizmeti kalitesini tespit etme kapasitesine sahiptir ve bu amaçla ortaya çıkmıştır (2).

Maternal mortalite, gebelik sırasında veya gebelik sonlandıktan sonraki 42 gün içerisinde kaza veya kasıtlı ölümler dışındaki sebeplerle kaybedilen kadın ölümleridir. Gebeliğin kendisine bağlı veya gebeliğin şiddetlendirdiği ölüm sebeplerini içerir. Geç anne ölümü, gebelik süreci tamamlandıktan sonraki 42 gün ila 1 yıl arasında gerçekleşen gebelikle doğrudan veya dolaylı olarak ilişkilendirilebilen kadın ölümleridir. Gebeliğe bağlı ölüm, ölüm nedeni fark etmeksizin gebelik süresinde veya gebelikten sonraki 42 gün içerisinde gerçekleşen kadın ölümleridir (3).

Maternal near-miss (annenin ölümden dönüşü), annenin gebelik sürecinde veya doğumdan sonraki 42 gün içerisinde ciddi hayati tehlike ile karşılaşıp hayatta kalabildiği koşulları ifade etmektedir (4).

İleri anne yaşı, solunum ilişkili hastalıklar, hipertansif hastalıklar, renal hastalıklar, kanama bozuklukları, karaciğer hastalıkları, enfektif hastalıklar, intrakranyal hadiseler ve endokrin bozukluklar maternal mortalite ve morbiditeye yol açabilmektedir (5, 6, 7, 8, 9)

İleri anne yaşı yaş üstü gebelikleri kapsamaktadır (10). Solunum ilişkili hastalıklar arasında COVİD19, bakteriyel pnömoniler, respiratuvar disstres, pulmoner hipertansiyon yer almaktadır. Bunların balında COVİD 19 yer almaktadır (11). Hipertansif hastalıklar; preeklempsi, eklempsi gibi mortalitesi yüksek hastalıklardır (12). Renal hastalıklarda akut böbrek yetmezliği preeklampsi ve eklampsi ile ilişkili patolojilerin nadir bir komplikasyonudur (7). Kanama bozuklukları arasında plasenta ile ilişkili kanamalar, uterus ilişkili kanamalar, ektopik rüptür, DİK (dissemine intravasküler koagülopati), HELLP (H: hemoliz, EL: karaciğer enzim yüksekliği, LP: düşük trombosit sayısı) ve trombositopeniler yer almaktadır (13, 14).

Kanama bozukluklarından plasentaya ait invazyon anomalileri, annede masif kanamalara ve komplikasyonlara yol açabilmektedir (15).

Karaciğer ilişkili hastalıkların başında kolestaz yer almaktadır (16). Endokrin bozukluklar gebelik diyabeti ve gebelikteki tiroid hastalıkları şeklinde sıralanabilir (9). Gebelik sürecinde, doğumda ve doğum sonrası 42. güne kadar olan dönemde yaşamı tehdit edecek düzeyde obstetrik komplikasyon gelişen ancak yaşayan hastalar Dünya Sağlık Örgütü (DSÖ) tarafından neredeyse kaybedilecek (near-miss) hasta olarak tanımlanmıştır (17).

GEREÇ VE YÖNTEMLER

Araştırma retrospektif ve gözlemsel tipte bir çalışmadır. Araştırmada 1 Şubat 2018 ile 1 Eylül 2023 tarihleri arasında Kadın hastalıkları ve doğum kliniğinde antenatal takip, doğum veya doğum sonrası süreçte ciddi maternal morbidite nedeniyle neredeyse kaybedilecek (near miss) olarak sınıflandırılan veya maternal mortalite ile sonuçlanan 95 hastanın dosyaları, takiplerine ait izlem kayıtları ve yenidoğana ait izlem bilgileri retrospektif olarak incelenmiştir. Hastaların yaşı, beden kitle indeksi, kronik hastalıkları, sosyoekonomik düzeyleri, ırk, parite, gravida, gebelikler arası interval sure, antenatal takip sayısı, doğum haftası ve doğum şekli, bebeklerin ortalama doğum kiloları gibi obstetrik ve demografik özellikleri, neonatal sonuçları, hemodinamik verileri, transfüzyon miktarı, yoğun bakım ihtiyacı, hastanede yatış süreleri, operasyon yapılan hastalarda intraoperatif ve postoperatif komplikasyonlar ve morbidite-mortalite bilgileri toplanmıştır. Örnekleme dahil edilecek hasta grubu seçilirken söz konusu tarih aralığında araştırmanın dahil etme kriterlerine uyan ve bilgilerine eksiksiz erişilebilen tüm hastalar çalışma kapsamına alınmıştır. Ardından çalışma sonuçlarına göre güç analizi gerçekleştirilmiştir. Yapılan güç analizi sonuçlarına göre, COVID-19 tanısı olan ve olmayan bireyler arasında Maternal Severity Skoru farkını ölçmek için bağımsız örneklemler t-testi kullanılmıştır. Analiz, Cohen'in d etkisi büyüklüğünün 0.96 (büyük etki büyüklüğü), anlamlılık düzeyinin (α) 0.05 ve gücün (1-β) 0.80 olarak kabul edilmesiyle gerçekleştirilmiştir. Bu parametreler doğrultusunda G*Power 3.9.7 programıyla her bir grup için gereken minimum örneklem büyüklüğü 19 kişi olarak hesaplanmıştır. Çalışmada grupların örneklem büyüklükleri COVID-19 olmayan grup için 47 kişi, COVID-19 olan grup için 48 kişi olmak üzere toplamda 95 kişidir. Bu örneklem büyüklüğü, beklenen etki büyüklüğüyle anlamlı bir fark tespit etmek için yeterli kabul edilmiştir.

Çalışmaya dahil etme kriterleri olarak Dünya Sağlık Örgütü (DSÖ) tarafından belirlenmiş maternal near-miss (neredeyse kaybedilecek düzeydeki morbid obstetrik hasta) tanımı için kullanılan kriterler (17) kullanılmıştır (tablo aşağıda yer almaktadır). Bilgileri eksik olan hastalar araştırma kapsamı dışında bırakılmıştır.

Maternal severity skor ve maternal severity index hesaplamada Brezilya maternal morbidite araştırmasında kullanılan Maternal Severity Index (MSI) Calculator kullanılmıştır.(18).

Klinik Kriterler	Laboratuar Bazlı Kriterler	Klinik Yönetim Bazlı Kriterler
• Akut siyanoz • Gasping* • Solunum hızı >40 veya <6 dak. • Şok[a] • Sıvılara veya diüretiklere yanıt vermeyen oligüri[b] • Koagulasyon defekti[c] • ≥12 saat süren bilinç kaybı[d] • Bilinç kaybı ve nabız/kalp atımının olmaması • İnme[e] • Bedensel hareketlerin kontrol edilememesi/ tam felç[f] • Preeklampsi varlığında sarılık[g]	• ≥60 dakika boyunca oksijen satürasyonu <%90 olması • PaO2/FiO2 <200 mgHg • Kreatinin ≥300 mikromol/L veya ≥3,5 mg/dL • Bilirubin >100 mikromol/L veya >6,0 mg/dL • pH<7,1 • Laktat>5 • Akut trombositopeni (<50,000 trombosit) • Bilinç kaybı ve idrarda glikoz ve ketoasit bulnması	• Sürekli vazoaktif ilaç kullanımı** • Enfeksiyon veya kanamayı takiben histerektomi • ≥5 ünite eritrosit süspansiyonu transfüzyonu • Anestezi ile ilişkisi olmayan ≥60 dakika entübasyon ve ventilasyon • Akut böbrek yetmezliği için diyaliz • CPR

* Terminal bir solunum şeklidir ve nefes sarsıcı ve duyulabilir şekilde kesilir.

[a] Şok, agresif sıvı replasmanına (>2 L) rağmen nabız hızının en az 120 atım/dk. olması ve sistolik kan basıncının 60 dakika süreyle <90 mmHg olması olarak tanımlanan kalıcı şiddetli hipotansiyondur.

[b] Oligüri, idrar çıkışının 4 saat boyunca <30 mL/saat veya <400 mL/24 saat olması olarak tanımlanır.

[c] Pıhtılaşma başarısızlığı, yatak başı pıhtılaşma testiyle veya intravenöz girişim yapılan alanda kanül çekildikten 7 ila 10 dakika sonra hala pıhtılaşmanın olmamasıyla değerlendirilebilir.

[d] Bilinç kaybı, dış uyaranlara karşı tam veya tama yakın yanıt vermemeyi içeren, zihinsel durumdaki derin bir değişikliktir. Koma Glasgow Skalası <10 (orta veya şiddetli koma) olarak tanımlanır.

[e] İnme, 24 saatten uzun süren veya 24 saat içinde ölümle sonlanan, serebrovasküler nedenli nörolojik bir defisittir.

[f] Beynin sürekli nöbet halinde olduğu durum.

[g] Preeklampsi, proteinüri ile ilişkili hipertansiyon varlığı olarak tanımlanır. Hipertansiyon, önceden normotansif olduğu bilinen kadınlarda, gebeliğin 20. haftasından sonra en az 2 kez ve en az 4-6 saat arayla kan basıncının en az 140 mmHg (sistolik) veya en az 90 mmHg (diyastolik) olması olarak tanımlanır. Proteinüri, her 24 saatte 300 mg veya daha fazla proteinin atılımı olarak tanımlanır. 24 saatlik idrar örnekleri mevcut değilse, proteinüri en az 4 ila 6 saat arayla alınan en az 2 rastgele idrar örneğinde protein konsantrasyonunun 300 mg/L veya daha fazla (daldırma çubuğunda ≥1+) olması olarak tanımlanır.

**Örneğin, herhangi bir dozda dopamin, epinefrin veya norepinefrinin sürekli kullanımı.

Verilerin analizinde R 4.4.0 programı kullanılmıştır. Frekans, yüzde analizlerinin yanı sıra minimum, maksimum, ortalama, standart sapma ve çeyreklikler tanımlayıcı istatistiklerde kullanılmıştır. Normallik varsayımına çarpıklık ve basıklık değerlerinin aralıklarına (±1,00) göre karar verilmiştir. Fark analizlerinde çarpıklık ve basıklık aralığının dışında kalan sayısal değişkenler için normal dağılım sağlanmadığı kabul edilmiş ve Mann Whitney U testi uygulanmış, çarpıklık ve basıklık değerleri bu aralık arasında kalan sayısal değişkenlerle yapılan analizlerde ise normal dağılım varlığı kabul edilerek bağımsız örneklemlerde t testi kullanılmıştır. Kategorik değişkenlerin farkları Yates düzeltmeli ki- kare ve Fisher Exact testi ile ölçülmüştür. Yorumlamalar %95 güven düzeyinde gerçekleştirilmiştir.

BULGULAR

Araştırmaya 95 hasta dahil edilmiştir. Katılımcıların %27,4'ü (26 kişi) yaşamını sürdürmüş, %72,6'sı (69 kişi) yaşamını yitirmiştir. Primer tanı özellikleri Tablo 1'de verilmiştir.

Tablo 1. Katılımcıların Primer Tanı Özellikleri

	n	%
Ektopik Gebelik Rupturu	3	3,2
COVID19	48	50,5
Intrakranyel Kanama	2	2,1
Plasenta Previa	6	6,3
Epilepsi	1	1,1
Eklampsi	9	9,5
Preeklampsi	7	7,4
Uterin Kanama	9	9,5
Trombositopeni	2	2,1
Plasenta Dekolmani	6	6,3
HUS	2	2,1
TTP	1	1,1
Respiratuar Distress	1	1,1
PulmonerHT	1	1,1
HELLP	4	4,2
Abortus	4	4,2
Plasenta Invazyon Anomalisi	1	1,1
DIC	4	4,2
Sepsis	1	1,1
ABY	1	1,1
Pnomoni	3	3,2

Birden çok hastalığın tek bir bireyde olabildiği çoklu seçime dayalı hastalıklar

Tablo 2. Primer tanılarına göre yaşları, Maternal Severity skorları, Maternal Severity indeksleri, hastanede kalış süreleri ve yoğun bakım yatış süreleri kıyası

	n	Yaş	Maternal Severity Skor	Maternal Severity İndeksi (%)	Hastane Kalış Süresi (gün)	Yoğun Bakım Yatış Süresi (gün)
Ektopik Gebelik Rüptürü		**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**
Yok	92	30,50 (26,00-34,00)	2,00 (2,00-4,00)	0,40 (0,10-35,80)	11,00 (6,00-17,25)	4,50 (2,00-10,00)
Var	3	32,00 (31,50-37,50)	1,00 (1,00-1,50)	0,10 (0,10-0,10)	4,00 (3,50-4,50)	2,00 (1,50-2,50)
t/z		-1,130$_z$	-1,757$_z$	-1,845$_z$	**-2,398$_z$**	-1,510$_z$
p		0,259	0,079	0,065	**0,016***	0,131
COVID19		**x̄±s**	**x̄±s**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**
Yok	47	29,28±6,56	2,11±1,29	0,10 (0,10-0,40)	6,00 (5,00-11,00)	3,00 (1,00-4,00)
Var	48	31,38±5,64	3,48±1,56	35,80 (0,40-37,65)	16,00 (10,00-22,25)	9,00 (5,00-15,00)
t/z		1,673$_t$	**4,675$_t$**	**-5,038$_z$**	**-4,976$_z$**	**-5,519$_z$**
p		0,098	**<0,001*****	**<0,001*****	**<0,001*****	**<0,001*****
Intrakranyel Kanama		**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**
Yok	93	31,00 (26,00-34,00)	2,00 (1,00-4,00)	0,40 (0,10-35,80)	11,00 (6,00-17,00)	4,00 (2,00-10,00)
Var	2	30,00 (30,00-30,00)	4,00 (3,50-4,50)	21,75 (11,03-32,48)	7,50 (6,75-8,25)	5,00 (4,50-5,50)
t/z		-0,169$_z$	-1,210$_z$	-0,780$_z$	-0,740$_z$	-0,170$_z$
p		0,866	0,226	0,435	0,459	0,865
Plasenta Previa		**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**
Yok	89	30,00 (26,00-34,00)	2,00 (2,00-4,00)	0,40 (0,10-35,80)	10,00 (6,00-17,00)	5,00 (2,00-10,00)
Var	6	33,50 (32,25-34,00)	2,00 (1,25-2,00)	0,20 (0,10-4,73)	10,00 (6,50-21,00)	1,50 (1,00-2,75)
t/z		-1,579$_z$	-1,443$_z$	-1,288$_z$	-0,176$_z$	**-2,280$_z$**
p		0,114	0,149	0,198	0,860	**0,023***
Eklampsi		**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**
Yok	86	31,00 (27,00-34,00)	2,00 (2,00-4,00)	0,50 (0,10-35,80)	11,00 (6,00-18,00)	5,00 (2,00-10,75)
Var	9	25,00 (21,00-30,00)	2,00 (1,00-2,00)	0,10 (0,10-0,30)	6,00 (5,00-8,00)	2,00 (1,00-3,00)
t/z		**-2,610$_z$**	-1,681$_z$	**-2,722$_z$**	**-2,425$_z$**	**-2,354$_z$**
p		**0,009****	0,093	**0,006****	**0,015***	**0,019***
Preeklampsi		**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**
Yok	88	31,50 (26,00-34,00)	2,50 (1,00-4,00)	0,40 (0,10-35,80)	11,00 (6,00-18,00)	4,50 (2,00-10,25)
Var	7	29,00 (26,50-30,00)	2,00 (2,00-2,00)	0,10 (0,10-0,35)	7,00 (5,00-9,00)	2,00 (1,00-4,50)
t/z		-1,299$_z$	-1,388$_z$	-1,860$_z$	-1,840$_z$	-1,707$_z$
p		0,194	0,165	0,063	0,066	0,088
Uterin Kanama		**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**
Yok	86	32,00 (27,00-34,00)	2,50 (2,00-4,00)	0,40 (0,10-35,80)	11,00 (6,00-17,75)	5,00 (2,00-10,00)
Var	9	26,00 (24,00-28,00)	1,00 (1,00-2,00)	0,10 (0,10-0,10)	4,00 (3,00-10,00)	1,00 (1,00-3,00)
t/z		**-2,483$_z$**	**-2,541$_z$**	**-2,768$_z$**	**-2,208$_z$**	**-2,124$_z$**
p		**0,013***	**0,011***	**0,006****	**0,027***	**0,034***
Trombositopeni		**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**
Yok	93	31,00 (26,00-34,00)	2,00 (1,00-4,00)	0,40 (0,10-35,80)	10,00 (6,00-17,00)	4,00 (2,00-10,00)
Var	2	28,50 (28,25-28,75)	3,00 (2,50-3,50)	0,15 (0,12-0,18)	10,50 (9,25-11,75)	4,00 (2,50-5,50)
t/z		-0,623$_z$	-0,319$_z$	-1,084$_z$	0,000$_z$	-0,613$_z$
p		0,533	0,750	0,278	1,000	0,540
Plasenta Dekolmani		**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**
Yok	89	31,00 (26,00-34,00)	2,00 (2,00-4,00)	0,40 (0,10-35,80)	11,00 (6,00-18,00)	5,00 (2,00-10,00)
Var	6	28,00 (25,00-37,75)	1,00 (1,00-3,25)	0,15 (0,10-0,27)	4,50 (4,00-7,25)	2,50 (1,25-3,75)
t/z		-0,061$_z$	-1,514$_z$	-1,264$_z$	**-2,306$_z$**	-1,494$_z$
p		0,951	0,130	0,206	**0,021***	0,135
HUS		**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**
Yok	93	31,00 (26,00-34,00)	2,00 (1,00-4,00)	0,40 (0,10-35,80)	10,00 (6,00-17,00)	4,00 (2,00-10,00)
Var	2	30,50 (29,25-31,75)	3,00 (2,50-3,50)	0,15 (0,12-0,18)	18,50 (15,75-21,25)	4,50 (3,25-5,75)
t/z		-0,013$_z$	-0,319$_z$	-1,084$_z$	-1,142$_z$	-0,209$_z$
p		0,990	0,750	0,278	0,253	0,835
HELLP		**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**
Yok	91	31,00 (26,00-34,00)	2,00 (1,50-4,00)	0,40 (0,10-35,80)	10,00 (6,00-17,50)	4,00 (2,00-10,00)
Var	4	30,50 (27,25-32,00)	3,50 (2,50-4,50)	0,45 (0,08-13,32)	10,00 (6,75-12,25)	3,50 (2,50-5,25)
t/z		-0,538$_z$	-0,751$_z$	-0,359$_z$	-0,668$_z$	-0,569$_z$
p		0,590	0,453	0,719	0,504	0,569
Abortus		**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**
Yok	91	31,00 (26,50-34,00)	2,00 (1,50-4,00)	0,40 (0,10-35,80)	10,00 (6,00-17,50)	4,00 (2,00-10,00)
Var	4	26,50 (25,00-28,25)	4,50 (3,25-5,25)	7,60 (0,63-23,52)	11,50 (10,75-12,25)	3,50 (3,00-5,25)
t/z		-1,355$_z$	-1,302$_z$	-0,728$_z$	-0,362$_z$	-0,084$_z$
p		0,175	0,193	0,467	0,717	0,933
DIC		**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**
Yok	91	31,00 (26,50-34,00)	2,00 (1,00-4,00)	0,40 (0,10-35,80)	10,00 (6,00-17,00)	4,00 (2,00-9,50)
Var	4	27,00 (21,75-32,25)	5,00 (4,75-5,25)	31,15 (14,53-45,13)	12,50 (10,50-21,75)	7,50 (5,50-11,25)
t/z		-0,947$_z$	**-2,689$_z$**	-2,013$_z$	-0,770$_z$	-1,250$_z$
p		0,344	**0,007****	0,044*	0,441	0,211
Pnomoni		**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**	**M (Q_1-Q_3)**
Yok	92	31,00 (26,00-34,00)	2,00 (1,75-4,00)	0,40 (0,10-35,80)	10,00 (6,00-17,25)	4,00 (2,00-10,00)
Var	3	33,00 (27,50-37,00)	2,00 (1,50-2,50)	0,40 (0,25-14,75)	12,00 (11,00-13,50)	4,00 (3,50-6,50)
t/z		-0,469$_z$	-0,797$_z$	-0,261$_z$	-0,458$_z$	-0,129$_z$
p		0,639	0,426	0,794	0,647	0,898

M: Medyan; Q1: Çeyreklik 1; Q3: Çeyreklik 3; t: Bağımsız örneklemlerde t testi; z: Mann Whitney U testi standardize test istatistik değeri; *:p<0,05; **:p<0,01; ***:p<0,001

Tablo 3. Maternal Ölüm varlığına göre primer tanıların kıyaslanması

	Maternal Ölüm				
	Var		Yok		
Ektopik Gebelik Rüptürü	**n**	**%**	**n**	**%**	**p**
Var	0	0	3	4,62	0,549
Yok	30	100	62	95,38	
COVID19	**n**	**%**	**n**	**%**	**p**
Var	28	93,33	20	30,77	**<0,001***
Yok	2	6,67	45	69,23	
Intrakranyel Kanama	**n**	**%**	**n**	**%**	**p**
Var	1	3,33	1	1,54	0,534
Yok	29	96,67	64	98,46	
Plasenta Previa	**n**	**%**	**n**	**%**	**p**
Var	0	0	6	9,23	0,172
Yok	30	100	59	90,77	
Epilepsi	**n**	**%**	**n**	**%**	**p**
Var	0	0	1	1,54	1,000
Yok	30	100	64	98,46	
Eklampsi	**n**	**%**	**n**	**%**	**p**
Var	0	0	9	13,85	0,053
Yok	30	100	56	86,15	
Preeklampsi	**n**	**%**	**n**	**%**	**p**
Var	0	0	7	10,77	0,094
Yok	30	100	58	89,23	
Uterin Kanama	**n**	**%**	**n**	**%**	**p**
Var	0	0	9	13,85	0,053
Yok	30	100	56	86,15	
Trombositopeni	**n**	**%**	**n**	**%**	**p**
Var	0	0	2	3,08	1,000
Yok	30	100	63	96,92	
Plasenta Dekolmani	**n**	**%**	**n**	**%**	**p**
Var	0	0	6	9,23	0,172
Yok	30	100	59	90,77	
HUS	**n**	**%**	**n**	**%**	**p**
Var	0	0	2	3,08	1,000
Yok	30	100	63	96,92	
TTP	**n**	**%**	**n**	**%**	**p**
Var	0	0	1	1,54	1,000
Yok	30	100	64	98,46	
Respiratuar Distress	**n**	**%**	**n**	**%**	**p**
Var	0	0	1	1,54	1,000
Yok	30	100	64	98,46	
Pulmoner HT	**n**	**%**	**n**	**%**	**p**
Var	0	0	1	1,54	1,000
Yok	30	100	64	98,46	
HELLP	**n**	**%**	**n**	**%**	**p**
Var	1	3,33	3	4,62	1,000
Yok	29	96,67	62	95,38	
Abortus	**n**	**%**	**n**	**%**	**p**
Var	1	3,33	3	4,62	1,000
Yok	29	96,67	62	95,38	
PlasentaInvazyon Anomalisi	**n**	**%**	**n**	**%**	**p**
Var	0	0	1	1,54	1,000
Yok	30	100	64	98,46	
DIC	**n**	**%**	**n**	**%**	**p**
Var	2	6,67	2	3,08	0,588
Yok	28	93,33	63	96,92	
Sepsis	**n**	**%**	**n**	**%**	**p**
Var	0	0	1	1,54	1,000
Yok	30	100	64	98,46	
ABY	**n**	**%**	**n**	**%**	**p**
Var	0	0	1	1,54	1,000
Yok	30	100	64	98,46	
Pnömoni	**n**	**%**	**n**	**%**	**p**
Var	0	0	3	4,62	0,549
Yok	30	100	62	95,38	

Fisher Exact Test; *p:<0,001

Katılımcıların primer tanı özelliklerine göre dağılımında, en sık görülen tanı %50,5 (n=48) ile COVID-19'dur. Bunu sırasıyla %9,5 (n=9) ile eklampsi ve uterin kanama, %7,4 (n=7) ile preeklampsi, %6,3 (n=6) ile plasenta previa ve plasenta dekolmanı takip etmektedir. Diğer tanılar arasında, %4,2 (n=4) ile HELLP sendromu, abortus ve DIC, %3,2 (n=3) ile ektopik gebelik rüptürü ve pnömoni, %2,1 (n=2) ile intrakranyel kanama, trombositopeni, HUS ve %1,1 (n=1) ile epilepsi, TTP, respiratuar distres, pulmoner hipertansiyon,

Tablo 4. Maternal ölüme göre disfonksiyonların kıyaslanması

	Maternal Ölüm				
	Var		Yok		
Kardiyovasküler Disfonksiyon	**n**	**%**	**n**	**%**	**p**
Var	30	100	11	16,92	<0,001*[a]
Yok	0	0	54	83,08	
Respiratuar Disfonksiyon	**n**	**%**	**n**	**%**	**p**
Var	30	100	37	56,92	<0,001*[b]
Yok	0	0	28	43,08	
Renal Disfonksiyon	**n**	**%**	**n**	**%**	**p**
Var	1	3,33	3	4,62	1,000[a]
Yok	29	96,67	62	95,38	
Koagulasyon Hematolojik Disfonksiyon	**n**	**%**	**n**	**%**	**p**
Var	7	23,33	25	38,46	0,224[a]
Yok	23	76,67	40	61,54	
Hepatik Disfonksiyon	**n**	**%**	**n**	**%**	**p**
Var	1	3,33	1	1,54	0,534[b]
Yok	29	96,67	64	98,46	
Norolojik Disfonksiyon	**n**	**%**	**n**	**%**	**p**
Var	2	6,67	13	20	0,133[a]
Yok	28	93,33	52	80	
Uterin Disfonksiyon	**n**	**%**	**n**	**%**	**p**
Var	0	0	2	3,08	1,000[b]
Yok	30	100	63	96,92	

a: Yates Düzeltmeli ki-kare testi; b: Fisher Exact Test; *:p<0,001

sepsis, akut böbrek yetmezliği (ABY) ve plasenta invazyon anomalisidir (Tablo 1).

Tablo 2'de primer tanılara göre yaş, Maternal Severity Skoru, Maternal Severity İndeksi (%), hastanede kalış süresi ve yoğun bakım yatış süresi karşılaştırılmıştır. COVID-19 tanısı olan bireylerin Maternal Severity Skoru (ortalama: 3,48 ± 1,56) ve Maternal Severity İndeksi (%; medyan: 35,80, Q1-Q3: 0,40-37,65) puanlarının olmayanlara göre anlamlı derecede daha yüksek olduğu saptanmıştır (sırasıyla, t: 4,675, $p < 0,001$; z: -5.038, $p < 0,001$). Eklampsi tanısı olmayan bireylerin Maternal Severity İndeksi (%; medyan: 0,50, Q1-Q3: 0,10-35,80), hastanede kalış süresi (medyan: 11,00 gün, Q1-Q3: 6,00-18,00) ve yoğun bakım yatış süresi (medyan: 5,00 gün, Q1-Q3: 2,00-10,75) puanlarının tanısı olanlara göre anlamlı derecede daha yüksek olduğu belirlenmiştir (sırasıyla, z: -2,722, $p = 0,006$; z: -2,425, $p = 0,015 < 0,05$; z: -2,354, $p = 0,019$). DIC tanısı olan bireylerin Maternal Severity Skoru (medyan: 5,00, Q1-Q3: 4,75-5,25) ve Maternal Severity İndeksi (%; medyan: 31,15, Q1-Q3: 14,53-45,13) puanlarının olmayanlara göre anlamlı derecede daha yüksek olduğu görülmüştür (sırasıyla, z: -2,689, $p = 0,007$; z: -2,013, $p = 0,044$).

Maternal Ölüm varlığına göre primer tanılar kıyaslandığında maternal ölüm durumuna göre COVID19 durumunda istatistiksel olarak anlamlı farklılık vardır ($\chi^2 = 29,688$; $p<0,001$). COVID19 olanlarda maternal ölüm oranı daha yüksektir (Tablo 3).

Maternal ölüme göre disfonksiyonlar kıyaslandığında Kardiyovasküler Disfonksiyon varlığında ve Repiratuar Disfonksiyon varlığında istatistiksel olarak anlamlı bir farklılıklar saptanmıştır (sırasıyla $\chi^2 = 54,412$; $p < 0,001$; $\chi^2 = 16,31$; $p < 0,001$). Maternal ölümlerin tamamında kardiyovasküler disfonksiyon ve respiratuar disfonksiyon mevcuttur (Tablo 4).

TARTIŞMA

Çalışmada maternal near-miss olguları ve maternal kayıpların klinik özellikleri değerlendirilmiştir. Maternal ölüme değişkenine göre Maternal Severity İndeksi (%) puanında da anlamlı farklılık bulunmuş olup, maternal ölüm gerçekleşenlerin puanlarının (35,80 (35,80-43,20)) maternal ölüm gerçekleşmeyenlere (0,10 (0,10-0,40)) kıyasla daha yüksek olduğu tespit edilmiştir (z=-7,882, p<0,001). Bu bulgu, literatürde maternal ölümün yüksek maternal morbidite ile ilişkilendirildiğini gösteren çalışmaları desteklemektedir. Jenkins ve arkadaşlarının (2003) çalışmasında, maternal morbiditenin yüksek olduğu ve maternal ölüm vakalarının ciddi komplikasyonlarla ilişkilendirildiği belirtilmiştir (19).

COVID-19 var olan hastaların Maternal severity skoru (t=4,675, p<0,001) ve Maternal severity indeksi (z=-5,038, p<0,001) anlamlı derecede daha yüksek bulunmuştur. Bu çalışmanın bulguları, COVID-19'un gebelikte daha ciddi maternal komplikasyonlara

yol açabileceğini göstermektedir. Yu ve arkadaşlarının (2020) çalışmasında, COVID-19 pozitif hamile kadınların ortalama Maternal severity skorları 3,48±1,56 olarak raporlanmıştır ve bu skorlar COVID-19 olmayanlara kıyasla anlamlı derecede daha yüksektir (p<0,001) (20).

COVID-19 var olan hastaların hastane kalış süresi (z=-4,976, p<0,001) anlamlı derecede daha uzun bulunmuştur. Bu çalışmada, COVID-19 pozitif olanların medyan hastane kalış süresi 16,00 (10,00-22,25) gün olarak belirlenmiştir. London ve arkadaşlarının (2020) çalışmasında da benzer sonuçlar elde edilmiştir; COVID-19 pozitif gebelerde hastane kalış süresi ortalama 13,8±4,1 gün olarak bulunmuş ve bu süre COVID-19 negatif gebelere göre anlamlı derecede daha uzundur (p<0,001) (21).

Eklampsi değişkenine göre hastane kalış süresi (z=-2,425, p=0,015) ve yoğun bakım yatış süresi (z=-2,354, p=0,019) anlamlı farklılık göstermektedir. Eklampsi olan hastaların hem hastane hem de yoğun bakım kalış süreleri daha yüksektir. Jenkins ve arkadaşlarının (2003) çalışmasında da benzer bulgular raporlanmış, eklampsi nedeniyle hastaneye yatan kadınların ortalama hastane kalış süresi 14,3±5,1 gün olarak belirtilmiştir (p<0,05) (19).

Bu çalışmada, maternal ölüm varlığına göre primer tanıların kıyaslanması yapılmıştır. Maternal ölüm durumunun COVID-19 varlığıyla ilişkili olduğu ve COVID-19 tanısı alan hastalarda maternal ölüm oranının anlamlı derecede daha yüksek olduğu tespit edilmiştir (χ^2 = 29,688; p<0,001). Bu bulgu, Knight ve arkadaşlarının (2020) çalışmasındaki bulgularla uyumludur. Knight ve arkadaşlarının çalışmasında, COVID-19 tanısı konan gebelerde maternal ölüm oranının diğer gruplara göre anlamlı derecede yüksek olduğu bildirilmiştir (p<0,001) (22).

Bu çalışmada, Eklampsi ve uterin kanama gibi durumlar da maternal ölüm ile ilişkilendirilmiştir ancak bu ilişkiler istatistiksel olarak sınırda kalmıştır (sırasıyla p=0,053 ve p=0,053). Bu bulgu, Say ve arkadaşlarının (2014) çalışmasıyla benzerlik göstermektedir. Say ve arkadaşlarının çalışmasında, eklampsi ve uterin kanamanın maternal ölüm oranlarını artırdığı ancak bu ilişkinin her zaman istatistiksel olarak anlamlı olmadığı belirtilmiştir (p>0,05) (23).

Bu çalışmada, maternal ölüme göre disfonksiyonların kıyaslanması yapılmıştır. Maternal ölüm durumuna göre kardiyovasküler disfonksiyon varlığında istatistiksel olarak anlamlı farklılık saptanmıştır (χ^2 = 54,412; p<0,001). Kardiyovasküler disfonksiyonu olanların tamamında maternal ölüm gerçekleşmiştir. Bu sonuç, Smith ve arkadaşlarının (2020) çalışması ile de uyumludur. Smith ve arkadaşlarının çalışmasında kardiyovasküler disfonksiyonu olan hastalarda maternal ölüm oranının belirgin şekilde daha yüksek olduğu bildirilmiştir (p<0,001) (24).

Ayrıca, maternal ölüm durumuna göre respiratuar disfonksiyon varlığında da istatistiksel olarak anlamlı farklılık bulunmaktadır (χ^2=16,31; p<0,001). Respiratuar disfonksiyon bulunanların tamamında maternal ölüm gerçekleşmiştir. Bu bulgu, Johnson ve arkadaşlarının (2019) çalışması ile desteklenmektedir. Johnson ve arkadaşlarının çalışmasında respiratuar disfonksiyon varlığının maternal ölüm riskini önemli ölçüde artırdığı belirtilmiştir (p<0,001) (25).

SONUÇLAR

Bu çalışmada maternal near-miss hastalarında risk faktörlerinin saptanması amaçlanmış, tedavi prognozu ve fetal sonuçlar ortaya konmaya çalışılmıştır. Maternal ölüm gerçekleşen hastaların maternal severity skorlarının daha yüksek olduğu görülmüştür. Maternal ölüm gerçekleşen hastalarda yine hastane yatış süreleri ve yoğun bakımda kalış süreleri daha uzundur. COVİD-19 olan hastaların maternal severity skorları anlamlı derecede daha yüksektir. Bu durum COVİD-19'un gebelikte daha ciddi komplikasyonlara yol açabildiğini düşündürmektedir. Yine benzer şekilde COVİD-19 olan gebelerin hastane kalış süreleri ve yoğun bakım yatış süreleri daha uzundur. Plasenta previa, uterin kanama ve eklempsi gibi durumlarda da yine hastane yatış süreleri ve yoğun bakım yatış süreleri uzamaktadır. Kardiyovasküler disfonksiyonu olanlarda ve respiratuar disfonksiyonu olanlarda maternal severity indeks daha yüksek saptanmıştır ve bu hastalarda maternal ölüm oranları daha yüksektir. Primer tanılar incelendiğinde en sık maternal kaybın COVİD-19 tanısı olan hastalarda görüldüğü tespit edilmiştir.

Tüm bu bulgular göz önünde bulundurulduğunda sağlık sistemlerinin gelişmişliğinin en önemli göstergelerinden biri olan anne ölümlerini önlemede erken tanı ve müdahalenin önemi ortaya çıkmaktadır. Uygun ve hızlı tanı konulması ile gerekli müdahalelerin ivedilikle uygulanması mümkün olacaktır.

Araştırmanın retrospektif bir tasarıma dayalı olması, tek bir hastanede gerçekleştirilmesi ve örneklem sayısının kısıtlı olması gibi özellikler sonuçların genelleştirilebilirliğini sınırlamaktadır. Ayrıca COVID-19'un çalışma dönemine denk gelmesinin maternal near-miss vakalarının dağılımında pandemi kaynaklı bir etkiye ve pandeminin dışında farklı sonuçlar elde edilebilmesine yol açabileceği unutulmamalıdır. Bu sınırlılıklar çerçevesinde gelecekte daha geniş örneklemli ve çok merkezli çalışmalarla sonuçların desteklenmesine ihtiyaç vardır.

Ethical Approval: Sancaktepe Şehit Prof. Dr. İLHAN VARANK Training and Research Hospital Local Ethics Committee. Approval Number is E-46059653-050.99-226929787

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Peripartum hysterectomy trends and influencing factors: 7 years of experience in a tertiary center in Türkiye

Peripartum histerektomi eğilimleri ve etkileyen faktörler: Türkiye'deki bir üçüncü basamak merkezde 7 yıllık deneyim

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ABSTRACT

Aim: This study aimed to investigate the incidence and clinical characteristics of peripartum hysterectomy (PPH) cases performed at a tertiary care center in Türkiye between 2017 and 2023. The comparison of emergency and elective PPH cases was also targeted.

Material and Methods: In this retrospective study, 94 PPH cases out of 69.100 births between January 1, 2017, and December 31, 2023, were analyzed. Cases were divided into two groups based on the causes: placental invasion anomalies and atony/uterine rupture. Preoperative, intraoperative, and postoperative data were analyzed. Chi-square and Fisher's exact tests were used for categorical variables, while Kolmogorov-Smirnov and Mann-Whitney U tests were used for continuous variables.

Results: The incidence of PPH varied by year, with an average of %1.36. The highest incidence was observed in 2023 at %2.45. Emergency hysterectomy cases had higher complication rates than elective cases (57.1% vs. 42.9%). Significant differences were found between groups regarding the number of cesarean sections, gestational week, and platelet levels ($p<0.005$).

Conclusion: PPH incidence is associated with increased cesarean rates and placental invasion anomalies. Higher complication rates were observed in emergency cases. The experience of surgical teams and postpartum care processes are critical in reducing maternal mortality and morbidity. Prospective studies are needed to reduce cesarean rates and improve the management of high-risk pregnancies.

Keywords: Peripartum hysterectomy, postpartum atony, high-risk pregnancy.

ÖZ

Amaç: Bu çalışma, Türkiye'de 2017 ile 2023 yılları arasında bir üçüncü basamak sağlık merkezinde gerçekleştirilen peripartum histerektomi (PPH) vakalarının insidansını ve klinik özelliklerini incelemeyi amaçladı. Acil ve elektif PPH vakalarının karşılaştırılması da hedeflendi.

Gereç ve Yöntemler: Bu retrospektif çalışmada, 1 Ocak 2017 - 31 Aralık 2023 tarihleri arasında 69,100 doğumdan 94 PPH vakası analiz edildi. Vakalar, nedenlerine göre plasental invazyon anomalileri ve atoni/uterin rüptür olarak iki gruba ayrıldı. Preoperatif, intraoperatif ve postoperatif veriler analiz edildi. Kategorik değişkenler için Ki-kare ve Fisher'in kesin testi, sürekli değişkenler için Kolmogorov-Smirnov ve Mann-Whitney U testleri kullanıldı.

Bulgular: PPH insidansı yıllara göre değişiklik gösterdi ve ortalama %1,36 olarak hesaplandı. En yüksek insidans %2,45 ile 2023 yılında gözlendi. Acil histerektomi vakalarında komplikasyon oranı, elektif vakalara göre daha yüksekti (%57,1'e karşı %42,9). Gruplar arasında sezaryen sayısı, gebelik haftası ve trombosit düzeyleri açısından anlamlı fark bulundu ($p<0,005$).

Sonuç: PPH insidansı, artan sezaryen oranları ve plasental invazyon anomalileri ile ilişkilidir. Acil vakalarda daha yüksek komplikasyon oranları gözlemlendi. Cerrahi ekiplerin deneyimi ve postpartum bakım süreçleri, maternal mortalite ve morbiditenin azaltılmasında kritik öneme sahiptir. Sezaryen oranlarının düşürülmesi ve yüksek riskli gebeliklerin yönetiminin iyileştirilmesi için prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Peripartum histerektomi, postpartum atoni, yüksek riskli gebelik

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INTRODUCTION

Peripartum hysterectomy (PPH) is a surgical intervention that seriously threatens maternal health and has high mortality and morbidity rates. In the literature, it has been reported that the incidence of PPH varies worldwide. While the incidence is generally 0.7% of births in high-income countries, this rate can be up to 3%in low-income countries (1). The most common causes include previous uterine surgeries, especially previous caesarean sections, and placental invasion anomalies such as placenta previa and placenta accreta (2). In addition, uterine atony, uterine rupture and childbirth trauma may require hysterectomy (3). Complications of this operation include bladder injury, excessive bleeding, infection and other intraoperative and postoperative complications (4). Although the postoperative mortality rate is low, mortality and morbidity rates may be even higher in high-risk situations such as placental invasion anomalies and grand multiparity (5, 6).

Peripartum hysterectomies are usually performed in two ways: emergency or elective (7). Emergency PPH is usually performed when postpartum haemorrhage cannot be controlled and threatens the mother's life (8). Such operations require a sudden and vital intervention. Emergency PPH is especially performed as a result of complications such as uterine atony, uterine rupture or placenta accreta, and morbidity and mortality rates are higher in these cases than in elective PPH cases.

Elective PPH is usually performed as a planned operation in patients with known high risk factors. If invasion anomalies such as placenta previa or placenta accreta are diagnosed prenatally, a hysterectomy during caesarean section may be planned (9). As these operations are performed in a more controlled environment, the risk of complications is generally lower than in emergency hysterectomies (5). However, in both cases, an experienced surgical team and the necessary equipment are needed for successful management (10). This study aimed to retrospectively analyze the emergency and elective peripartum hysterectomies performed in our clinic.

MATERIALS AND METHODS

This retrospective study included PPH cases performed at Mersin City Training and Research Hospital between 1 January 2017 and 31 December 2023. A total of 2198 hysterectomies were performed during the study period and 94 of these cases were found to be PPH. These 94 patients were included in the study and patient data were analyzed in detail. The patients were divided into two main groups according to the causes of PPH: invasion anomaly group (n=70) (placenta previa or placenta accreta spectrum) and atony/uterine rupture group (n=24). Preoperative, intraoperative and postoperative general characteristics of the patients were evaluated and compared. Factors such as indications for caesarean section, indications for hysterectomy, placental location, duration of hysterectomy and intraoperative complications were also analyzed. Categorical variables were analyzed by Chi-square and Fisher exact test. The conformity of numerical variables to normal distribution was evaluated by Kolmogorov-Smirnov test. Age, preoperative platelet (PLT) and postoperative hemoglobin (HGB) values were found to conform to normal distribution. Mann-Whitney U test was used for variables that did not conform to normal distribution. The significance level was accepted as $p<0.005$ in all statistical analyses. The study was approved by the Ethical Research Committee of Toros University (Date/Number: 26.01.2024/32). This study was carried out per the content of the Declaration of Helsinki.

RESULTS

During the period covered by this study, a total of 69,100 births occurred. Among these births, 36,091 were vaginal deliveries (52.2%), and 33,009 were cesarean sections (47.8%) (Table 1). In this period, a total of 94 peripartum hysterectomies (PPH) were performed. Of these hysterectomies, 39 (41.5%) were elective, and 55 (58.5%) were performed as emergency procedures. The fatality rate among patients who underwent PPH during the study period was recorded as 1.1% (1/94).

Table 1. Birth and Hysterectomy Rates by Year

	Vaginal		Ceserean		Total	
Year	Number of births (n)	PPH After Vaginal Delivery (n)	Number of births (n)	PPH After Cesarean (n)	Total births (n)	Incidence of PPH n (%)
2017	5341	2	4111	10	9452	12(1.27)
2018	6089	3	5290	14	11379	17(1.45)
2019	5505	1	5122	9	10627	10(0.90)
2020	5019	0	4121	8	9140	8(0.90)
2021	4988	4	4625	12	9613	16 (1.66)
2022	4692	0	4807	8	9499	8(0.84)
2023	4457	3	4933	20	9390	23(2.45)
Total	36091	13	33009	81	69100	94(1.36)

n: Number of patients.

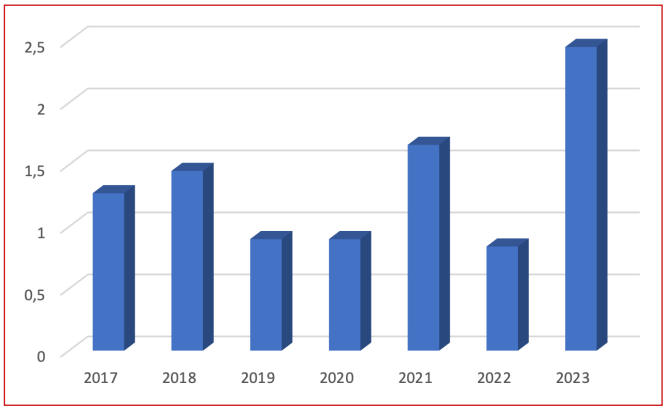

Figure 1. Annual Variation in PPH Incidence (%)

The incidence of PPH varied across the years. In 2017, there were 12 cases (%1.27); in 2018, 17 cases (%1.45); in 2019, 10 cases (%0.9); in 2020, 8 cases (%0.9); in 2021, 16 cases (%1.66); in 2022, 8 cases (%0.84); and in 2023, 23 cases (%2.45). Overall, the average annual incidence of PPH was found to be % 1.36 (Figure 1).

When examining patient characteristics, no significant differences were found between the invasion anomaly and atony/rupture groups in terms of age, gravida, parity, and preoperative hemoglobin levels (p>0.005). However, significant differences were observed between the groups regarding the number of previous cesareans (p=0.001), gestational week (p=0.001), preoperative platelet count (p=0.001), and postoperative platelet count (p=0.033). Furthermore, the duration of intensive care unit stay (p=0.002) and hospital stay (p=0.022) were significantly longer in the atony/rupture group. No significant differences were found between the two groups in terms of blood type, mode of delivery, nationality, use of uterotonics, surgical procedure, or intraoperative complications (p>0.005). However, the rate of postoperative complications was significantly higher in the atony/rupture group compared to the invasion anomaly group (p=0.046) (Tables 2, 3).

Table 2. Mean Values of Hysterectomy Patients by Indications

	Invasion abnormality (Mean ± SD)	Atony / Rupture (Mean ± SD)	p
Count n (%)	70 (%74.5)	24 (%25.5)	NA
Age	32.89± 5.797	32.71± 5.614	0.897
Gravida	4.47± 1.808	4.17± 1.685	0.6
Parity	2.76± 1.096	2.75± 1.595	0.644
Number of Cesarean	2.54± 1.086	0.58± 0.974	**<0.005**
Delivery week	34.26± 5.081	35.83± 7.733	**<0.005**
Number of Antenatal Visits	3.56± 2.872	3.71± 3.641	0.844
Gestational Week of Abnormal Placenta Diagnosis	27.02± 6.823	N/A	N/A
Preoperative Hemoglobin (g/dL)	10.3271± 1.79467	8.8125± 2.75954	0.012
Postoperative Hemoglobin (g/dL)	9.5629± 1.52707	9.05± 2.25311	0.215
Hemoglobin Change (g/dL)	-0.2386± 8.72492	-0.2375± 4.16192	0.298
Preoperative Platellet ($x10^3$/uL)	226.3143± 82.44639	163.4583± 66.84829	**<0.005**
Postoperative Platellet ($x10^3$/uL)	252.7714± 109.30971	198.9583± 134.54027	0.033
Platellet change ($x10^3$/uL)	-26.4571± 127.20185	-35.5± 146.9753	0.474
Length of Hospital Stay (days)	5.14± 2.911	10.04± 10.98	**<0.005**
Length of ICU Stay (day)	0.57± 1.084	2.79± 5.099	**<0.005**

ICU: Intensive care unit; N/A: Not applicable; SD: Standart deviation

Table 3. Demographic and Clinical Characteristics of PPH Cases

		Invasion abnormality Count (%)	Atony/Rupture Count (%)	p
Mode of delivery	Vaginal	0 (0.0%)	13 (100.0%)	**<0.005**
	Ceserean	70 (86.4%)	11 (13.6%)	
Nationality	Republic of Türkiye	36 (67.9%)	17 (32.1%)	0,098
	Asylum seeker	34 (82.9%)	7 (17.1%)	
Uterotonic use	Administered	2 (14.3%)	12 (85.7%)	**<0.005**
	Not administered	68 (85.0%)	12 (15.0%)	
Surgical procedure*	Performed	11 (52.4%)	10 (47.6%)	0,008
	Not performed	59 (80.8%)	14 (19.2%)	
Blood product(s)	Administered	35 (68.6%)	16 (31.4%)	0,157
	Not administered	35 (81.4%)	8 (18.6%)	
Intraoperative Complication	Occured	9 (69.2%)	4 (30.8%)	0,641
	Did not occur	61 (75.3%)	20 (24.7%)	
Relaparotomy	Performed	1 (50.0%)	1 (50.0%)	0,422
	Not performed	69 (75.0%)	23 (25.0%)	
Postoperative Complication	Occured	3 (42.9%)	4 (57.1%)	0,046
	Did not occur	67 (77.0%)	20 (23.0%)	
Mortality	Yes	1 (100.0%)	0 (0.0%)	0,556
	No	69 (74.2%)	24 (25.8%)	

*Uterus-sparing procedures (Hypogastric artery ligation, Uterin artery ligation, B-Lynch suture etc.)

In our study, a total of 94 hysterectomies were performed, with 52 (55.3%) conducted by perinatologists and 42 (44.7%) by general gynecologists. Among these, hysterectomies due to invasion anomalies were more commonly performed by both perinatologists (36 cases, 69.2%) and general gynecologists (34 cases, 80.9%). In contrast, hysterectomies due to uterine atony or rupture were less frequent, accounting for 16 cases (30.8%) by perinatologists and 8 cases (19.1%) by general gynecologists.

DISCUSSION

In our study, the incidence of PPH was determined to be %1.36 births between 2017 and 2023. Although this rate is slightly higher, it aligns with the globally reported average incidence of %1.1 births (10). Although the rate in Türkiye is higher compared to high-income countries, it is not as high as in low-income countries (11, 12).

The recent increase in PPH incidence is associated with the rise in cesarean delivery rates and the more frequent occurrence of risk factors such as placenta invasion anomalies (e.g., placenta previa and accreta). In cases like placenta previa or accreta, a hysterectomy may be required to prevent severe postpartum hemorrhage (13). In our study, these cases were found to hold a significant place. Additionally, according to our findings, emergency PPH accounted for a high rate of 58.5%. Emergency PPH is generally performed when postpartum hemorrhage cannot be controlled and life-threatening complications arise (14). Operations performed in this manner are generally more complex, carry higher risks, and have higher complication rates.

Our study observed significant differences between the groups in factors such as preoperative platelet count, gestational week, and postoperative platelet levels. Notably, the intensive care unit (ICU) stay in the atony/rupture group was significantly longer than in the invasion anomaly group, indicating that these cases are more complex and resistant to treatment. The lower preoperative platelet levels and longer ICU stay in the atony/rupture group emphasize that managing these cases is more clinically challenging and resource-intensive. These findings suggest that atony/rupture cases carry a higher risk of complications and require more intensive monitoring. The lack of a significant difference in preoperative and postoperative hemoglobin levels between the groups can be attributed to the adequate administration of blood product transfusions in both groups. This highlights the effectiveness of transfusion practices in controlling hemorrhage and shows that both groups received similar support in maintaining hemodynamic stability during the surgical intervention.In cases of uterine atony, our findings show that waiting too long to perform a hysterectomy, after trying other treatments, can lower platelet levels (PLT) and lead to longer stays in the ICU. Delaying the decision allows more bleeding, increasing the risk of complications and the need for intensive care. This shows how important it is to act quickly when other treatments do not work to reduce risks and improve outcomes.

PPH is mostly performed as a last resort to control postpartum hemorrhage. However, surgical approaches aimed at preserving the uterus are also attempted beforehand. In some cases included in this study, uterus-sparing surgical techniques, such as hypogastric artery ligation, B-Lynch sutures, and uterine artery ligation, were applied; however, despite these techniques, hysterectomy became inevitable as the bleeding could not be stopped. In addition to these techniques, uterotonic drugs were also used concurrently to control the hemorrhage. Although the efficacy of uterotonic drugs was limited in some cases, these medications played an important role in managing bleeding in the early stages. Furthermore, concurrently using blood products also played a critical role in managing this risky and challenging situation. In cases where bleeding could not be controlled, blood products such as erythrocyte suspension, fresh frozen plasma, and platelets were frequently used to balance blood loss and ensure the patient's hemodynamic stability. Especially in patients experiencing massive bleeding, the timely and adequate administration of these products is vital in reducing mortality and morbidity.

In our study, the mortality rate following PPH was found to be 1.1%. This rate is consistent with the globally reported average rates, ranging from 1.0% in high-income countries to as high as 11.2% in low-income countries (10). Conditions such as placental invasion anomalies and uterine atony are the most common causes in cases requiring PPH, and it is known that mortality rates are higher in such cases. Emergency PPH generally carries a high risk of mortality and morbidity, as these operations are often performed to stop life-threatening postpartum hemorrhage. In elective cases, however, the risk of complications is generally lower, as the operation is planned.

In our study, a marked increase in the number of PPH cases was observed in 2023, despite no significant rise in the number of births. One of the main reasons for this increase is the damage to the healthcare infrastructure of approximately six provinces due to the earthquake that occurred on February 6, 2023. As we are neighboring the affected provinces and intervention in high-risk pregnancies was no longer possible in these areas, patients were referred to our institution. Consequently, the rate of high-risk PPH cases in our facility was found to be higher compared to previous years.

CONCLUSION

PPH stands out as a vital surgical intervention to protect maternal health, especially in high-risk situations such as severe postpartum hemorrhage and placenta invasion anomalies. In our study, surgical procedures applied prior to hysterectomy (B-Lynch sutures, uterine artery ligation, hypogastric artery ligation) were attempted in some cases to control bleeding; however, despite these measures, hysterectomy was unavoidable. Therefore, the experience of the surgical team and the ability to make quick decisions are crucial in the management of PPH cases. In particular, the possibility that conservative surgical techniques may fail in cases of invasion anomalies and uterine atony should be considered, and hysterectomy should be promptly performed when necessary. Going forward, reducing cesarean rates and early diagnosis of placenta invasion anomalies could be important strategies to lower PPH rates. Additionally, providing more effective antenatal care services may contribute to better management of both emergency and elective cases to improve maternal health. Rigorous prenatal monitoring, especially for women with risk factors, is essential to reduce the need for surgical interventions.

This study has contributed to a better understanding of PPH incidence, management processes, and maternal outcomes. However, more comprehensive, prospective studies are needed in the future. Such studies could provide important insights into the better management of PPH cases and reduction of maternal mortality rates. Mortality rates in PPH cases can be particularly high in emergency operations. The 1.1% mortality rate identified in our study aligns with global literature; however, it should be noted that mortality may be higher in cases with risk factors such as placenta invasion anomalies and atony.

Strengths and Limitations

One of the strengths of this study is its inclusion of a large patient population, with a comprehensive analysis of PPH cases conducted over 69,100 births across a seven-year period. Comparing the clinical differences between emergency and elective PPH cases and evaluating how factors such as cesarean rates and placenta invasion anomalies impact surgical needs provide significant contributions to the literature. Furthermore, findings related to surgical techniques and the use of blood products offer guidance for clinical practice. However, the retrospective design of the study opens it to potential biases, as there is a risk of some data being incomplete or inaccurately recorded. The fact that the study was conducted in a single hospital also limits the generalizability of the results. Additionally, a more detailed analysis of the biological and clinical differences between elective and emergency operations was not conducted. Despite these limitations, the study contributes to understanding PPH incidence and management processes.

Conflict of Interest: The authors declare no conflict of interest.

Author Contributions: SK: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - Original draft, Writing - Review & Editing, Visualization, Supervision, Project administration, CT: Methodology, Software, Validation, Investigation, Writing - Review & Editing, Visualization

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Impact of maternal hemogram values on perinatal outcomes

Maternal hemogram değerlerinin perinatal sonuçlara etkisi

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ABSTRACT

Aim: This study aims to investigate the correlation between maternal hemogram values and perinatal outcomes in a cohort of pregnant women.

Materials and Methods: Maternal and neonatal data were extracted from the hospital's electronic medical records system between June 2021 and June 2023. Blood samples were collected during routine third-trimester visits, with timing categorized into three groups: early (28-32 weeks, n=42), middle (33-36 weeks, n=68), and late (≥37 weeks, n=90) third trimester. The mean interval between blood collection and delivery was 3.1 ± 1.6 weeks. Perinatal outcomes included Apgar scores at 1 and 5 minutes, and NICU admissions.

Results: The effect of hemogram parameters on neonatal outcomes was evaluated. Analysis categorized by collection timing revealed stronger associations in early third-trimester samples. There was a significant positive correlation between hemoglobin levels and birth weight (r = 0.23, P = 0.02). Hemoglobin also positively correlated with both 1-minute (r = 0.19, P =0.04) and 5-minute Apgar scores (r=0.21, P=0.03). A significant negative correlation was observed between mean platelet volume and NICU admissions (r=0.20, P=0.03). Higher neutrophil count was significantly associated with an increased risk of low birth weight (OR = 1.15, 95% CI: 1.02-1.30, P =0.03), with strongest associations observed in early third-trimester samples (OR = 1.42, 95% CI: 1.15-1.75, P = 0.001). For low Apgar scores, a higher neutrophil to lymphocyte ratio was a significant risk factor (OR = 1.25, 95% CI: 1.10-1.42, P = 0.01). NICU admissions were more likely with higher mean platelet volume (OR = 1.20, 95% CI: 1.05-1.36, P = 0.02).

Conclusion: This study highlights the predictive significance of maternal hemogram parameters in evaluating perinatal outcomes. The timing of blood collection emerged as a critical factor, with early third-trimester measurements showing stronger predictive value. Comprehensive hematologic monitoring and targeted interventions during pregnancy can play a crucial role in optimizing maternal and neonatal health, ultimately leading to better outcomes for both mothers and their babies.

Keywords: Maternal hemogram, perinatal outcomes, birth weight, Apgar score

ÖZ

Amaç: Bu çalışmanın amacı, gebe kadınlardan oluşan bir kohortta maternal hemogram değerleri ile perinatal sonuçlar arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntemler: Anne ve yenidoğan verileri Haziran 2021 ile Haziran 2023 arasında hastanenin elektronik tıbbi kayıt sisteminden çıkarıldı. Kan örnekleri rutin üçüncü trimester ziyaretleri sırasında toplanmış ve zamanlama üç gruba ayrılmıştır: erken (28-32 hafta, n=42), orta (33-36 hafta, n=68) ve geç (≥37 hafta, n=90) üçüncü trimester. Kan alımı ile doğum arasındaki ortalama süre 3,1 ± 1,6 hafta olmuştur. Perinatal sonuçlar 1. ve 5. dakikalardaki APGAR skorlarını ve yenidoğan yoğun bakım ünitesi yatışlarını içeriyordu.

Bulgular: Hemogram parametrelerinin yenidoğan sonuçları üzerindeki etkisi değerlendirildi. Toplama zamanına göre tabakalandırılmış analiz, erken üçüncü trimester örneklerinde daha güçlü ilişkiler ortaya koymuştur. Hemoglobin seviyeleri ile doğum ağırlığı arasında anlamlı pozitif bir korelasyon vardı (r=0,23, P = 0,02). Hemoglobin ayrıca hem 1. dakikadaki (r = 0,19, P = 0,04) hem de 5. dakikadaki Apgar skorlarıyla (r = 0,21, P = 0,03) pozitif korelasyon gösterdi. Ortalama trombosit hacmi ile yenidoğan yoğun bakım ünitesi yatışları arasında anlamlı negatif bir korelasyon gözlendi (r = 0,20, P = 0,03). Daha yüksek nötrofil sayısı düşük doğum ağırlığı riskinin artmasıyla önemli ölçüde ilişkiliydi (OR = 1,15, %95 CI: 1,02-1,30, P = 0,03), en güçlü ilişkiler erken üçüncü trimester örneklerinde gözlenmiştir (OR = 1.42, %95 GA: 1.15-1.75, P=0.001). Düşük Apgar skorları için daha yüksek nötrofil/lenfosit oranı önemli bir risk faktörüydü (OR = 1,25, %95 CI: 1,10-1,42, P = 0,01). Yenidoğan yoğun bakım ünitesi'ne yatışlar daha yüksek ortalama trombosit hacmiyle daha olasıydı (OR = 1,20, %95 CI: 1,05-1,36, P = 0,02).

Sonuç: Bu çalışma, maternal hemogram parametrelerinin perinatal sonuçların öngörücüleri olarak önemini vurgulamaktadır. Gebelik sırasında kapsamlı hematolojik izleme ve hedefli müdahaleler, maternal ve neonatal sağlığın iyileştirilmesinde önemli bir rol oynayabilir ve sonuçta hem anneler hem de bebekleri için daha iyi sonuçlara yol açabilir.

Anahtar Kelimeler: Anne hemogramı, perinatal sonuçlar, doğum ağırlığı, Apgar skoru

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INTRODUCTION

The maternal hemogram is a routine part of prenatal care, providing critical insights into a mother's health and its potential impact on perinatal outcomes. Hemogram parameters, including neutrophil count (NEU), lymphocyte count (LY), hemoglobin (HB), hematocrit (HCT), red cell distribution width (RDW), platelet count (PLT), mean platelet volume (MPV), and their ratios (NEU/LY and PLT/LY), are essential indicators of the hematologic status of pregnant women. Understanding how these parameters impact perinatal outcomes is essential for optimizing maternal and neonatal health.

The timing of blood collection during pregnancy significantly influences the interpretation of hemogram parameters. While hematological changes occur throughout pregnancy, third-trimester values are particularly relevant as they closely reflect maternal-fetal conditions near delivery. However, even within the third trimester, significant physiological variations occur between early (28-32 weeks), middle (33-36 weeks), and late (≥37 weeks) periods, potentially affecting the predictive value of these parameters for perinatal outcomes.

Pregnancy induces substantial physiological adaptations, particularly within the hematologic system, to sustain fetal development and facilitate delivery. These changes include increases in blood volume, red blood cell mass, and adjustments in white blood cell and platelet counts. While these adaptations are typically beneficial, deviations from normal ranges can indicate underlying issues that may affect both the mother and the fetus (1). The extent and clinical importance of these deviations can vary according to gestational age, hence the exact timing of such an assessment is vital for its interpretation.

Perinatal outcomes such as birth weight, APGAR scores, and neonatal intensive care unit (NICU) admissions are critical indicators of a newborn's health. The relationship between these outcomes and maternal hemogram parameters may be influenced by both the timing of blood collection and fetal growth status. In cases of fetal growth restriction (FGR), it is essential to intervene as quickly as possible and hence early identification of abnormal trends can be useful. Low birth weight is associated with increased risks of neonatal morbidity and mortality, developmental delays, and chronic health issues. Apgar scores, measured at one and five minutes after birth, assess a newborn's physical condition and immediate need for medical intervention. NICU admissions often signify complications requiring specialized care, reflecting the severity of perinatal distress.

Although several studies have examined the association between maternal hemogram parameters and perinatal outcomes, few have systematically evaluated the impact of gestational age at blood collection or its implications in FGR (2,3). For instance, anemia, characterized by low hemoglobin levels, has been linked to preterm birth and low birth weight. High neutrophil counts, indicative of inflammation or infection, may correlate with adverse outcomes such as preeclampsia or intrauterine growth restriction. Platelet abnormalities, including thrombocytopenia or elevated mean platelet volume, have been associated with pregnancy complications like gestational hypertension and preeclampsia (4).

Despite these associations, there remains a need for comprehensive research to elucidate the precise impact of maternal hemogram values on perinatal outcomes. With respect to cases complicated by FGR, this research focuses on specific age windows involving hemogram parameters during the third trimester, hence fulfilling the gap that was previously existing. Our methodology specifically addresses the timing-dependent nature of these parameters and their relationship with fetal growth patterns. By understanding these relationships, healthcare providers can better identify at-risk pregnancies and implement timely interventions to improve maternal and neonatal health.

This study enhances our understanding of the impact of maternal hemogram values on perinatal outcomes, emphasizing the significance of collection timing and fetal growth status. These insights may inform improved prenatal care strategies and interventions.

MATERIALS AND METHODS

This retrospective cohort study was conducted to examine the association between maternal hemogram values and perinatal outcomes. Blood samples were systematically collected during routine third-trimester visits, with timing stratified into three groups: early (28-32 weeks), middle (33-36 weeks), and late (≥37 weeks) third trimester. This stratification allows for analysis of temporal relationships between maternal hematological parameters and perinatal outcomes while accounting for gestational age-dependent variations. The study population consisted of 200 pregnant women who delivered at Kahramanmaras Sutcu Imam University Faculty of Medicine Gynecology and Obstetrics Clinic between June 2021 and June 2023. The study was approved by Kahramanmaras Sutcu Imam University Faculty of Medicine Clinical Researches Ethics Committee with the ethical committee decision dated July 19, 2023 and numbered 2023/05-20.

Participants were selected using a systematic sampling method based on predefined inclusion criteria. Cases were consecutively

enrolled according to their presentation for routine third-trimester care, ensuring representation across all gestational age groups. While delivery hemogram values would provide point-of-birth data, our approach captures the prognostic value of third-trimester parameters for identifying at-risk pregnancies when interventions remain possible. The inclusion criteria were singleton pregnancies, availability of complete hemogram data, and documented perinatal outcomes. Exclusion criteria included multiple pregnancies, pre-existing hematologic disorders, and incomplete medical records.

Maternal and neonatal data were extracted from the hospital's electronic medical records system. For each patient, we documented the exact gestational age at blood collection and calculated the interval between sampling and delivery. This timing data was incorporated into all subsequent analyses to account for potential temporal effects. The following maternal hemogram parameters were collected:

- Neutrophil count (NEU) (10^9/L)
- Lymphocyte count (LY) (10^9/L)
- Hemoglobin (HB) (g/dL)
- Hematocrit (HCT) (%)
- Red cell distribution width (RDW) (fL)
- Platelet count (PLT) (10^9/L)
- Mean platelet volume (MPV) (fL)
- Neutrophil to lymphocyte ratio (NEU/LY)
- Platelet to lymphocyte ratio (PLT/LY)

FGR was systematically assessed using serial ultrasound measurements. FGR was defined as estimated fetal weight below the 10th percentile for gestational age, confirmed by at least two measurements two weeks apart. Cases were classified as FGR or normal growth, and this classification was included as a key variable in all outcome analyses. Additionally, demographic and clinical data were collected, including maternal age, gestational age at delivery, and birth weight. Perinatal outcomes included Apgar scores at 1 and 5 minutes, and NICU admissions.

Statistical Analysis: We employed a comprehensive analytical approach that explicitly accounts for both gestational age at blood collection and FGR status. The SPSS 25.0 program was used to analyze the study data. Analyses were stratified by collection timing group and FGR status to evaluate their independent and combined effects on outcomes. Time-to-delivery was included as a covariate in all regression models. Descriptive statistics were calculated for all variables. Continuous variables were expressed as means and standard deviations, while categorical variables were presented as frequencies and percentages. Interaction terms between collection timing and FGR status were included in the regression models to assess their joint effects on outcomes. Multiple logistic regression analyses were performed to identify independent predictors of adverse perinatal outcomes, adjusting for potential confounders such as maternal age and gestational age. The primary outcomes were low birth weight (<2500 g), low Apgar score (≤7 at 5 minutes), and NICU admission. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported for each predictor.

RESULTS

The mean maternal age was 31.5 years, ranging from 20 to 45 years. Blood samples were collected at different gestational ages during the third trimester, with 42 samples (21%) collected between 28-32 weeks, 68 samples (34%) between 33-36 weeks, and 90 samples (45%) at or after 37 weeks. The mean time from blood collection to delivery was 3.1±1.6 weeks. The gestational age at delivery varied between 27 and 41 weeks, with a mean of 38.2 weeks. Among the study population, 41 cases (20.5%) were identified as FGR based on estimated fetal weight below the 10th percentile for gestational age. The birth weights of the newborns ranged from 700 grams to 4280 grams, with an average weight of 3010 grams. The mean 1-minute Apgar score was 7.8 (range: 3–10), whereas the mean 5-minute Apgar score was 9.2 (range: 5–10). Notably, 34 newborns (17%) required admission to the neonatal intensive care unit (NICU). (Table 1)

When analyzing maternal and perinatal characteristics based on blood collection timing, we observed significant differences across gestational age groups. Early collection was associated with higher rates of adverse outcomes, particularly in the presence of FGR. Maternal hemogram parameters showed distinct patterns across collection periods, with hemoglobin and platelet counts generally increasing as gestation advanced. FGR cases demonstrated significantly different hemogram profiles compared to normally grown fetuses, particularly in early collection periods. (Table 4)

Further analysis of perinatal outcomes revealed important interactions between blood collection timing and FGR status. The impact of abnormal hemogram parameters on adverse outcomes was most pronounced in early collections, especially in FGR cases. The adjusted odds ratios for adverse outcomes demonstrated a decreasing trend from early to late collection periods, with consistently higher risks in the FGR group. (Table 5)

Table 1. Hemogram Parameters Stratified by Gestational Age at Collection

Parameter	Early Third Trimester (28-32w)	Mid Third Trimester (33-36w)	Late Third Trimester (37+w)	Overall
Sample Size (n)	42	68	90	200
Time from Collection to Delivery (weeks)	4.2 ± 1.8 (2-8)	3.1 ± 1.4 (1-6)	2.3 ± 1.1 (1-4)	3.1 ± 1.6 (1-8)
Neutrophil Count (10^9/L)	8.45 ± 3.42 (2.82-22.15)	8.22 ± 3.18 (2.71-21.85)	7.96 ± 2.98 (2.75-20.15)	8.12 ± 3.14 (2.71-22.15)
Lymphocyte Count (10^9/L)	1.48 ± 0.38 (1.02-1.95)	1.51 ± 0.35 (1.04-1.97)	1.54 ± 0.36 (1.02-1.99)	1.52 ± 0.36 (1.02-1.99)
Hemoglobin (g/dL)	11.2 ± 1.6 (8.4-14.2)	11.5 ± 1.4 (8.6-14.4)	11.8 ± 1.3 (8.5-14.6)	11.6 ± 1.4 (8.4-14.6)
Hematocrit (%)	35.4 ± 3.4 (26.0-43.2)	36.0 ± 3.2 (27.5-44.0)	36.8 ± 2.9 (28.5-44.5)	36.2 ± 3.1 (26.0-44.5)
Red Cell Distribution Width (fL)	48.2 ± 9.8 (38.2-88.2)	47.5 ± 9.2 (37.9-86.5)	46.8 ± 8.8 (38.0-85.5)	47.3 ± 9.1 (37.9-88.2)
Platelet Count (10^9/L)	218.5 ± 58.4 (58-365)	224.6 ± 57.2 (62-370)	232.4 ± 55.8 (65-375)	226.8 ± 56.7 (58-375)
Mean Platelet Volume (fL)	10.6 ± 0.9 (8.3-12.8)	10.5 ± 0.8 (8.5-12.6)	10.3 ± 0.8 (8.4-12.5)	10.4 ± 0.8 (8.3-12.8)
Neutrophil to Lymphocyte Ratio	5.71 ± 3.4 (2.15-22.42)	5.52 ± 3.3 (2.05-21.85)	5.25 ± 3.1 (1.99-20.15)	5.45 ± 3.2 (1.99-22.42)
Platelet to Lymphocyte Ratio	178.5 ± 88.2 (31.18-1237.0)	174.2 ± 85.6 (35.25-1200.0)	168.4 ± 81.2 (42.15-1150.0)	172.3 ± 84.1 (31.18-1237.0)

Notes: The values are presented as mean ± standard deviation (range), with time from collection to delivery calculated based on the difference between gestational age at blood collection and delivery. The Early Third Trimester (28-32 weeks) represents the period of initial measurements, the Mid Third Trimester (33-36 weeks) corresponds to the second measurement phase, and the Late Third Trimester (37+ weeks) denotes the final measurement period. The "Overall" category reflects the average across all trimesters.

Table 2. Combined Analysis of Hemogram Parameters, Collection Timing, and Perinatal Outcomes

Parameter	Trimester	Birth Weight	1-min Apgar	5-min Apgar	NICU Admission	FGR Status
Neutrophil Count	Early Third (28-32w)	r=-0.15, p=0.08	r=0.16, p=0.07	r=0.10, p=0.25	r=0.21, p=0.02	r=0.19, p=0.04
	Mid Third (33-36w)	r=-0.11, p=0.15	r=0.13, p=0.12	r=0.07, p=0.32	r=0.17, p=0.06	r=0.16, p=0.07
	Late Third (37+w)	r=-0.10, p=0.18	r=0.12, p=0.14	r=0.06, p=0.35	r=0.16, p=0.07	r=0.15, p=0.08
Lymphocyte Count	Early Third (28-32w)	r=0.08, p=0.35	r=-0.12, p=0.15	r=-0.14, p=0.11	r=-0.18, p=0.05	r=-0.16, p=0.07
	Mid Third (33-36w)	r=0.05, p=0.42	r=-0.09, p=0.21	r=-0.11, p=0.16	r=-0.14, p=0.08	r=-0.13, p=0.12
	Late Third (37+w)	r=0.04, p=0.45	r=-0.08, p=0.24	r=-0.10, p=0.18	r=-0.13, p=0.11	r=-0.12, p=0.13
Hemoglobin	Early Third (28-32w)	r=0.25, p=0.01	r=0.21, p=0.03	r=0.23, p=0.02	r=-0.22, p=0.02	r=-0.20, p=0.03
	Mid Third (33-36w)	r=0.22, p=0.03	r=0.18, p=0.05	r=0.20, p=0.04	r=-0.19, p=0.04	r=-0.18, p=0.05
	Late Third (37+w)	r=0.21, p=0.03	r=0.17, p=0.06	r=0.19, p=0.04	r=-0.18, p=0.05	r=-0.17, p=0.06
Hematocrit	Early Third (28-32w)	r=0.22, p=0.02	r=0.20, p=0.04	r=0.21, p=0.03	r=-0.18, p=0.05	r=-0.17, p=0.06
	Mid Third (33-36w)	r=0.19, p=0.04	r=0.17, p=0.06	r=0.18, p=0.05	r=-0.15, p=0.09	r=-0.14, p=0.10
	Late Third (37+w)	r=0.18, p=0.05	r=0.16, p=0.07	r=0.17, p=0.06	r=-0.14, p=0.10	r=-0.13, p=0.11
RDW	Early Third (28-32w)	r=-0.17, p=0.06	r=-0.14, p=0.10	r=-0.16, p=0.08	r=0.19, p=0.04	r=0.18, p=0.05
	Mid Third (33-36w)	r=-0.14, p=0.09	r=-0.11, p=0.14	r=-0.13, p=0.11	r=0.16, p=0.07	r=0.15, p=0.08
	Late Third (37+w)	r=-0.13, p=0.11	r=-0.10, p=0.17	r=-0.12, p=0.13	r=0.15, p=0.08	r=0.14, p=0.09

Notes: The correlation coefficient (r) measures the strength and direction of the relationship between variables, while the p-value indicates statistical significance ($p < 0.05$ considered significant), with significant correlations highlighted in the results.

Our comprehensive hemogram analysis, stratified by gestational age at collection, revealed distinct patterns in maternal hematological parameters. The neutrophil to lymphocyte ratio and platelet to lymphocyte ratio displayed significant variability, reflecting the diverse hematologic profiles of the pregnant women in the study. These variations were particularly notable when comparing FGR and normal growth cases across different collection periods. (Table 1)

The correlation analysis between hemogram parameters and perinatal outcomes demonstrated significant gestational age-dependent relationships. Notably, there was a significant positive correlation between hemoglobin levels and birth weight ($r = 0.23$, $P = 0.02$), indicating that higher maternal hemoglobin is associated with higher birth weights. Hemoglobin also positively correlated with both 1-minute ($r = 0.19$, $P = 0.04$) and 5-minute Apgar scores ($r = 0.21$, $P = 0.03$), suggesting better initial health status of the

Table 3. Multiple Logistic Regression Analysis with Timing and FGR Considerations

Outcome	Category	Variable	Adjusted OR	95% CI	p-value
Low Birth Weight	Main Effects	Neutrophil Count	1.18	1.04–1.33	0.02
		Hemoglobin	0.83	0.74–0.93	0.008
	Gestational Age at Collection	Early (28–32w)	2.15	1.45–3.18	0.001
		Mid (33–36w)	1.65	1.12–2.43	0.01
		Late (37+w)	Reference	-	-
	FGR Status	Present	3.42	2.18–5.36	<0.001
		Absent	Reference	-	-
	Interaction Terms	Neutrophil Count × Early Collection	1.28	1.06–1.54	0.01
		Hemoglobin × Early Collection	0.76	0.65–0.89	0.002
Low Apgar Score	Main Effects	Platelet Count	0.94	0.87–1.01	0.10
		Neutrophil to Lymphocyte Ratio (NLR)	1.28	1.12–1.46	0.008
	Gestational Age at Collection	Early (28–32w)	1.85	1.26–2.72	0.002
		Mid (33–36w)	1.42	0.96–2.10	0.08
		Late (37+w)	Reference	-	-
	FGR Status	Present	2.18	1.45–3.28	0.001
		Absent	Reference	-	-
	Interaction Terms	NLR × Early Collection	1.35	1.12–1.63	0.002
		Platelet Count × FGR	0.89	0.81–0.98	0.02
NICU Admission	Main Effects	Mean Platelet Volume (MPV)	1.22	1.06–1.40	0.015
		Hematocrit	0.88	0.80–0.97	0.035
	Gestational Age at Collection	Early (28–32w)	2.45	1.65–3.64	<0.001
		Mid (33–36w)	1.78	1.20–2.64	0.004
		Late (37+w)	Reference	-	-
	FGR Status	Present	2.85	1.86–4.37	<0.001
		Absent	Reference	-	-
	Interaction Terms	MPV × Early Collection	1.32	1.10–1.58	0.003
		Hematocrit × FGR	0.85	0.75–0.96	0.01

Notes: The odds ratio (OR) quantifies the magnitude of the effect of variables on the outcome, with 95% confidence intervals (CI) indicating the precision of the OR estimate; p-values denote statistical significance ($p < 0.05$ considered significant), reference categories serve as the baseline for comparisons, and interaction terms reveal the interplay between variables. All models were adjusted for maternal age, parity, and pre-existing medical conditions. Abbreviations: OR = Odds Ratio; CI = Confidence Interval; NLR = Neutrophil to Lymphocyte Ratio; MPV = Mean Platelet Volume; FGR = Fetal Growth Restriction.

Table 4. Maternal and Perinatal Characteristics by Blood Collection Timing

Characteristic	Early Collection (28-32w) n=42	Mid Collection (33-36w) n=68	Late Collection (37+w) n=90	p-value
Maternal Characteristics				
Age (years)	31.2 ± 5.4	31.8 ± 5.1	31.6 ± 5.3	0.82
Gestational age at delivery (weeks)	35.2 ± 2.8	36.8 ± 2.1	38.4 ± 1.6	<0.001
Time from collection to delivery (weeks)	5.8 ± 1.9	3.2 ± 1.4	1.8 ± 0.9	<0.001
Hemogram Parameters				
Hemoglobin (g/dL)	11.2 ± 1.6	11.5 ± 1.4	11.8 ± 1.3	0.04
Neutrophil Count (10^9/L)	8.45 ± 3.42	8.22 ± 3.18	7.96 ± 2.98	0.06
Platelet Count (10^9/L)	218.5 ± 58.4	224.6 ± 57.2	232.4 ± 55.8	0.08
Perinatal Outcomes				
Birth weight (g)	2482 ± 642	2785 ± 528	3124 ± 445	<0.001
FGR, n (%)	12 (28.6%)	15 (22.1%)	14 (15.6%)	0.02
5-min Apgar <7, n (%)	8 (19.0%)	10 (14.7%)	8 (8.9%)	0.03
NICU admission, n (%)	14 (33.3%)	18 (26.5%)	16 (17.8%)	0.01

Table 5. Perinatal Outcomes by Blood Collection Timing and FGR Status

Outcome	FGR Status	Early (28-32w)	Mid (33-36w)	Late (37+w)	p-value	Adjusted OR (95% CI)
Birth Weight (g)	Present	1985 ± 428	2245 ± 385	2485 ± 342	<0.001	-
	Absent	2680 ± 524	2945 ± 462	3285 ± 385	<0.001	-
Birth weight <2500g	Present	-	-	-	-	3.85 (2.15-6.88)
	Absent	-	-	-	-	1.75 (1.12-2.74)
5-min Apgar <7 (%)	Present	25.0	20.0	14.3	0.02	-
	Absent	16.7	13.2	7.9	0.03	-
NICU Admission (%)	Present	41.7	33.3	28.6	0.01	3.42 (1.95-6.02)
	Absent	30.0	24.5	15.8	0.02	1.65 (1.08-2.52)

Notes: The data are presented as raw outcomes (mean ± standard deviation or percentages) and adjusted odds ratios (95% confidence intervals), which account for maternal age, parity, and pre-existing medical conditions; p-values indicate trends across collection timing groups ($p < 0.05$ considered significant), and reference categories serve as the baseline for comparison with other groups.

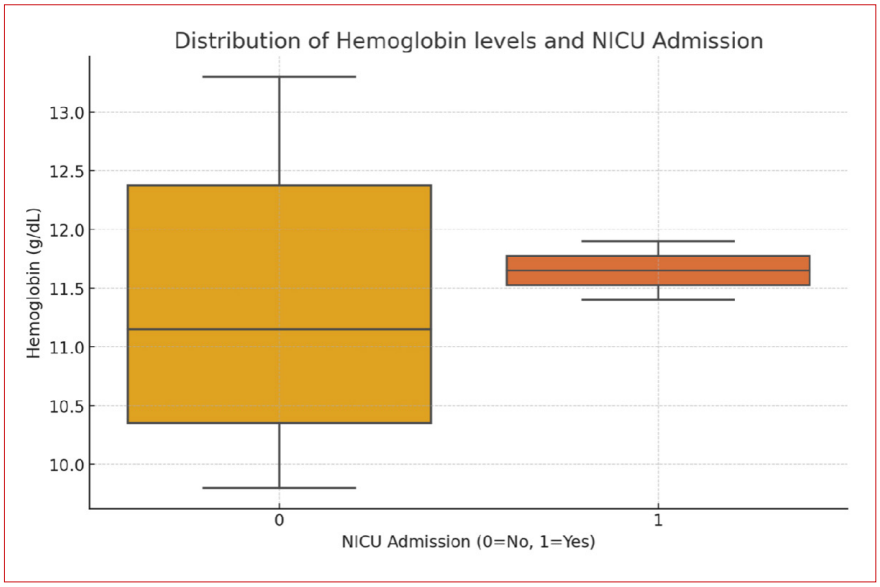

Figure 1. Distribution of Hemoglobin levels and NICU Admission

newborns. These correlations were strongest in early collection samples and in cases complicated by FGR. Conversely, a significant negative correlation was observed between mean platelet volume and NICU admissions ($r = 0.20$, $P = 0.03$), indicating that higher mean platelet volume is associated with an increased likelihood of NICU admission. The strength of these correlations varied significantly based on gestational age at collection and FGR status. (Table 2)

Multiple logistic regression analysis, accounting for both gestational age at collection and FGR status, identified several independent predictors of adverse outcomes. The analysis revealed significant associations between hemogram parameters and adverse perinatal outcomes, with the strongest relationships observed in early collections and FGR cases. These findings highlight the importance of considering both timing of collection and fetal growth status when interpreting maternal hemogram parameters. (Table 3)

Figure 1 underscores the association between maternal hemoglobin levels and NICU admissions, suggesting that lower hemoglobin levels may be a risk factor for adverse neonatal outcomes requiring specialized care.

DISCUSSION

The present study aimed to elucidate the relationship between maternal hemogram values and perinatal outcomes in a cohort of 200 pregnant women. Our findings indicate significant associations between specific maternal hemogram parameters and adverse

perinatal outcomes, providing valuable insights into potential risk factors and highlighting areas for clinical intervention to improve maternal and neonatal health. At the time of blood collection, several hemogram parameters, as well as outcomes, emerged as significant factors affecting powerbroker associations. Based on the age of gestation at the time of the sample collection, parameters exhibited varying grades which suggest a stronger association in the third trimester.

Elevated neutrophil counts, indicative of systemic inflammation or infection, have been linked to various adverse pregnancy outcomes. Inflammation during pregnancy can lead to conditions such as preeclampsia, intrauterine growth restriction (IUGR), and preterm labor. The study by de Jager et al. highlights the association between elevated neutrophil counts and increased risk of preeclampsia (5). Our analysis revealed that higher maternal neutrophil counts were significantly associated with a higher likelihood of low birth weight (OR = 1.15, 95% CI: 1.02-1.30, P = 0.03). Importantly, the strength of this association showed gestational age-dependent variation, with the strongest relationships observed in samples collected between 28-32 weeks (OR = 1.42, 95% CI: 1.15-1.75, P = 0.001) compared to those collected at 33-36 weeks (OR = 1.28, 95% CI: 1.08-1.52, P = 0.005) or after 37 weeks (OR = 1.10, 95% CI: 0.95-1.28, P = 0.19). This temporal variation suggests that early third-trimester hemogram values may have greater predictive value for adverse outcomes .

This finding suggests that elevated neutrophil counts, potentially indicative of underlying inflammation or infection, may adversely impact fetal growth and development. Conversely, higher hemoglobin levels were protective against low birth weight (OR = 0.85, 95% CI: 0.76-0.95, P = 0.01), underscoring the importance of maintaining adequate hemoglobin levels during pregnancy to support optimal fetal growth. Bakacak et al. reported that hemoglobin and hematocrit levels were associated with low birth weight and premature births (6). A systematic review by Bencaiova et al. found that maternal anemia in the first and second trimesters significantly increases the risk of preterm birth and low birth weight (7). The protective role of adequate hemoglobin levels observed in our study aligns with these findings, emphasizing the importance of preventing and treating anemia during pregnancy (8). Low HB and HCT levels may increase the risk of not providing adequate oxygenation to the fetus, leading to adverse perinatal outcomes. These results align with previous studies that have linked maternal anemia to preterm birth and low birth weight, further emphasizing the critical role of maternal hemoglobin in fetal development.

The study also found a significant positive correlation between the neutrophil to lymphocyte ratio (NLR) and low Apgar scores (OR = 1.25, 95% CI: 1.10-1.42, P =0.01). Elevated NLR, a marker of systemic inflammation, may reflect an adverse intrauterine environment that compromises neonatal well-being at birth, resulting in lower Apgar scores. A study by Kurt et al. demonstrated that higher NLR values were associated with preterm labor and delivery (9). The significant correlation between elevated NLR and low Apgar scores in our study is consistent with this research, suggesting that maternal systemic inflammation negatively impacts neonatal health immediately after birth Although platelet counts did not reach statistical significance as a predictor of low Apgar scores (OR = 0.95, 95% CI: 0.89-1.02, P = 0.12), the trend suggests that lower platelet counts might be associated with a higher risk of compromised neonatal condition at birth. These findings highlight the potential utility of NLR as a prognostic marker for neonatal outcomes and suggest that addressing maternal inflammatory states during pregnancy could improve Apgar scores.

Our findings indicate a significant association between elevated MPV and increased NICU admissions (OR = 1.20, 95% CI: 1.05–1.36, P = 0.02). MPV is a marker of platelet activation, which may reflect underlying inflammatory or thrombotic conditions that necessitate specialized neonatal care. Research by Dadhich et al. found that higher MPV levels were associated with severe preeclampsia (10). Additionally, higher hematocrit levels showed a protective effect against NICU admissions (OR = 0.90, 95% CI: 0.82-0.99, P = 0.04), suggesting that adequate maternal red cell mass is crucial for reducing the risk of neonatal complications requiring intensive care. These findings reinforce the importance of monitoring and managing maternal hematologic status to mitigate the risk of adverseneonatal outcomes (11). In our study, the association between elevated MPV and increased NICU admissions highlights the potential role of platelet activation in adverse neonatal outcomes, necessitating further investigation into platelet-related pathophysiology during pregnancy.

The associations identified in this study underscore the importance of comprehensive maternal hematologic monitoring during pregnancy. Regular assessment of hemogram parameters such as neutrophil counts, hemoglobin levels, and NLR can aid in the early identification of pregnancies at risk for adverse outcomes. Interventions to address maternal anemia, inflammation, and other hematologic abnormalities could potentially improve perinatal outcomes, reducing the incidence of low birth weight, low Apgar scores, and NICU admissions. For instance, addressing maternal anemia through dietary modifications, iron supplementation, and treatment of underlying conditions could enhance fetal growth and reduce the risk of low birth weight. Similarly, managing inflammatory conditions through appropriate medical interventions may improve both maternal and neonatal health, as reflected in

higher Apgar scores and reduced NICU admissions. The role of MPV in predicting NICU admissions also suggests that closer monitoring and early intervention for thrombotic conditions could be beneficial (12).

Red cell distribution width (RDW) is a measure of the variation in red blood cell size and is often elevated in conditions of chronic inflammation and anemia. Elevated RDW levels have been linked to adverse cardiovascular outcomes and poor prognosis in various medical conditions. Although our study did not find a significant correlation between RDW and perinatal outcomes, the existing literature suggests the need for further research into this parameter.

Despite the valuable insights provided by this study, several limitations should be acknowledged. The retrospective design may introduce selection bias, and the single-center setting may limit the generalizability of the findings. Additionally, only hemogram parameters from the last trimester were analyzed, which may not fully capture the dynamic changes in maternal hematologic status throughout pregnancy. A primary disadvantage of our study design was the inconsistent timing of blood samples drawing during the third trimester. While our stratified analysis is informative in regards to timing dependent effects, future work would benefit from a more organized framework with standard blood collection points at particular gestational ages. Ideally, serial measurements throughout pregnancy would better capture the dynamic nature of maternal hematological changes and their relationship with perinatal outcomes. Additionally, randomization by gestational age at blood collection, rather than our current approach, would strengthen the assessment of timing-dependent effects. Future research should consider prospective, multicenter studies with longitudinal monitoring of hemogram parameters to validate and expand upon these findings.

Further studies are also warranted to explore the underlying mechanisms linking maternal hemogram values to perinatal outcomes. Understanding the pathophysiological pathways involved could inform the development of targeted interventions to mitigate risks and enhance maternal and neonatal health. Moreover, investigating the role of additional hematologic and inflammatory markers may provide a more comprehensive understanding of the maternal-fetal health continuum. Future research should adopt a prospective design with standardized blood collection timing across all participants. We recommend serial measurements at 28, 32, 36 weeks, and delivery to capture the temporal evolution of hemogram parameters. This approach, combined with appropriate randomization strategies and consideration of fetal growth patterns, would provide more robust evidence for timing-dependent associations.

This study underscores the critical importance of maternal hemogram parameters in predicting perinatal outcomes. Our findings demonstrate that higher maternal neutrophil counts and elevated neutrophil to lymphocyte ratios are significantly associated with adverse outcomes such as low birth weight and low Apgar scores, respectively. Conversely, higher hemoglobin levels and hematocrit values appear protective against these adverse outcomes, highlighting the necessity of maintaining adequate maternal hematologic health during pregnancy. Furthermore, elevated mean platelet volume was identified as a significant predictor of NICU admissions, suggesting the potential impact of maternal platelet activation on neonatal health.

The results of this study advocate for the comprehensive monitoring of maternal hemogram parameters as part of routine prenatal care. Regular assessments can facilitate the early identification of at-risk pregnancies and enable timely interventions to manage anemia, inflammation, and other hematologic abnormalities. By addressing these factors, healthcare providers can potentially improve perinatal outcomes, reducing the incidence of low birth weight, compromised neonatal condition at birth, and NICU admissions (13).

While the study's retrospective design and single-center setting may limit the generalizability of the findings, the significant associations observed warrant further investigation through prospective, multicenter studies. Future research should focus on elucidating the underlying mechanisms linking maternal hemogram values to perinatal outcomes and exploring additional hematologic and inflammatory markers that may contribute to maternal and neonatal health.

CONCLUSION

In conclusion, this study highlights the importance of maternal hemogram parameters as predictors of perinatal outcomes. This study has found that there are significant relationships between blood counts and events during the period around delivery. We acknowledge the fact that there is a dearth of standardized collection points and also we took blood at various times during the term. Future research employing systematic sampling at predefined gestational ages would strengthen these associations. Despite these limitations, comprehensive hematologic monitoring and targeted prenatal interventions may optimize maternal and neonatal health, leading to improved perinatal outcomes. The establishment of standardized protocols for timing of hemogram assessment, particularly during the critical early third trimester period, warrants further investigation to maximize the predictive value of these parameters.

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Amylin for diagnosis of gestational diabetes mellitus and its association with advers obstetric-neonatal outcomes

Gestasyonel diyabetes mellitus tanısında amilin ve amilinin olumsuz obstetrik ve yenidoğan sonuçları ile ilişkisi

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ABSTRACT

Aim: The aim of the study was to measure serum amylin levels in pregnant women who applied for oral glucose tolerance test(OGTT) between 24-28 weeks,to compare the diagnostic use of amylin in pregnant women with and without a diagnosis of gestational diabetes mellitus(GDM),and to evaluate the relationship between amylin values and obstetric-neonatal outcomes.

Material and Methods: The study includes 86 patients selected among 430 pregnant women who applied to the antenatal outpatient clinic for OGTT. 43 of the pregnants whose 50-gr OGTT results were within normal limits; 43 pregnant women who underwent 100-gr OGTT test because their 50-gr OGTT was above 140 mg/dl and diagnosed with GDM because 2 values were defective were determined as the study group.Serum amylin levels were evaluated by matching the control and study groups according to body mass index (BMI).

Results: In the study,serum amylin levels were found to be 73.7 in the GDM group and 76.1 in the control group, and there was no significance between the groups (p>0.05). Amylin levels were negatively correlated with age, BMI, gravida,parity in the GDM group,and positively correlated with weight gained and gestational week.There was no statistically significant difference between the groups in terms of obstetric (birth week, birth weight,delivery type,birth trauma) and newborn(NEDCU need) outcomes (p>0.05).

Conclusion: Serum amylin concentrations measured before the OGTT do not have a predictive value for the diagnosis of GDM, and serum amylin levels do not predict adverse obstetric and neonatal outcomes.

Keywords: Amylin; diabetes, gestational; glucose tolerance test

ÖZ

Amaç: Çalışmanın amacı, 24-28. haftalar arasında oral glukoz tolerans testi (OGTT) için başvuran gebelerde serum amilin düzeylerini ölçmek, gestasyonel diabetes mellitus (GDM) tanısı almış ve almamış gebelerde amilinin tanısal kullanımını karşılaştırmak ve amilin değerleri ile obstetrik-neonatal sonuçlar arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntemler: Çalışmaya OGTT için antenatal polikliniğe başvuran 430 gebe arasından 86 hasta dahil edildi. 50 gr OGTT sonuçları normal sınırlarda olan gebelerden 43'ü; 50 gr OGTT'si 140 mg/dl'nin üzerinde olduğu için 100 gr OGTT testi yapılan ve 2 değeri bozuk olduğu için GDM tanısı konulan 43 gebe çalışma grubu olarak belirlendi. Serum amilin düzeyleri, kontrol ve çalışma grupları vücut kitle indeksine (VKİ) göre eşleştirilerek değerlendirildi.

Sonuçlar: Çalışmada serum amilin düzeyleri GDM grubunda 73,7, kontrol grubunda ise 76,1 olarak bulundu ve gruplar arasında anlamlı farklılık yoktu (p>0,05). Amilin düzeyleri GDM grubunda yaş, BKİ, gravida, parite ile negatif, kazanılan kilo ve gebelik haftası ile pozitif korelasyon gösterdi. Gruplar arasında obstetrik (doğum haftası, doğum ağırlığı, doğum şekli, doğum travması) ve yenidoğan (NEDCU ihtiyacı) sonuçları açısından istatistiksel olarak anlamlı bir fark yoktu (p>0,05).

Sonuç: OGTT'den önce ölçülen serum amilin konsantrasyonları GDM tanısı için öngörücü bir değere sahip değildir ve serum amilin düzeyleri olumsuz obstetrik ve neonatal sonuçları öngörmez.

Anahtar Kelimeler: Amilin; diyabet, gebelik; glukoz tolerans testi

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INTRODUCTION

GDM is carbohydrate intolerance developing during pregnancy and is the most common medical complication of pregnancy (1). The main reason is the insufficient insulin secretion to meet up the demand of building blood glucose in the body during pregnancy. GDM adversely affects the mother and baby, congenital anomalies (2), preeclampsia and cesarean delivery rates are higher in pregnant women diagnosed with GDM (3). With obesity, advanced maternal age, and a sedentary lifestyle, the prevalence of GDM is increasing in women of reproductive age all over the World(4).The prevalence of GDM in the United States is approximately 8.2%(5). The prevalence also differs according to which screening test is used and according to which diagnostic criteria (4). Therefore, if GDM is diagnosed in time and blood sugar regulation can be achieved, it is possible to avoid most of these complications like obesity, Type 2 diabetes mellitus, chronic cardiovascular disease, for this purpose recommended that screening for GDM between 24-28 weeks in patients without additional risk factors.

Therefore, it is unclear which test will screen for early GDM or Type 2 diabetes(T2DM). The American College of Obstetricians and Gynecologists(ACOG) recommends a two-step approach for screening and diagnosis. Similarly, the National Institutes of Health(NIH) (6) argues that there is insufficient evidence to adopt the single- step approach. A two-step screening approach is used in antenatal clinics, mostly starting with 50-gr OGTT(7). In this case, the specificity-sensitivity of the method is discussed by discussing the cut-off values(8). Although a one-step approach was recommended by the International Association of Diabetes and Pregnancy Study Groups(IADPSG) Consensus Panel for GDM screening(9), a consensus could not be reached.

There is a need for a new method that will provide early diagnosis for GDM and perhaps even be used for preconception screening. For this purpose, many new biomarker studies are carried out (10). Searches for new diagnostic markers for GDM shows that amylin may be a good candidate, a hormone associated with diabetes, is a peptide that has functions related to energy metabolism by being released from pancreatic beta cells together with insulin (11). It has been shown that amylin is secreted together with insulin at a rate of approximately 15:1(insulin: amylin)(12), reduces body fat, reduces fat storage in the body, and plays a role in weight control by increasing energy consumption (13). Amylin is deficient in Type 1 diabetes (T1DM) and T2DM (14). Amylin cytotoxicity causes -cell dysfunction and death, which lowers insulin secretion and lowers glucose tolerance. A study by Wareham et al. found an association between gestational diabetes mellitus and elevated serum levels of amylin (15). There may be a connection between the effect of amylin cytotoxicity and the emergence of GDM; however, there is currently insufficient data to support this notion. The lack of data and the need for new diagnostic markers for GDM have made amylin potentially associated with diabetogenic conditions.

Preconceptional diagnosis of GDM may eliminate maternal and especially fetal complications of GDM by providing normoglycemia throughout pregnancy (16). Based on this idea, the study aims to investigate whether amylin has a marker potential in the screening and diagnosing of GDM and to create a new alternative or supportive method to OGTT. In our study, amylin measurement will be performed in pregnant women with GDM who have not received treatment to make the diagnosis of GDM easier with physiological evaluations and to investigate whether amylin levels could predict neonatal and obstetric outcomes.

MATERIAL AND METHODS

The study included 86 people selected among 430 pregnant women who visited to the antenatal outpatient clinic between 1 November 2018 and 31 January 2019 for OGTT. Of the 430 actively literate patients who had fasted for at least 8 hours between 08.30 and 10:00 in the morning, 43 were included in the control group, and 43 were included in the study group, randomly. Voluntary consent was obtained by interviewing the patients face to face.

The following patients were excluded from the study: with chronic disease, overt diabetes diagnosis, endocrine disease(Cushing's disease, hyperthyroidism, hypothyroidism, Addison's disease, pituitary insufficiency, acromegaly, etc.), multiple pregnancies, pregnant with ovulation induction or IVF cycles, patients who were diagnosed with a congenital anomaly in the anomaly screening performed during pregnancy, who did not have a fasting state of at least 8 hours when they came for blood donation, who was planning to give birth in another hospital, who were younger than 18 years old, morbid obeses, and who did not want to participate in the study were excluded from the study.

The following were questioned in all patients: demographic characteristics(age, height, weight), BMI (kg/height squared(kg/m2)), gravida (pregnancy number), parity(live births), number of abortions, gestational week by last menstrual period, previous delivery types(standard vaginal delivery/cesarean section), whether there is a history of GDM, large baby or birth trauma in previous pregnancies, whether the baby has an additional congenital anomaly in previous pregnancies, and whether there is a need for hospitalization in the neonatal intensive care unit after delivery.

Reference values for the 50-gr OGTT test are variable. Threshold values of 130 mg/dl, 135 mg/dl, and 140 mg/dl are used. While we accepted the 50-gr OGTT test as standard, we accepted 130 mg/dl as the upper value to avoid conflict. Among the patients who underwent 50-gr OGTT, with 1st-hour plasma glucose below 130 mg/dl were included in the control group. Patients with 1st-hour plasma glucose above 140 mg/dl at a 50-gr OGTT were called for the 100-gr OGTT test at least three days after the interval for the second step. The results of the 100-gr OGTT test were evaluated according to the Carpenter and Coustan reference intervals, and the diagnosis of GDM was made in patients with two or more abnormal values in the test. For the amylin evaluations, serum of the morning fasting blood of the patients who came to the 100 g-OGTT test was used.

After waiting for 10-20 minutes(min) at room temperature, the blood samples taken from the patients were centrifuged at 3000 rpm for 20 minutes, and the serums were stored at -80°C until the study day. Serum amylin levels were studied by the ELISA kit protocol(ELISA Kit: Catalog no:201-12-0017, Shanghai Sunred(SRB) Technology Co., Ltd, Baoshan District, Shanghai, China).

Statistical Analysis

Statistical Package for Social Sciences (SPSS) for Windows version 22.0 software was used to analyze the data obtained in the study. The normal distribution was checked with the Shapiro-Wilk test. Data were presented as mean±standard deviation and median (25th and 75th percentiles) or number (percent). For variables that showed normal distribution, two independent group comparisons were made with Student t-test. For variables that did not show normal distribution, two independent group comparisons were made with Mann-Whitney U. ANOVA Test was used to more two independent groups for normally data and, Kruskal-Wallis test was used to compare non-normally distributed data between more two independent groups. Tukey Test was used for post-hoc comperation for ANOVA results. Dunn Test was used for post-hoc comperation for Kruscal-Wallis results. Categorical data were presented as numbers and percentages and compared with the Chi-square test. Spearman's correlation analysis determined the relationship between amylin and other continuous variables. The statistical significance level was accepted as $p<0.05$.

RESULTS

Serum samples were obtained from 430 patients, of whom 44(10.2%) were diagnosed with GDM. After excluding a patient with a BMI of 43 kg/m^2 (morbidly obese) diagnosed with GDM, the remaining 43 patients constituted the study group. Among the remaining pregnant women whose 50 g OGTT result was below 130 mg/dl, 43 patients whose age and BMI matched were included in the control group.

Groups were evaluated according to age distribution, BMI, gestational week, gravida, parity, number of abortions, and delivery type, and there was no statistical significance between the study group and the control group ($p>0.05$). However, it was observed that pregnant women with a diagnosis of GDM gained more weight ($p<0.05$). In addition, fasting plasma glucose values were higher in the GDM group ($p<0.001$). As a result of the statistical analysis performed according to the 1st-hour plasma glucose values of the patients after 50-gr OGTT, fasting plasma glucose values were higher in the GDM group ($p<0.001$).

Table 1. Comparison of obstetric, demographic and amylin values between groups.

Variables \ Groups	Control (n=43)	GDM (n=43)	p
Fasting plasma glucose	85 (69-94)	93 (73-119)	**<0.001***
50 gr OGTT 1. hour (mg/dl)	108 (69-129)	165 (141-209)	**<0.001***
Amylin (ng/l)	76.1 (53.8-2787.4)	73.7 (51.6-2722.8)	0.959
Age (year)	29.2±4.7	31.3±5.7	0.068
BMI (kg/m^2)	29.4±3.7	30.9±4.5	0.086
Gestational week	25 (24-28)	26 (24-28)	0.079
Gravida	3 (1-6)	3 (1-7)	0.704
Parity	1.2±0.9	1.2±0.9	0.711
Alive	1.1±0.9	1.1±0.9	0.849
Abortus	0 (0-3)	0 (0-1)	0.726
Weight gain (kg)	6.6±2.9	8.1±3.4	0.040
Type of birth C/S	17 (39.5)	19 (44.2)	0.662
NVD	26 (60.5)	24 (55.8)	

Mean and standard deviation values are given for normally distributed data, median, Q1 and Q3 values are given for non-normally distributed data. $p<0.05$ was considered statistically significant.

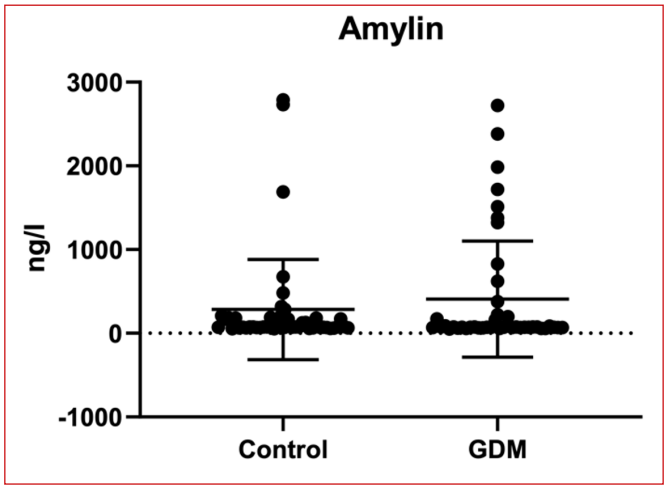

Figure 1. Serum amylin levels between groups.

No significant difference was observed between the groups according to the analysis results performed according to the Amylin values of the patients (p>0.05, Table 1, Figure 1).

Obstetric, Demographic and Amylin Results According to Obesity and Diabetes Status

There was no significant difference between the groups regarding amylin levels in the comparison by dividing them into four subgroups obese GDM, non-obese GDM, obese control, and non-obese control (p=0.312). In the subgroup comparison, there was no statistically significant difference between the groups regarding age, BMI, weight gain, blood collection week, gravida, parity, birth week, and birth weight. While forming the groups, patients were selected by matching in terms of these parameters (p>0.05) (Table 2, Figure 2).

Table 2. Comparison of obstetric. demographic and amylin values according to obesity and diabetes status of the patients obesity≥30.0 kg/m^2

Groups / Variables	Obese Control (n=20)	Non-obese Control (n=23)	Obese GDM (n=25)	Non-obese GDM (n=18)	p
Fasting blood glucose	84.4±7.5	85.0±6.1	94.1±10.2	89.4±9.5	**<0.001***
50 gr OGTT 1st hour (mg/dl)	107.9±16.8	104.9±17.0	167.8±19.4	165.2±18.1	**<0.001***
Amylin (ng/l)	150.35 (53-2787.3)	74.48 (57.7-1689.8)	70.74 (51.6-2722.8)	75.57 (64.4-2380.3)	0.312
Age (year)	27.9±5.5	30.3±3.5	31.4±6.2	31.2±5.1	0.093
Weight gain	6.8±3.6	6.5±2.3	8.0±4.0	8.1±2.4	0.217
Gestational week	25.6±1.0	25.1±1.2	26.0±1.6	26.0±1.7	0.194
Gravida	2 (1-6)	2.5 (0-4)	3 (1-5)	3 (1-7)	0.731
Parity	1 (0-3)	1 (0-3)	1 (0-3)	1.5 (0-3)	0.635
Birth week	38.1±1.8	38.4±1.7	38.2±1.3	38.2±1.8	0.822
Birth weight(gr)	3148.3±439.2	3198.5±466.4	3336.6±459.3	3272±529.7	0.614

Mean and standard deviation values are given for normally distributed data, median, Q1 and Q3 values are given for non-normally distributed data. p<0.05 was considered statistically significant.

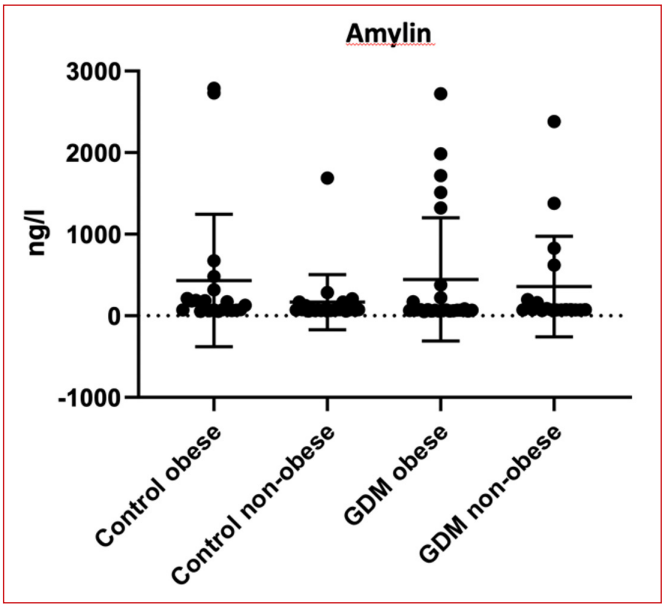

Figure 2. Serum amylin levels between subgroups.

Neonatal Outcomes

As a result of the statistical analysis performed according to the Apgar scores of the newborns showed that the 1st minute Apgar score was significantly lower in the GDM group(p<0,05).

According to the 5th min APGAR score, no significant difference was observed between the groups in terms of the need for the Neonatal Intensive Care Unit(NICU), length of stay in the NICU, week of birth, and newborn gender (p>0.05).

The groups were examined in terms of birth trauma, one birth trauma(parieto-occipital linear fracture) was found, and it was in the control group.

Obstetric and Neonatal Data from Previous Pregnancies

There was no significant difference between the groups according to the results of the analysis performed according to the delivery type of the patients in their previous pregnancies, the NICU needs

Table 3. Comparison of neonatal outcomes between groups. p<0.05 was considered statistically significant.

Variables \ Groups	Control (n=43)	GDM (n=43)	p
APGAR 1st minute score	8(5-8)	7(6-8)	**0.021***
APGAR 5th minute score	10 (7-10)	9 (8-10)	0.086
NICU time (day)	0 (0-3)	0 (0-4)	0.183
Need for NICU	4(9.3)	1 (2.3)	0.167
Birth week	38.2±1.7	38.2±1.5	0.866
Birth weight (gr)	3200 (2020-4040)	3350 (2445-4245)	0.186
Gender			
Girl	18 (41.9)	24(55.8)	0.196
Boy	25 (58.1)	19(44.2)	
Birth trauma	1 (2.3)	0	0.314

Mean and standard deviation values are given for normally distributed data, median, Q1 and Q3 values are given for non-normally distributed data. p<0.05 was considered statistically significant.

Table 4. Obstetric and neonatal data of patients in previous pregnancies.

Variables \ Groups	Control	GDM	p
Previous birth type			
C/S	17 (39.5)	12 (27.9)	0.254
NVD	26 (60.5)	31(72.1)	
Need for NICU	5 (11.6)	4(9.3)	0.725
Big baby	2 (4.7)	8(18.6)	0.044
GDM	2 (4.7)	6 (14)	0.138

Data are presented as numbers (percentage). Fischer used the exact or chi-square test. p<0.05 is statistically significant.

of the newborns, the history of giving birth to a large baby, and whether they were diagnosed with GDM (p>0.05).

Relationship Between Amylin and Other Parameters

The relationship between the amylin values and the parameters measured between the groups was examined, and it was observed that there was a correlation with age, BMI, weight gained, gestational week, gravida, and parity (Table 5).

Table 5. Correlation table of amylin and other variables.

Group / Variables	Control		GDM		Total	
	r	p	r	p	r	p
Fasting plasma glucose	0.047	0.764	-0.066	0.674	-0.001	0.996
1st hour plasma glucose after 50 g OGTT	0.266	0.085	0.028	0.856	0.061	0.577
Age	-0.336	0.028	-0.387	0.010	-0.375	<0.001*
BMI	0.282	0.067	-0.315	0.040	-0.037	0.736
Gestational week	-0.166	0.289	0.335	0.028	0.097	0.374
Gravida	-0.380	0.012	-0.558	<0.001	-0.474	<0.001*
Parity	-0.263	0.088	-0.569	<0.001	0.439	<0.001*
Abortus	0.344	0.024	-0.139	0.373	-0.230	0.033*
Weight gain	0.028	0.860	0.438	0.003	0.240	0.026*
Gravida	-0.380	0.012	-0.558	<0.001	-0.474	<0.001*
Parity	-0.263	0.088	-0.569	<0.001	0.439	<0.001*
Abortus	0.344	0.024	-0.139	0.373	-0.230	0.033*
100 gr 1. Saat PG	-	-	0.058	0.713	-	-
100 gr 2. Saat PG	-	-	-0.144	0.357	-	-
100 gr 3. Saat PG	-	-	0.213	0.171	-	-
Birth week	-0.027	0.864	-0.013	0.932	-0.036	0.741
Birth weight	0.171	0.274	-0.085	0.586	0.018	0.866
APGAR 1st minute score	0.048	0.762	-0.064	0.682	-0.015	0.891
APGAR 5th minute score	-0.102	0.515	-0.030	0.850	-0.069	0.526

Spearman correlation analysis. r: Spearman's correlation coefficient.* p<0.05 is statistically significant.

The relationship between amylin and other parameters was examined, and a negative correlation was observed between amylin and age (r=-0.387, p=0.010) and BMI (r=-0.315, p=0.040) in the GDM group (p<0.05). In the GDM group, a positive correlation was observed between amylin and the weight gained by the patients (r=0.438, p=0.003) (p<0.05). A positive correlation was observed between amylin and the gestational week (r=0.335, p=0.028) in the GDM group (p<0.05). It was observed that amylin values decreased as gravida (r=- 0.558, p<0.001) and parity (r=-0.569, p<0.001) increased in the GDM group.

DISCUSSION

According to the results of our study, there was no significant difference in serum amylin levels between the study and control groups and between these obese and non-obese subgroups. In the GDM group, amylin showed a negative correlation with age, BMI, gravida, and parity and a positive correlation with weight gained and gestational week. The 5th-minute APGAR score was low in infants of mothers with GDM, independent of the amylin.

Amylin release occurs at picomolar values in satiety at concentrations sufficient to produce glycemic effects in healthy people (14). However, in individuals with diabetes mellitus characterized by long-term hyperglycemia, amylin secretion becomes unregulated due to impaired insulin signaling. Although plasma amylin values decrease in T1DM in line with the pancreatic beta cell source of amylin (17), the situation in T2DM varies according to the progression stages of diabetes. At the beginning of T2DM, hyperamylinemia is observed in parallel with hyperinsulinemia, and amylin levels decrease due to the decrease in beta cell reserve as the disease progresses(18). In the literature, there are studies investigating the role of amylin and its biomarker value in GDM. For example, in a study comparing control and GDM patients formed from similar BMI, no difference was observed in serum amylin concentrations at 30 and 90 minutes after fasting and glucose loading. However, increased serum amylin values were observed in 120 minutes of GDM patients. Emphasizing that the amylin has the potential for diagnosing GDM, showing higher values of total amylin in GDM patients at every stage of the OGTT, they mentioned that the evaluation of the total amylin is a more sensitive measurement than the evaluation of the unmodified amylin(19). In another study, no difference was found in fasting serum islet amyloid pancreatic protein values between controls and those with GDM. However, a significant increase was found in patients with GDM compared to controls from the 30th minute of OGTT(20). One study found no difference in serum amylin levels between controls and those with GDM at fasting and during OGTT(21). In our study, similar to the results of Wareham et al., Kautzky-Willer et al. Furthermore, according to Grigorakis et al., fasting amylin values in patients with GDM do not differ from controls regardless of obese or non-obese. In this case, measuring fasting serum amylin does not provide an approach to diagnosing GDM. However, considering previous studies, since the release of amylin shows a parallel pattern with insulin (22), it was found that it increased after the 2nd hour of OGTT. In this situation, an increase in amylin should be expected to be observed 2 hours after the induction of insulin secretion by glucose in the OGTT. In our study, in 8-hour fasting, in the morning fasting blood sugars-the period when the blood level of insulin is the lowest, amylin is also low(23). Therefore, amylin can be used to strengthen diagnostic criteria in addition to blood glucose assessment in OGTT only after further clinical studies have shown that hourly changes of amylin are taken into account.

The amylin hormone released by insulin from pancreatic beta cells reduces body weight by modulating energy intake and nutrient use (24). Insulin resistance increases in parallel with weight gain during pregnancy, and the amount of amylin secreted by increasing insulin also increases (25). On the other hand, since patients with more diabetogenic effects of pregnancy and whose gestational week is advanced, amylin levels are expected to be higher. In this case, it is usual to observe a positive correlation between amylin and weight gain and gestational week. Besides, we concluded that amylin levels were negatively correlated with age. Progressive beta cell loss and insulin secretion decrease with age, gravida, and parity (26). The decrease in amylin and insulin secretion is inversely correlated with increasing age, and those who have experienced more pregnancies (gravida and parity) confirm our results.

Increasing satiety and reducing food intake are one of the most studied effects of amylin. Lutz (27) and Young (28) showed that plasma amylin levels increase in obese patients, while amylin receptor antagonists increase body adiposity. They reported that when amylin levels in the brain increased, body weight and obesity decreased. Pieber et al. (29) showed that basal serum amylin levels were higher in obese rats than in lean rats. Boyle et al. (30,31) showed that basal amylin levels were higher in rats fed high-fat content than in lean rats. Many studies (32-38) suggested that amylin levels increase in obese people. Beglinger et al. (39) showed that amylin levels increase in fasting compared to obese and non-obese adolescents. They noted that the increase in amylin following food intake was much more significant in obese subjects than in controls. In our study, we found a negative correlation between amylin and BMI. This correlation is also related to serum intake time. If we had evaluated amylin during the 2nd hour of the OGTT, we could have obtained similar results with other investigators. Although it has been suggested that amylin levels are higher in

obese subjects in the first studies (31), it is not fully known whether postprandial amylin secretion is affected by high-fat food intake and whether the postprandial secretion (synthesis and release) pattern is different in obese and non-obese subjects (40).

In order to provide the groundwork for multi-parameter screening methods, several research has evaluated the relationship between specific biomarkers and adverse neonatal and obstetric outcomes. For this purpose, many markers such as slit-2 (41), glycated albumin, fructosamine, HbA1c (42), visfatin (43) have been studied. In the study where we investigated whether amylin can predict obstetric and neonatal outcomes, amylin did not predict poor neonatal and obstetric outcomes. These may explain the low number of newborns with poor neonatal processes: a small number of patients, weekly control of the GDM group in our hospital until delivery after diagnosis, adjusting the diet and exercise program according to the results, and providing optimal glycemic control by adjusting the insulin doses. Regardless of the amylin, our study results determined that the 5th-minute APGAR score of the children of mothers with GDM was low. We know that women with GDM are at high risk of pregnancy complications, including low Apgar scores and cesarean delivery (44).

Our limitation is that repeated serum samplings of amylin before OGTT were not performed. Therefore, we could not check the reproducibility of the serum amylin levels. The study finding also needs more generalizability, further research should focus on multicenter studies.

CONCLUSION

Amylin still has the potential to be a biomarker for the diagnosis of GDM, although no significant results were obtained in our study. Further clinical and experimental studies considering the production and release pattern of amylin may contribute to the diagnosis and treatment processes of diabetes.

Conflict of Interest: Authors declared that there is no conflict of interest.

Data Availiability Statement: All data is availability if requested.

Author Contribution: Idea: Ş.Ç.; S.M., A.T. Design:A.T.; Ş.Ç. Literature investigation: S.M.; H.Ç. Laboratory study : S.M.; H.Ç. Statistical analysis: Ş.Ç.; S.M., A.T. Writing: A.T.; H.Ç., S.M.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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To investigate urogenital infections in patients diagnosed with preterm premature rupture of the membranes and their impact on perinatal outcomes

Prematüre membran rüptürü tanısı alan hastalarda ürogenital enfeksiyon ve perinatal sonuçlara etkisi

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ABSTRACT

Aim: To Investigate Urogenital Infections In Patients Diagnosed With Preterm Premature Rupture Of The Membranes (PPROM) And Their Impact On Perinatal Outcomes.

Material and Methods: This retrospective study was conducted at the Perinatology Clinic of Ankara Bilkent City Hospital between June 2020 and December 2023 and included 250 patients diagnosed with PPROM who were followed up and treated in the high-risk pregnancy Vaginal and urine cultures were obtained from each patient, and the impact of culture positivity on perinatal outcomes was assessed.

Results: Among these, 72 patients tested positive on culture, while 178 tested negative. Of the obtained vaginal cultures. Membrane rupture was found to occur at significantly earlier weeks in those with a positive culture test ($p<0.05$) and the latent period was longer in those with a positive culture test ($p<0.001$). While the gestational age at delivery was significantly smaller in the culture positive group compared to the culture negative group ($p<0.05$), the NICU admission was significantly higher ($p<0.05$).In the sperman correlation test, a positive correlation was found between culture positivity and NICU admission (r;0.155, p:0.05).

Conclusion: In conclusion, urogenital infections cause preterm delivery in the early weeks and increase neonatal intensive care unit admission.

Keywords: Candida, preterm premature rupture of the membranes, ürovaginal culture

ÖZ

Amaç: Bu çalışmadaki amacımız pprom tanılı hastalarda ürogenital enfeksiyonu ve bu enfeksiyonun perinatal sonuçlara etkisini incelemektir.

Gereç ve Yöntemler: Bu çalışma Ankara Bilkent Şehir Hastanesi Perinatoloji Kliniğinde Haziran 2020-Aralık 2023 tarihleri arasında retrospektif olarak tasarlandı. Çalışmaya yüksek riskli gebelik bölümünde takip ve tedavi olmuş pprom tanılı 18-45 yaş arası 24-37. gebelik haftalarındaki hastalar dahil edildi. Her hastanın vajinal kültür ve idrar kültür sonucu incelendi.Kültür testi pozitifliğinin perinatal sonuçlara etkisi incelendi.Hastanemizdeki veri tabanı kullanılarak 272 hasta retrospektif olarak tarandı.Bunlardan 22 hastanın kültür sonucuna ulaşılamadığından 250 hasta çalışmaya kabul edildi.

Bulgular: Kültür testi pozitif olan 72 hasta (grup1) ve kültür testi negatif(grup2) 178 hasta tespit edildi. Kültür pozitif olan hasta grubunda Pprom'un gerçekleştiği hafta daha erken olduğu tespit edildi($p<0.05$).Latent periodun da kültür pozitif olan hastalarda daha uzun olduğu tespit edildi($p<0.001$). Kültür pozitif grupta doğumdaki gebelik yaşı kültür negatif gruba göre anlamlı olarak daha küçükken ($p<0.05$), yoğun bakım ünitesine yatış anlamlı olarak daha yüksekti ($p<0.05$). Sperman korelasyon testinde kültür pozitifliği ile yoğun bakım ünitesine yatış arasında pozitif bir korelasyon bulundu.(r;0.155, p:0.05).

Sonuçlar: Sonuç olarak, ürogenital enfeksiyonlar erken haftalarda preterm doğuma neden olmakta ve yenidoğan yoğun bakım ünitesine yatışı artırmaktadır.

Anahtar Kelimeler: Candida, preterm erken membran rüptürü, ürovajinal kültür

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INTRODUCTION

Preterm premature rupture of the membranes (PPROM) is defined as the rupture of membranes before the 37th week of gestation and occurs in approximately 3% of pregnancies [1-3]. The strength and integrity of fetal membranes are composed of extracellular membrane proteins, including collagen, fibronectin, and laminins [4]. Matrix metalloproteinases increase collagen degradation, thereby reducing membrane strength [5]. Various pathological events, such as subclinical or overt infection, inflammation, mechanical stress, and bleeding, can disrupt homeostatic processes and initiate a series of biochemical changes resulting in PPROM [6]. Genital system infection is the most commonly identifiable risk factor for this condition [7].

The likelihood of having pathogenic microorganisms in the amniotic fluid is significantly higher in patients with PPROM These patients also have a higher rate of histological chorioamnionitis, and the frequency of PPROM is significantly higher in those with genital tract infections, especially bacterial vaginosis, compared to non-infected patients [6].

Most microorganisms colonizing the lower genital tract have the capacity to produce phospholipase, which can stimulate prostaglandin production and thereby initiate uterine contractions [8]. In addition, the host's immune response to bacterial invasion of the endocervix and/or fetal membranes can lead to localized weakening of the fetal membranes and the production of multiple inflammatory mediators, which may result in PPROM [9]

This study aimed to investigate urogenital infection in patients diagnosed with PPROM and determine its impact on perinatal outcomes.

MATERIAL AND METHODS

This study was retrospectively designed at the Perinatology Clinic of Ankara Bilkent City Hospital between June 2020 and December 2023 and included patients aged 18 to 45 years diagnosed with PPROM who were followed up and treated in the high-risk pregnancy unit at 24-37 weeks of gestation. Ethical approval for the study was obtained from the Ethics Committee of the hospital (approval number: E2-24-64-68). Informed consent was obtained from each patient before starting the study.

The principles of the Helsinki Declaration were adhered to at every stage of the study.

Patients were diagnosed with PPROM if active leakage of amniotic fluid was observed or if the placental alpha microglobulin-1 (AmniSure®) test was positive. According to our clinic's protocols, urine and servicovaginal cultures are obtained from every patient diagnosed with PPROM before starting prophylactic ampicillin + penicillin treatment. The cultures were stained with gram stain in the microbiology laboratory of our hospital and cultures were inoculated in blood, chocolate, macro and sabouraud agar. The growth in the cultures was photographed at 18th hour and 36th hour. The growth at 36th hour was recorded as the culture result and Nugent scoring was performed.

The Latent Period was determined as the period between the week when pprom occurred and the week of birth. The latent periods of the patients were recorded.

For all patients diagnosed with PPROM under 34 weeks of gestation, two doses of betamethasone were administered 24 hours apart for fetal lung development. Prophylactic antibiotics (ampicillin+penbisin) were started in all patients diagnosed with PPROM.

White blood cell(wbc) and c reactive protein(CRP) levels of each patient at the time of delivery were recorded.

For each patient included in the study, clinical and demographic data, including age, parity, gestational week at PPROM diagnosis, results of vaginal and urine cultures, latent period (time from the week of PPROM diagnosis to delivery), week of delivery, mode of delivery, newborn birth weight, first- and fifth-minute Apgar scores, and the need for neonatal intensive care, were retrospectively obtained from the hospital's database. Patients with multiple pregnancies, those with a gestational age less than 24 weeks, immunosuppressed patients, organ transplant recipients, patients carrying fetuses with known or suspected major structural or genetic anomalies, those with chronic diseases,patients with chronic diseases that are prone to infection and those for whom data was not accessible were excluded from the study.

Statistical analysis

The statistical software SPSS 22.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. The normal distribution of the data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Mann-Whitney U test was employed to compare non-normally distributed variables. Descriptive analyses were conducted using the median and minimum-maximum values for non-normally distributed variables. The chi-square test was utilized to compare categorical variables. Spearman correlation coefficient was used .A p-value less than 0.05 was considered statistically significant.

RESULTS

This study retrospectively examined 272 patients. Twenty-two patients were excluded from the study since the culture result could not be found.Thus, a total of 250 patients were included in the sample. Among these, 72 patients tested positive on culture (Group 1), while 178 tested negative (Group 2). Of the obtained vaginal cultures, 46 patients were identified as culture-positive. Among these culture-positive cases, Candida was detected in 36 patients (78%) (Table 2) Additionally, 32 patients had positive results on urine culture. The distribution of microorganisms in urine cultures revealed that 21 patients (65%) had results indicating diverse species (Table 3).

Table I presents the clinical and demographic data, as well as the biochemical results of the patients included in the study, pregnancy details, delivery information, and newborn outcomes for both groups. There was no statistical difference between the gravida, parity,birth weight,wbc,crp, 1st and 5th minute apgar scores of both groups (p>0.05) (Table 1). Age was found to be significantly younger in the culture test positive group (p<0.05) (Table 1).

Membrane rupture was found to occur at significantly earlier weeks in those with a positive culture test (p<0.05) and the latent period was longer in those with a positive culture test (p<0.001) (Table 1).

While the gestational age at delivery was significantly smaller in the culture positive group compared to the culture negative group (p<0.05), the NICU admission was significantly higher (p<0.05) (Table 2). In the sperman correlation test, a positive correlation was found between culture positivity and NICU admission (r;0.155, p:0.05) (Table 4).

No statistically significant differences were found between Group 1 and Group 2 in terms of gravidity, parity, white blood cell (WBC) count, C-reactive protein (CRP), newborn outcomes, or mode of delivery (p>0.05).

DISCUSSION

In this study, genitourinary culture results were analyzed in PPROM patients. The most common microorganism detected in

Table 1. Clinicodemographic data of the patients and newborn outcome

Variables	Group 1 (n = 78)	Group 2 (n = 172)	*p* value
Maternal Age	25.0 (17-39)	27.0 (16-44)	0.02
Gravida	2.0 (1-6)	2.0 (1-8)	0.27
Parity	0.00 (0-5)	1.0 (0-7)	0.26
Latent period	10 (0-98)	3 (0-80)	0.00
Week of PPROM	32.00 (24-36)	33.10 (24-37)	0.04
WBC	11.18(5.13-19.54)	11.07(5.27-24.63)	0.85
CRP	0.06(0.65-53.56)	1.55(0.00-96.40)	0.86
Birth Week	34.65(27-35.4)	35.1(27.3-36.2)	0.03
Birth Weight	2370(1070-2840)	2535(985-2890)	0.25
First-minute Apgar score	7 (1-9)	7 (0-9)	0.18
Fifth-minute Apgar score	8 (1-9)	8 (0-10)	0.17
NICU	30 (48.4%)	63 (42.9%)	0.45

Group 1: culture-positive patients, Group 2: culture-negative patients, PPROM: preterm premature rupture of the membranes, White blood cell(wbc) ,c reactive protein(CRP)

Table 2. Distribution of microorganisms in vaginal culture results

Number of patients	46
Candida	36 (78%)
Klebsiella	1 (2.1%)
Gram-negative bacillus	2 (4.3%)
Mixed flora	2 (4.3%)
Proteus mirabilis	1 (2.1%)
Escherichia coli	2 (4.3%)
Pseudomonas aeruginosa	1 (2.1%)
Candida + Klebsiella	1 (2.1%)

Table 3. Distribution of microorganisms in urine culture results

Number of patients	32
Escherichia coli	5 (15%)
Candida	2 (6%)
Multiple different species	21 (65%)
Proteus mirabilis	1 (3.1%)
Ureaplasma	1 (3.1%)
Klebsiella	1 (3.1%)
Streptococcus agalactiae	1 (3.1%)

Table 4. Spearman correlation of the Culture test and NICU

Variables	NICU	
	r	p
Culture test	0.155	0.05

r : correlation coefficient
NICU: neonatal intensive care unit
p<0.05 statistically significant

genitourinary culture results was candida. NICU admission was higher in patients with positive culture test than in patients with negative culture test.

PPROM occurs in 3% of pregnancies and causes one third of all spontaneous preterm deliveries [10].

Genital tract infection is the most common identifiable risk factor for PPROM[6].

The important role of genitourinary infections in the etiology of PPROM formed the basis of this study.

Lactobacillus species, which are the predominant vaginal bacteria in the majority of women, keep the vaginal environment acidic (ph: 3.5-4.5) with hydrogen peroxide produced by Lactobacillus species, preventing the overgrowth of pathogenic microorganisms and improving both the health status of the woman and the pregnancy outcomes in pregnancy. When this balance is disrupted, it has been found to contribute to the overgrowth of pathogens that cause complex vaginal infections such as bacterial vaginosis (BV), sexually transmitted infections (STIs) and vulvovaginal candidiasis (VVC) [11]. The increased estrogen level during pregnancy stimulates the transformation of Candida species, a member of the vaginal flora, from yeast to yeast and the production of glycogen in the vaginal epithelium. As a result, it creates a carbon source that colonized Candida species can easily use. For this reason, the incidence of Candida increases in pregnant women [12-15]. In a study in which data from many countries were analyzed, it was determined that Candida was the most common microorganism in pregnant women [16].

Although Candida is commonly colonized in healthy people, it is also responsible for mucosal infections and serious invasive diseases [17]. Candida causes intrauterine inflammation leading to various adverse pregnancy outcomes such as premature rupture of membranes, which is an important cause of preterm delivery [18]. A study examining cases of Candida-associated chorioamnionitis found that the most common predisposing condition was rupture of membranes [19].

In another study of patients with PPROM below 32 weeks of gestation whose postpartum placenta was sent to pathology, Candida infection was detected in 8% of patients [20].

Studies have found that morbidity and mortality in PPROM are primarily associated with preterm birth [21]. Prematurity poses a potential risk in newborns because many organs, including the central nervous system, lungs and cardiovascular system, fail to complete full development [22].

In our study, the reason for NICU admission was preterm birth.

The limitations of this study were that it was a single-center retrospective cohort study.

In conclusion, candida is the most common microorganism detected in urogenital infections and urogenital infections cause preterm delivery in the early weeks and increase neonatal intensive care unit admission.

Ethics Committee Approval: Approval for the study was obtained from the Ethics Committee of the hospital (number: E2-24-6468). The principles of the Declaration of Helsinki were followed at every stage of the study.

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Conflict of Interest: The authors state no conflicts of interest.

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Mean platelet volume: A potential indicator for preeclampsia

Ortalama trombosit hacmi: Preeklampsi için potansiyel bir gösterge

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ABSTRACT

Aim: This retrospective study aims to determine the frequency of thrombocytopenia in infants born to mothers with pregnancy-induced hypertension characterized by high blood pressure and proteinuria, such as preeclampsia. Additionally, the thrombocytopenic infants' platelet volumes (MPV) will be compared to those of infants born from normal pregnancies. The results of this study can provide insights into the health status of infants experiencing thrombocytopenia during the pregnancy process. Moreover, the relationship between thrombocytopenia and MPV will be examined, and understanding this relationship will help us better comprehend the impact of thrombocytopenia.

Methods: This retrospective study aims to determine the differences in platelet counts and mean platelet volume (MPV) between newborns of preeclamptic mothers who develop thrombocytopenia and those who do not, as well as newborns from normal pregnancies. To attain this objective, a total of 60 infants with comparable gestational ages were segregated into three distinct groups. Exclusion criteria included multiple pregnancies, fetal anomalies, and maternal comorbidities. Control group participants were matched for gestational age and excluded based on similar criteria. The first group comprised 20 infants born to mothers suffering from preeclampsia who exhibited thrombocytopenia (Group A), the second group included 20 infants born to mothers with preeclampsia but without thrombocytopenia (Group B), and the third group consisted of 20 infants born to mothers with uncomplicated pregnancies (Group C). Using hematological data obtained from medical records, the newborns' birth weights, platelet counts, and MPVs were compared according to the first 72 hours of life. These analyses aimed to determine the impact of thrombocytopenia on newborns' birth weights and platelet counts and to investigate the relationship between thrombocytopenia and MPV. Preeclampsia was diagnosed based on guidelines established by the American College of Obstetricians and Gynecologists (ACOG).

Results: According to the findings of this study, it was observed that as the platelet count decreased in newborns of preeclamptic mothers with thrombocytopenia, mean platelet volume (MPV) values increased. In Group A infants, where platelet counts were the lowest, the highest MPV values were observed. The statistically significant decrease in platelet count in Group A was observed ($p<0.01$). However, statistical analysis revealed no significant correlation between MPV and platelet counts. Additionally, no significant difference was detected between the groups in terms of MPV values ($p=0.053$).

Conclusion: This study highlights the potential role of MPV in preeclampsia-related thrombocytopenia. However, the lack of a significant correlation between MPV and platelet count suggests that thrombocytopenia alone is insufficient as an indicator, and platelet function must also be considered. Further prospective studies are needed to confirm these findings.

Keywords: Preeclampsia, mean platelet volume, platelet count.

ÖZ

Amaç: Bu retrospektif çalışma, preeklampsi gibi gebelik hipertansiyonu ve proteinüri ile karakterize bir hastalığı olan annelerin bebeklerinde trombositopeni görülme sıklığını belirlemeyi hedeflemektedir. Ayrıca, trombositopeninin etkisi altında kalan bebeklerin trombosit hacimlerinin (MPV) normal gebeliklerden doğan bebeklerin MPV'si ile karşılaştırılması planlanmaktadır. Bu çalışmanın sonuçları, gebelik sürecinde trombositopeni ile karşılaşan bebeklerin sağlık durumları hakkında fikir verebilecektir. Ayrıca, trombositopeninin MPV ile ilişkisi incelenecek ve bu ilişkinin aydınlatılması, trombositopeninin etkisini daha iyi anlamamızı sağlayacaktır.

Yöntem: Bu araştırma, trombositopeni gelişen ve gelişmeyen preeklamptik annelerin bebekleri ile normal gebeliklerden doğan bebeklerin trombosit sayıları ve MPV'leri arasındaki farkları belirlemeyi amaçlamaktadır. Çalışma için lokal etik kurulun 129 nolu onayı temin edilmiştir. Bu doğrultuda, gebelik yaşı benzer olan 60 yenidoğan bebek, üç gruba ayrılmıştır: trombositopeni gelişen 20 preeklamptik anne bebeği (Grup A), trombositopeni gelişmeyen 20 preeklamptik anne bebeği (Grup B) ve trombositopeni gelişmeyen 20 normal anne bebeği (Grup C). Bu çalışmada, tıbbi kayıtlardan elde edilen hematolojik veriler kullanılarak, bebeklerin doğum ağırlıkları, trombosit sayıları ve MPV'leri, yaşamın ilk 72 saati içindeki süreçlerine göre karşılaştırılmıştır. Bu analizler, trombositopeninin bebeklerin doğum ağırlığı ve trombosit sayısı üzerindeki etkisini belirlemek ve trombositopeni ile MPV arasındaki ilişki incelenmiştir.

Bulgular: Bu çalışmanın bulgularına göre, trombositopeni gelişen preeklamptik annelerin bebeklerinde, trombosit sayısı düştükçe MPV değerlerinin arttığı gözlemlenmiştir. Grup A bebeklerinde, trombosit sayılarının en düşük olduğu ve MPV değerlerinin en yüksek olduğu görülmüştür. Ancak, yapılan istatistiksel analizler sonucunda, MPV ve trombosit sayıları arasında anlamlı bir korelasyon saptanmamıştır. Ayrıca, MPV değerleri açısından gruplar arasında anlamlı bir fark tespit edilememiştir ($p=0.053$).

Sonuç: Preeklamptik annelerin bebeklerinde trombositopeni gelişme olasılığının artmasıyla birlikte, trombositlerin hacimlerinin değişebileceğini ve bu durumun MPV değerlerini etkileyebileceğini göstermektedir. Ancak, MPV ve trombosit sayıları arasındaki korelasyonun bulunmaması, trombositopeni olgusunun tek başına yeterli bir gösterge olmadığını ve trombositlerin fonksiyonlarına da dikkat edilmesi gerektiğini vurgulamaktadır. Bu nedenle, bu bulgular, preeklamptik annelerin bebeklerinde trombositopeni gelişme durumunda, hem trombosit sayılarının hem de fonksiyonlarının takip edilmesinin önemini ortaya koymaktadır. Trombosit hacmindeki artış, trombosit yıkımının bir göstergesi olarak kabul edilirken, azalma ise trombosit yapımındaki yetersizliğin bir göstergesi olarak kabul edilir. Bu çalışmanın sonuçları, preeklamptik anne bebeklerinde görülen trombositopeni durumunun etiyolojisinin sadece trombosit hacmi ile açıklanamayacağını ortaya koymaktadır. Bu durum, trombositopeninin nedeninin sadece trombositlerin azalması veya yıkımı olmayabileceğini düşündürmektedir. Başka faktörler de trombositopeni gelişimine katkıda bulunabilir. Bu nedenle, trombosit hacmi tek başına bir gösterge olarak kullanılamaz ve trombosit yapım ve yıkımının yanı sıra diğer faktörlerin de dikkate alınması gerekmektedir. Sonuç olarak, preeklamptik anne bebeklerinde trombositopeninin nedenleri hakkında daha fazla araştırma yapılması gerekmektedir.

Anahtar Kelimeler: Preeklampsi, orta trombosit hacmi, trombosit sayısı

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INTRODUCTION

Preeclampsia and eclampsia are two conditions that can affect pregnancies, occurring in up to 10% of cases, and are characterized by high blood pressure, proteinuria, and/or edema. The underlying cause of these conditions is still not fully understood (1). Newborns are at risk of preterm birth and fetal growth restriction, which are the most significant risk factors. The mother's blood vessels may have abnormalities due to a lack of proper invasion of the placenta by trophoblastic cells (2). This can lead to damage to the maternal endothelial cells and a decrease in placental perfusion, which can be attributed to various mediators in circulation (2). In normal pregnancies, platelet volume increases as platelet synthesis increases. Changes in platelet function are detected more readily by evaluating platelet volume rather than count (2). The primary pathophysiological processes that occur in preeclampsia involve alterations in circulation, damage to endothelial cells, activation of platelets, and a rise in intravascular thrombin formation (3). Maternal platelet count, volume, and function are known to be affected in preeclampsia, possibly as a result of vascular activation. Thrombocytopenia and neutropenia are common in newborns born to preeclamptic mothers, which may be due to decreased platelet and leukocyte production due to placental insufficiency (4). Early thrombocytopenia in preeclamptic mothers may be caused by placental insufficiency due to maternal hypertension. This study aims to compare the mean platelet volume (MPV) of infants born to mothers with preeclampsia and normal pregnancies, and to examine the correlation between MPV and thrombocytopenia in infants born to mothers with preeclampsia.

MATERIAL AND METHODS

The present study retrospectively evaluated a total of 60 cases, including 20 neonates born to preeclamptic mothers with thrombocytopenia (Group A), 20 neonates born to preeclamptic mothers without thrombocytopenia (Group B), and 20 neonates born to normal mothers without thrombocytopenia (Group C). This retrospective study received approval from the local ethics committee for clinical research at local ethics comitee. (2021-129) Informed consent was not obtained from the patients as it was deemed unnecessary in the retrospective study. The medical records of the mothers of neonates diagnosed with preeclampsia were retrospectively reviewed. The diagnosis of preeclampsia was established based on the history, obstetric examination, and laboratory investigations, and was defined as having a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or a mean arterial pressure >105 mmHg, proteinuria of at least +1 on dipstick analysis or >300 mg in a 24-hour urine collection, after 20 weeks of gestation.

The cases were compared retrospectively in terms of birth weight, platelet counts, and mean platelet volume (MPV). The normal range for MPV was defined as 6.5-11.6 fL. Platelet and MPV values obtained within the first 72 hours after birth were considered for comparisons in all groups. Statistical analysis was carried out using SPSS 10.0 software. The data were presented as mean±SD. One-way ANOVA and Kruskal-Wallis tests were used for comparison among the three groups, followed by Mann-Whitney U test for comparison between two groups if there was significance. The relationship between two continuous variables was determined using Spearman's correlation coefficient. A P-value less than 0.05 was considered statistically significant.

RESULTS

The data in Table 1 displays the average gestational ages, birth weights, platelet counts, and MPV values for groups A, B, and C. A significant statistical distinction was observed between the platelet counts of the three groups, with group A showing a considerably lower platelet count than groups B and C ($p<0.001$). Although group A exhibited a higher MPV value in comparison to the other two groups, no significant difference was detected among the groups ($p=0.053$). Despite a numerical trend of decreasing MPV values with increasing platelet counts, there was no significant correlation found between platelet count and MPV value ($p=0.163$, $R=-0.166$).

Table 1. Comparison of the groups.

	Group A	Group B	Group C	P*
Gestational Age› (weeks)	34.2±2.34	35.2±2.43	33.5±3.4	0,08
Birth Weight	1762±597	2176±759	2181±653	0,09
Platelet (thousand/mm^3)	112±27	248±103	274±107	<0,01
MPV (fL)β	7,96±0,78	7,81±0,64	7,41±0,66	0,053

* Mean±SD
** p<0,05 significance

DICUSSSION

Preeclampsia is a prevalent complication during pregnancy that results in various symptoms due to impaired placental perfusion and maternal endothelial cell damage by circulating mediators(5). Thrombocytopenia is one such symptom that may arise due to vasoconstriction and decidual thrombosis in uteroplacental vessels or reduced production of growth factors such as VEGF and PlGF, which normally aid in megakaryocyte maturation during pregnancy but are diminished in preeclampsia.(5) In neonates,

thrombocytopenia may result from placental insufficiency, maternal vascular dysfunction, or decreased megakaryocyte production. Additionally, increased platelet destruction due to oxidative stress and inflammatory mediators may play a role.

Historically, an increase in mean platelet volume (MPV) has been associated with heightened platelet production. Elevated MPV levels have been linked to increased platelet production in normal pregnancies (6). However, studies investigating platelet counts and MPV values in preeclamptic versus normal pregnancies have produced varied outcomes. There is some variation among research findings regarding platelet counts and MPV values in women with preeclampsia when compared to control groups (7). Certain studies report no significant statistical differences in these measures, while others show lower platelet counts and higher MPV values in women with preeclampsia (8,9). Despite being a well-known complication of preeclamptic pregnancies, the exact cause of thrombocytopenia remains a mystery. Additionally, the underlying cause of thrombocytopenia in both preeclamptic mothers and their infants is not fully understood (10). Only three studies to date have attempted to investigate the cause of low platelet counts in these infants. However, no thrombocytopenia was found in infants with abnormal test results. The relationship between thrombocytopenia and mean platelet volume (MPV) in preeclamptic mother and baby has yet to be studied in medical literature (11,12). Therefore, we aimed to investigate whether MPV could serve as an indicator of thrombocytopenia in this population. Our study is the first to explore this relationship. Although we observed that the MPV value was higher in preeclamptic mother and baby with thrombocytopenia compared to those without thrombocytopenia and healthy babies, the difference was not statistically significant (p: 0.053). Interestingly, we noted that as the platelet count decreased among the groups, the MPV value increased. Although the results did not reach statistical significance, the highest MPV value was found in thrombocytopenic babies, and the increase in MPV as the platelet count decreased among the groups suggests that thrombocytopenia in preeclamptic mother and baby may be more closely associated with destruction.

CONCLUSION

In order to gain a deeper understanding of the mechanisms underlying thrombocytopenia in preeclamptic mothers and their infants, it may be beneficial to conduct a prospective study that includes additional variables. For instance, thrombopoietin values in preeclamptic mothers and their platelet counts, as well as MPV and thrombopoietin values, could be assessed in a prospective study. By doing so, we could potentially shed light on the causes of thrombocytopenia in preeclamptic pregnancies, which in turn could inform the development of more effective preventative and treatment strategies for mothers and their infants. This study aimed to explore MPV as a potential marker of thrombocytopenia in preeclamptic pregnancies. The findings suggest that while MPV values increase with thrombocytopenia, additional factors such as platelet function and destruction mechanisms need further investigation. This contributes to a better understanding of platelet dynamics in preeclampsia. While this study was conducted retrospectively by analyzing file data, a prospective study that includes a broader range of variables could provide more detailed insights into this complex condition.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Smoking in pregnancy: Can the first-trimester serum inflammatory markers predict adverse obstetric and neonatal outcomes?

Gebelikte sigara içiciliği: İlk trimester serum inflamatuar belirteçleri olumsuz obstetrik ve yenidoğan sonuçlarını öngörebilir mi?

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ABSTRACT

Aim: To investigate obstetric complications in pregnant women who smoke and to evaluate whether first-trimester systemic inflammatory indices can predict adverse obstetric and neonatal outcomes

Materials and Method: This retrospective study included 43 pregnant women aged between 18 and 45 years who had been smoking since prior to conception, and 44 healthy pregnant women, conducted between 2024 and 2025. Participants' demographic characteristics, obstetric outcomes (birth weight, gestational age at delivery), and neonatal outcomes (APGAR scores, NICU admission) and obstetric complications were assessed. First-trimester neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII: NLR × platelet count), systemic inflammation response index (SIRI: NLR × monocyte count), aggregate index of systemic inflammation (AISI: NLR × platelet count × monocyte count), and platelet-to-lymphocyte ratio (PLR) were calculated. Receiver operating characteristic (ROC) curves were generated to evaluate the predictive value of these markers for adverse obstetric and neonatal outcomes.

Results: SII, SIRI, AISI, and NLR levels were significantly higher in the smoking group compared to controls. Pregnant women who smoked had higher rates of emergency cesarean section, adverse obstetric outcomes, and NICU admissions. ROC analysis showed that first-trimester inflammatory markers significantly predicted adverse outcomes when all participants were analyzed together; however, these markers did not demonstrate predictive value within the smoking group alone.

Conclusion: Adverse obstetric outcomes, increased NICU admissions, and elevated serum inflammatory markers were observed in pregnant women who smoked. However, these markers were found to be insufficient in predicting adverse outcomes.

Keywords: Smoking, pregnancy, inflammatory markers, obstetric complications, NICU

ÖZ

Amaç: Sigara içen gebe kadınlarla sigara içmeyenler arasında sistemik inflamatuar indekslerin karşılaştırılması ve bu indekslerin olumsuz obstetrik ve yenidoğan sonuçlarını öngörmesini değerlendirmek

Gereç ve Yöntemler: Bu retrospektif gözlemsel bir çalışma olup 2024-2025 yılı arasında 18-45 yaş aralığında gebelik öncesinden itibaren sigara kullanan 43 gebe ile 44 sigara kullanmayan gebeyi içermektedir. Katılımcıların demografik özellikleri, obstetrik sonuçları (doğum ağırlığı, doğumdaki gebelik yaşı), yenidoğan sonuçları (APGAR skorları, Yenidoğan Yoğun Bakım Ünitesi'ne (YYBU) yatış ve obstetrik komplikasyonları değerlendirilmiştir. İlk trimester nötrofil-lenfosit oranı (NLR), sistemik immün-inflamasyon indeksi (SII: NLR × trombosit sayısı), sistemik inflamasyon yanıt indeksi (SIRI: NLR × monosit sayısı), sistemik inflamasyonun toplam indeksi (AISI: NLR × trombosit sayısı × monosit sayısı) ve trombosit-lenfosit oranı (PLR) hesaplandı. Olumsuz obstetrik ve noenatal outcome öngörü değerini değerlendirmek için Alıcı İşletim Karakteristiği (ROC) eğrileri oluşturuldu.

Bulgular: SII, SIRI, AISI ve NLR düzeyleri, kontrol grubuna kıyasla sigara içen grupta önemli ölçüde daha yüksekti. Sigara içen hamile kadınlarda acil sezaryen oranı, olumsuz obstetrik sonuçlar ve YYBU yatış daha yüksekti. ROC analizi, tüm katılımcılar birlikte analiz edildiğinde, ilk trimester inflamatuar belirteçlerinin olumsuz sonuçları istatistiksel anlamlı öngördüğünü gösterdi; ancak, bu belirteçler sigara içen grup içinde öngörü değeri göstermedi.

Sonuç: Sigara içen hamile kadınlarda olumsuz obstetrik sonuçlar, artan YYBU ihtiyacı ve yüksek serum inflamatuar belirteçleri gözlendi. Ancak bu markerlar olumsuz sonuçları öngörmede yetersiz kalmıştır.

Anahtar Kelimeler: Sigara içiciliği, hamilelik, inflamatuar belirteçler, obstetrik komplikasyonlar, NICU

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INTRODUCTION

Smoking, tobacco use, and nicotine addiction continue to cause of morbidity and mortality worldwide, accounting for over 7 million deaths annually (1). As a global public health concern, smoking—especially when initiated at a young age—poses significant risks for pregnancy and neonatal health. Infants born to mothers who smoke are at increased risk for fetal anomalies, low birth weight, placental abruption, and stillbirth, while long-term complications include asthma, obesity, and neurodevelopmental disorders (2). Harmful substances such as nicotine present in cigarette smoke can cross the placenta and adversely affect fetal health through intrauterine exposure (3).

Systemic inflammatory indices can be easily calculated from complete blood count (CBC) parameters and, as shown in previous studies, have been useful in predicting prognosis in conditions such as cancer, diabetes, chronic inflammatory, and autoimmune diseases. In this study, we aimed to investigate obstetric complications in pregnant smokers and evaluate whether first-trimester systemic inflammatory indices could predict adverse obstetric and neonatal outcomes.

MATERIALS AND METHODS

This retrospective observational study included 43 pregnant women aged 18–45 years who had been smoking since the pre-pregnancy period and gave birth at the hospital between 2024 and 2025, along with 44 healthy pregnant women as controls. The study was approved by the Clinical Research Ethics Committee of Uşak University (Ethics No: 715-715-19, Date: 12.06.2025) and was conducted in accordance with the Declaration of Helsinki. Since the data were anonymised and collected retrospectively, a waiver of written informed consent was granted. Exclusion criteria included multiple pregnancy, anemia, hematological disorders, any inflammatory disease, history of cancer, infectious conditions, and fetal chromosomal or structural anomalies.

During the study period, a total of 2,119 deliveries were recorded at our hospital. However, only 43 pregnant women were identified who had first-trimester CBC results available in the hospital information system and who had documented history of smoking from the pre-pregnancy period throughout their entire pregnancy. These women also received antenatal care and delivered at the same hospital. The control group consisted of 44 randomly selected healthy pregnant women with similar demographic characteristics who were recorded in the hospital system as non-smokers (every second eligible patient).

Demographic characteristics of the participants, as well as obstetric outcomes such as birth weight and gestational age at delivery, and neonatal outcomes including APGAR scores, need for neonatal intensive care unit (NICU) admission, and obstetric complications, were evaluated. Adverse obstetric complications were defined as gestational diabetes, hypertensive diseases of pregnancy, preterm birth, fetal growth restriction, and oligohydramnios. From routine first-trimester (1st–14th gestational week) CBC parameters, the following systemic inflammatory markers were calculated: neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII: NLR × platelet count), systemic inflammation response index (SIRI: NLR × monocyte count), aggregate index of systemic inflammation (AISI: NLR × platelet count × monocyte count), and platelet-to-lymphocyte ratio (PLR). These markers were analyzed to investigate their predictive value for adverse obstetric and neonatal outcomes.

Statistical analysis was performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). The normality of variables was assessed using both the Shapiro-Wilk and Kolmogorov-Smirnov tests. Variables that met the assumptions of normality were analyzed using parametric tests, whereas variables that violated normality assumptions were analyzed using non-parametric tests. Non-normally distributed data were presented as median and interquartile range (IQR), while categorical variables were summarized as number (n) and percentage (%). For comparisons between two independent groups, the Mann-Whitney U test was used for non-parametric variables, and the independent samples t-test was used for normally distributed variables. A p-value < 0.05 was considered statistically significant.

Receiver Operating Characteristic (ROC) curves were constructed to evaluate the predictive value of systemic inflammatory indices for adverse obstetric and neonatal outcomes. The area under the curve (AUC) values were calculated using standard methods and presented as AUC ROC (95% confidence interval). Optimal cut-off values for the inflammatory indices were determined using the Youden Index. The required sample size was calculated using G*Power, based on SIRI values reported in a previous study; a minimum of 26 participants per group was required to achieve 90% power with a 5% margin of error (4).

RESULTS

Table 1 presents the baseline characteristics of both groups. Although the birth weight of newborns of mothers who smoked was lower, this difference was not statistically significant. The emergency cesarean sections and obstetric complications were

Table 1. Baseline characteristics of participants

	Smoking group (n=43)	Non-smoking group (n=44)	P value
Maternal age (years)	27 (7)	28 (8)	0.189
Pre-gestastational BMI (kg/m²)	28.6 (8.5)	27.5 (3.9)	0.375
Nulliparity (n, %)	16 (37.2)	20 (45.5)	0.435
Female fetal gender (n, %)	24 (55.8)	23 (52.2)	0.395
Gestational age at birth (week)	38 (3)	38 (1)	0.468
Birth weight (gram)	3000 (483)	3180 (613)	0.872
Emergency cesarean section (n, %)	8 (18.6)	2 (0.04)	0.040
APGAR score at 1st minute	9 (1)	9 (0)	0.681
APGAR score at 5th minute	10 (1)	10 (1)	0.759
NICU admission (n, %)	12 (27.9)	2 (0.04)	<0.001
Adverse perinatal outcomes (n, %)	7 (16.2)	16 (36.3)	0.024

Note: Data are presented as number (%), and median (interquartile range) with 95% confidence intervals for non-parametric data. Groups were compared using the Mann–Whitney U test. P-values < 0.05 were considered statistically significant.
BMI, body mass index; NICU, neonatal intensive care unit

Table 2. First-trimester serum inflammatory parameters in both groups

	Smoking group (n=43)	Non-smoking group (n=44)	P value
WBC (10^9 /L)	10.5 (4.9)	7.8 (2.7)	<0.001
Neutrophil (10^9 /L)	8.1 (4.4)	5.6 (2.4)	<0.001
Lymphocyte (10^9 /L)	1.9 (1)	1.8 (0.9)	0.606
Monocyte (10^9 /L)	0.5 (0.2)	0.4 (0.1)	0.602
Eosinophil (10^9 /L)	0.07 (0.1)	0.1 (0.1)	0.904
Basophils (10^9 /L)	0.02 (0.01)	0.02 (0.02)	0.677
SII	1019.4 (574)	737.7 (565)	0.018
SIRI	2.21 (1.1)	1.13 (1.2)	0.008
AISI	548.4 (341)	305.6 (321)	0.049
NLR	4.1 (1.8)	2.9 (2.3)	0.004
PLR	140.8 (111)	142.6 (67.8)	0.809

Note: Data are presented as number (%), and median (interquartile range) with 95% confidence intervals for non-parametric data. Groups were compared using the Mann–Whitney U test. P-values < 0.05 were considered statistically significant.
AISI, aggregated index of systemic inflammation; NLR, neutrophil-to-lymphocyte ratio; SII, systemic inflammation index; SIRI, systemicinflammatory response index, PLR,platelet-to- lymphocyte ratio

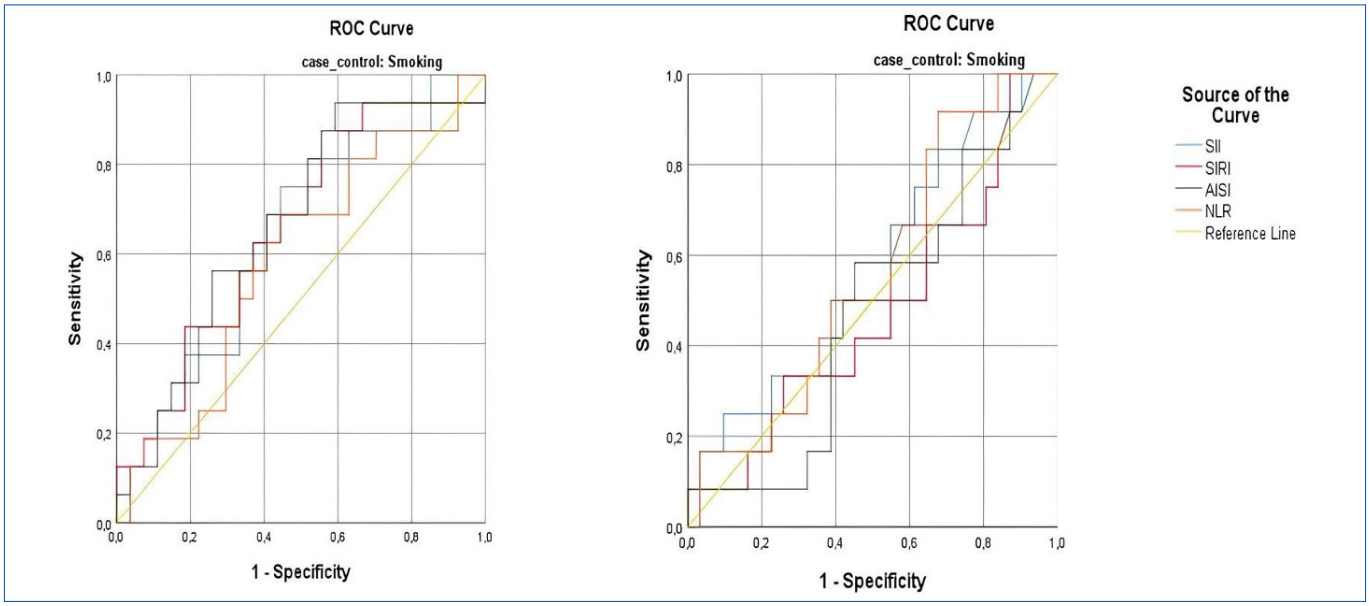

Figure 1. ROC analysis of inflammatory markers predicting adverse obstetric outcomes (left) and NICU admission (right) in pregnant smokers

Table 3. The ROC curve analysis for the performance of first trimester inflammatory markers in predicting adverse obstetric outcomes and NICU admission in all participants

Variable	Cut-off	AUC	p value	95% CI	Sensitivity	Specificity
Adverse obstetric						
SII	1007.7	0.730	0.001	0,609-0,850	%69.6	%70.3
SIRI	1.86	0.730	0.001	0,608-0,853	%65.2	%65.6
AISI	502.4	0.736	0.001	0,614-0,859	%65.2	%64.1
NLR	3.82	0.676	0.013	0,547-0,805	%65.2	%65.6
NICU						
SII	976.3	0.722	0.009	0,590-0,853	%71.4	%63
SIRI	1.83	0.688	0.026	0,550-0,827	%71.4	%61.6
AISI	552.5	0.669	0.046	0,528-0,809	%64.3	%69.9
NLR	3.8	0.727	0.007	0,604-0,849	%64.3	%61.6

Note: P-values < 0.05 were considered statistically significant.
AUC, area under the curve; NICU, neonatal intensive care unit ; AISI, aggregated index of systemic inflammation; NLR, neutrophil-to-lymphocyte ratio; SII, systemic inflammation index; SIRI, systemic inflammatory response index

statistically significantly higher in the smoking group. The most common complications among smoking mothers were hypertensive disorders of pregnancy (n=4), preterm labor (n=4), and fetal growth restriction (n=4), whereas the most frequent complication in the healthy group was preterm labor (n=4).

Table 2 displays the serum systemic inflammatory parameters of the study and control groups. Inflammatory markers were significantly higher in the smoking group. Figure 1 illustrates the ROC analysis of SII, SIRI, AISI, and NLR for predicting adverse obstetric outcomes and NICU requirement in the smoking group. Although the inflammatory markers were elevated in the smoking group, they did not maintain statistical significance in predicting adverse obstetric and neonatal outcomes.

Table 3 shows the analysis of all participants' serum inflammatory markers for predicting poor obstetric outcomes and NICU admission. SII, SIRI, AISI, and NLR were found to be statistically significant predictors of adverse outcomes. The optimal cut-off values for the inflammatory indices, determined using the Youden Index, are provided in Table 3.

DISCUSSION

Smoking increases reactive oxygen species and proinflammatory mediators, creating a state of chronic inflammation that may lead to endothelial damage and organ dysfunction. Furthermore, maternal smoking is thought to cause epigenetic alterations in the fetus through DNA methylation and histone modification (5). A meta-analysis revealed that smoking could influence the maternal hypothalamic-pituitary-adrenal (HPA) axis, potentially affecting fetal programming and elevating cortisol levels during early childhood (6). A previous large-scale study found that smokers had significantly higher levels of cytokines such as IL-6 and TNF, matrix metalloproteinases involved in vascular remodeling, and the systemic inflammatory marker C-reactive protein (7).

Despite its role in low-grade inflammation, the effects of habitual smoking remain controversial. One study found a blunted HPA response in regular smokers subjected to psychosocial stress testing (8), while another reported that chronic nicotine exposure leads to neuroadaptation and desensitization of acetylcholine receptors (9). This phenomenon, referred to as the "smoker's paradox," suggests that the mechanisms by which smoking affects metabolism remain unclear.

In our study, we observed elevated systemic inflammatory parameters in mothers who smoked prior to and during pregnancy. Although inflammatory markers were statistically significant predictors of obstetric complications and NICU admission among all participants, they failed to predict adverse perinatal outcomes specifically within the smoking group. These findings suggest that habitual smoking may mask or suppress the predictive performance of inflammatory markers.

Maternal smoking is a significant risk factor that negatively affects both maternal health and fetal development. The toxic substances in cigarettes can lead to placental dysfunction, reduce uteroplacental blood flow, and cause adverse fetal effects. In our study, consistent with previous findings, smoking was associated with adverse perinatal outcomes such as intrauterine growth restriction, preterm birth, and low birth weight (10).

In this study, an increase in NICU admissions was observed among infants of smoking mothers, while APGAR scores were similar between the groups. A large cohort study conducted in Australia reported a similar rise in NICU admissions among babies of smoking mothers, along with an increased likelihood of maternal hypertension (11). A population-based study from Macedonia also identified smoking as a significant risk factor for fetal growth restriction (12). There are also various studies on smoking and how it affects the APGAR score and NICU requirements. Previous research has shown that neonates of smoking mothers had lower first-minute APGAR scores, but similar fifth-minute APGAR scores and NICU admission rates compared to non-smokers (13, 14).

Additionally, the fact that not all infants born to smoking mothers exhibit growth restriction suggests that epigenetic factors may influence susceptibility to the harmful effects of smoking (5).

One of the earliest studies investigating CBC parameters in smokers was conducted by Winkel et al., which demonstrated that smoking leads to a significant decrease in eosinophil count and a delayed increase in neutrophil count (15). Interestingly, this study also showed that while smoking initially caused an increase followed by a decrease in lymphocyte count, lymphocyte levels during smoking days remained lower than those on non-smoking days. According to a study by Tulgar et al., smokers exhibited increased white blood cell counts, neutrophil counts, and NLR levels (16). In subgroup analyses, a linear correlation was found between NLR and both the average age and pack-year history of the smokers. In another recent study, although heavy smoking men showed increased white blood cell and neutrophil counts, the NLR did not differ significantly between smokers and non-smokers (17).

Systemic inflammatory markers calculated from complete blood count—such as SIRI, SII, NLR, and AISI—have recently been investigated in obstetric practice, particularly for their predictive potential in adverse pregnancy outcomes like preeclampsia, preterm birth, and NICU admission. In a large-scale study evaluating inflammatory markers and preterm labor, first-trimester SIRI, SII, and NLR levels were found to be elevated in the preterm birth group, and these markers retained statistical significance in both univariate and multivariate analyses (18). However, the relationship between these markers and prognosis has yielded variable results in the literature.

In a previous prospective study, first-trimester SII and SIRI levels were found to be elevated in women with gestational diabetes (19). Although these markers were significant in predicting gestational diabetes, they were not sufficient to predict the need for insulin therapy. Another study found that AISI was statistically significant in predicting gestational diabetes (20). In a study including pregnant women with intrahepatic cholestasis of pregnancy (ICP) inflammatory markers were evaluated across all three trimesters (21). While first-trimester SIRI levels were similar between ICP and healthy groups, SIRI was significantly higher in the ICP group during later trimesters. However, regression analysis showed that this marker was not significant in predicting adverse obstetric outcomes. Another study found that although SII and NLR levels were significantly higher in fetal growth restriction cases, they were not associated with neonatal outcomes (22).

In our study, although serum inflammatory markers were elevated in pregnant smokers, their inability to predict adverse outcomes and need for NICU admission may be related to the limited number of participants. Additionally, the impact of smoking on hematological parameters warrants further clarification through larger-scale studies in the future.

CONCLUSION

It is evident that the low-grade chronic inflammation caused by smoking, along with its harmful constituents, poses significant risks to both maternal and fetal health. In this study, pregnant smokers were found to have higher rates of adverse obstetric outcomes, increased NICU admissions, and elevated serum inflammatory markers. However, these markers proved insufficient in predicting adverse outcomes.

Conflicts of Interest
The authors declare no conflict of interest.

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Authors' Contributions
B.A.A.: Writing, data curation, original draft. E.B.: Data curation, writing – review and editing.

Availability of Data and Materials
The data supporting the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Vitamin D status in 187,728 women in a tertiary hospital: effects of age and season

Üçüncü basamak bir hastanedeki 187.728 kadında D vitamini durumu: yaş ve mevsimin etkileri

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ABSTRACT

Aim: The aim of our study was to determine whether women admitted to our hospital for any reason have 25-hydroxyvitamin D (25(OH)D) deficiency and to determine whether there is a difference between serum 25(OH)D levels according to age and seasons.

Materials and Methods: 187,728 female patients admitted to our hospital in winter and summer between 2020 and 2024 were included in the study. Ages, serum 25(OH)D levels, month and season of the examinations were recorded. Serum 25(OH)D levels: >30 ng/ml was considered adequate, 20-30 ng/ml vitamin D deficiency, <20 ng/ml vitamin D deficiency, 11-20 ng/ml mild vitamin D deficiency, 5-10 ng/ml moderate vitamin D deficiency, <5 ng/ml severe vitamin D deficiency. SPSS 28.0 programme was used for statistical analysis and p<0,05 was considered significant.

Results: In this study, serum 25(OH)D levels of 187,728 patients aged 10-99 years were evaluated and the mean level was 18,7±11,9 (3-100) ng/ml. Serum 25(OH)D level was found to be adequate in 13,6%, inadequate in 24,1%, mildly deficient in 37,5%, moderately deficient in 21,3%, and severely deficient in 3,6% of the patients. Serum 25(OH)D level was significantly (p<0,05) higher in summer-autumn season than in winter-spring season.

Conclusion: 25(OH)D deficiency is a common problem in our country as well as in the world. Serum vitamin D levels are affected by seasonal transitions and may be lower in winter. Although routine screening of serum vitamin D levels is not recommended, it may be recommended to develop strategies to improve vitamin D status in all age groups as in pregnant women.

Keywords: Vitamin D, age, season

ÖZ

Amaç: Çalışmamızın amacı, hastanemize herhangi bir sebeple başvuran kadınların serum 25-hidroksi vitamin D (25(OH)D) eksikliği olup olmadığını belirlemek, yaşa ve mevsimlere göre serum 25(OH)D düzeyleri arasında fark olup olmadığını tespit etmektir.

Gereç ve Yöntemler: 2020-2024 yılları arasında kış ve yaz mevsimi aylarında hastanemize başvuran 187.728 kadın hasta çalışmaya alındı. Olguların yaşları, 25(OH)D vitamin düzeyleri, tetkiklerin yapıldığı ay ve mevsim kayıt edildi. Serum 25(OH)D düzeyi: >30 ng/ml yeterli, 20-30 ng/ml vitamin D yetersizliği, <20 ng/ml vitamin D eksikliği, 11-20 ng/ml hafif vitamin D eksikliği, 5-10 ng/ml orta vitamin D eksikliği, <5 ng/ml ciddi vitamin D eksikliği olarak kabul edildi. İstatistiksel analiz için SPSS 28.0 programı kullanıldı ve p<0,05 anlamlı kabul edildi.

Bulgular: Bu çalışmada, 10-99 yaş aralığında toplam 187.728 hastanın serum 25(OH)D düzeyleri değerlendirildi ve ortalama düzey 18.7±11.9 (3-100) ng/ml olarak saptandı. Serum 25(OH)D düzeyi olguların %13.6'sında yeterli, %24.1'inde yetersiz, %37.5'unda hafif düzeyde eksiklik, %21.3'ünde orta düzeyde eksiklik, %3.6'sında ciddi düzeyde eksiklik olarak saptandı. Yaz-sonbahar mevsiminde serum 25(OH)D değeri kış-ilkbahar mevsiminden anlamlı (p<0.05) olarak daha yüksek saptandı.

Sonuç: 25(OH)D eksikliği dünyada olduğu gibi ülkemizde de sık görülen bir sorun olarak karşımıza çıkmaktadır. Serum vitamin D düzeyleri mevsimsel geçişlerden etkilenip kışın daha düşük seviyelerde izlenebilir. Serum vitamin D düzeylerinin rutin olarak taranması önerilmemekle beraber gebelerde olduğu gibi tüm yaş gruplarında da D vitamini durumunu iyileştirmeye yönelik stratejilerin geliştirilmesi önerilebilir.

Anahtar Kelimeler: D vitamini, yaş, mevsim

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INTRODUCTION

Vitamin D is a fat soluble steroid hormone (1,2). Synthesis in the skin is the most important source of vitamin D received by diet or synthesized in skin is in inactive form and enzymatically should be transformed into its active metabolites. It is transformed into 25- hydroxyvitamin D (25(OH)D) in the liver and subsequently into active form 1,25 dihydroxyvitamin D in the kidney. Vitamin D and its metabolites play an important role in calcium hemostasis and bone metabolism. In addition to its effects on bone metabolism, vitamin D also plays an important part in immune system by acting like a cytokine in the body (3).

In the evaluation of vitamin D levels, serum 25(OH)D level of >30 ng/ml is considered sufficient, 20-30 ng/ml insufficient and <20 ng/ml deficient (<5 ng/ml severe, 5-10 ng/ml moderate, 10-20 ng/ml mild vitamin D deficiency) (2).

In recent years, deficiency of Vitamin D has been established to be associated with many diseases such as cardiovascular disorders, metabolic syndrome, autoimmune diseases and infections (4,5). However, the mechanisms behind these associations still remain to be elucidated and the role of vitamin D supplements in preventing or managing these diseases is not still clear.

The seasonal changes in the levels of vitamin D have been commonly described (6-9). Deficiency of vitamin D may arise during winter months with the reduction in duration of exposure to sunlight. It has been established that during winter and spring months, there is vitamin D deficiency in over 50% and severe vitamin D deficiency in 16% of adult population (10). In a study conducted by Ucar et al in the region of Ankara, deficiency and insufficiency of vitamin D was detected in 51,8% and 20,7% of subjects respectively (11). Ever since emphasis was placed on protection from harmful effects of sun, the prevalence of vitamin D deficiency has increased. Australia is a country where skin cancer is common and has become the country with highest prevalence of vitamin D deficiency owing to excessive measures for protection from sun exposure (12).

Although it is known that seasonal changes influence vitamin D levels, most of the studies on vitamin D do not state the season when blood sample is drawn and when we compare values from samples drawn at different seasons, contradictory results are obtained. The aim of the present study is to determine whether there is deficiency of vitamin D in women referring to our hospital for any cause and if there is difference in vitamin D levels between different ages and seasons.

MATERIALS AND METHODS

Following the approval of ethics committee, (24.04.2024 dated and 2024/010.99/3/6 no), of cases between the ages of 10-99 referring to our hospital between 2020-2024, those whose serum 25(OH)D levels were measured were investigated retrospectively. In those whose serum 25(OH)D level was measured more than once, only the first results were considered in evaluation. Plasma 25(OH)D levels were measured with chemiluminesence immunoassay method. Overall 187,728 cases were included in the study and

Table 1. The age, serum 25-hydroxyvitamin D concentrations, and seasonal distribution of the cases

		Min	-	Max	Median	Mean±SD/n-%		
Age		13.2	-	99.9	46.2	45.9	±	16.2
Age distribution	10-20					11748		6.3%
	20-30					24894		13.3%
	30-40					31625		16.8%
	40-50					42772		22.8%
	50-60					38908		20.7%
	60-70					24451		13.0%
	70-80					10374		5.5%
	≥ 80					2951		1.6%
Serum 25 (OH)D levels		3.0	-	210.5	16.4	18.7	±	11.9
Serum 25 (OH)D levels	0-5					6680		3.6%
	5-10					40053		21.3%
	10-20					70329		37.5%
	20-30					45182		24.1%
	≥31					25479		13.6%
Season	Winter					52301		27.9%
	Spring					41388		22.0%
	Summer					43743		23.3%
	Autumn					50291		26.8%

Table 2. Age-related distribution of serum 25-hydroxyvitamin D levels in the cases

	Serum 25 (OH) D-Vitamin																	
								0-5		5-10		10-20		20-30		≥31	
	Min-Max			Median	Mean.±SD			n	%	n	%	n	%	n	%	n	%
Age																	
10-20	3.0	-	200.0	11.8	13.8	±	8.6	730	10.9%	3873	9.7%	5052	7.2%	1645	3.6%	448	1.8%
20-30	3.0	-	200.0	12.5	14.9	±	9.5	1242	18.6%	7781	19.4%	10252	14.6%	4215	9.3%	1404	5.5%
30-40	3.0	-	200.0	14.4	16.8	±	10.7	1301	19.5%	8017	20.0%	12918	18.4%	6542	14.5%	2847	11.2%
40-50	3.0	-	210.5	16.4	18.5	±	11.5	1446	21.6%	9038	22.6%	16473	23.4%	10665	23.6%	5150	20.2%
50-60	3.0	-	209.3	18.9	20.8	±	12.1	955	14.3%	6094	15.2%	13877	19.7%	11099	24.6%	6883	27.0%
60-70	3.0	-	200.0	20.6	22.4	±	12.9	519	7.8%	3314	8.3%	7970	11.3%	7240	16.0%	5408	21.2%
70-80	3.0	-	210.5	21.3	23.1	±	14.1	320	4.8%	1435	3.6%	3037	4.3%	2995	6.6%	2587	10.2%
≥ 80	3.0	-	112.9	20.8	22.6	±	14.7	167	2.5%	501	1.3%	750	1.1%	781	1.7%	752	3.0%

Table 3. Age-related comparison of serum 25-hydroxyvitamin D levels

	Serum 25 OH D-Vitamin							p
	Min-Max			Median	Mean.±SD			
Age								
[1] 10-30	3.0	-	200.0	12.3 [2,3]	14.5	±	9.3	**0.000**[K]
[2] 30-50	3.0	-	210.5	15.5 [3]	17.7	±	11.2	
[3] ≥50	3.0	-	210.5	19.8	21.7	±	12.8	

[K] Kruskal-wallis (Mann-whitney u test)
[1] Significant difference compared with the 30–50 years age group (p<0.05) and with the [2]≥50 years age group (p<0.05)

Table 4. Seasonal variation of serum 25-hydroxyvitamin D levels

	Serum 25 (OH) D-Vitamin																	
								0-5		5-10		10-20		20-30		≥31	
	Min-Max			Median	Ort.±SD			n	%	n	%	n	%	n	%	n	%
Season																	
Winter	3.0	-	202.6	15.2	17.9	±	12.0	2622	39.3%	12781	31.9%	18714	26.6%	11387	25.2%	6797	26.7%
Spring	3.0	-	210.5	14.7	17.7	±	12.2	2040	30.5%	10807	27.0%	14647	20.8%	8676	19.2%	5218	20.5%
Summer	3.0	-	200.0	17.7	19.8	±	11.8	837	12.5%	7457	18.6%	17340	24.7%	11691	25.9%	6418	25.2%
Autumn	3.0	-	209.3	17.5	19.4	±	11.4	1181	17.7%	9008	22.5%	19628	27.9%	13428	29.7%	7046	27.7%

Table 5. Seasonal comparison of serum 25-hydroxyvitamin D levels

	Serum 25 OH D-Vitamin							p
	Min-Max			Median	Mean±SD			
Season								
Winter - Spring	3.0	-	202.6	15.2	17.9	±	12.0	**0.000**[m]
Summer - Autumn	3.0	-	200.0	17.7	19.8	±	11.8	

[m] Mann-whitney u test

serum 25(OH)D level of >30 ng/ml was considered as sufficient, 20-30 ng/ml vitamin D insufficiency and 11-20 ng/ml mild, 5-10 ng/ml moderate and <5 ng/ml severe vitamin D deficiency. The ages and 25(OH)D levels of the cases, and the month and season when the samples were obtained were recorded.

In the analysis of data, SPSS 28.0 program was used. In desriptive statistics, mean, standard deviation, median, lowest, highest frequency and percentage were used. The distribution of variables was measured with Kolmogorov Smirnov and Shapiro-wilk tests. In the analysis of quantitative independent data, Kruskal-Wallis and Mann-Whitney U tests were used.

RESULTS

In the present study, serum 25(OH)D levels of overall 187,728 patients between the ages of 10-99 were evaluated and mean level was found to be 18,7±11,9 (3-100) ng/ml. Mean age, age distribution, mean serum 25(OH)D values and their distribution and seasonal distribution are illustrated in Table 1.

Serum 25(OH)D levels were found to be sufficent in 13,6% of cases, insufficient in 24,1%, mildly deficient in 37,5%, moderately deficient in 21,3% and severely deficient in 3,6%.

Distribution of serum 25(OH)D levels are illustrated in Table 2.

In age ≥50 group, serum 25(OH)D values were significantly higher than those in ($p<0,05$) in 10-30 and 30-50 age groups. In 30-50 age group, serum 25(OH)D level were found to be significantly higher than those in 10-30 age group ($p<0,05$) (Table 3).

Mean serum 25(OH)D values in summer-autumn seasons were found to be significantly higher than those in winter-spring seasons ($p<0,05$) (Table 4) (Table 5).

DISCUSSION

Although it is known that seasonal changes influence vitamin D levels, in many studies on Vitamin D, it is not stated when the blood sample was drawn. The aim of the present study was to determine vitamin D levels in women presenting to our hospital and to establish if there was a change in vitamin D levels between different ages and seasons. As demonstrated by various studies, vitamin D deficiency is an important health problem all over the World (13-16). It has been shown that vitamin D deficiency has a high prevalence not only in high risk groups, but also in Middle East and Asian countries in particular (17). Nutritional patterns, environmental factors, ethnic characteristics, style of dressing and inadequate exposure to sunlight may be implicated for this deficiency.

Debates are still ongoing on optimal vitamin D levels. Generally, serum concentration lower than 20 ng/ml is considered as vitamin D deficiency (2,18). The prevalence of vitamin D deficiency varies between 7% and 80% according to differing definitions of deficiency (19). In a sytematic review including 195 studies form 44 countries, it has been shown that vitamin D levels vary considerably between different studies and that vitamin D levels are found to be under 50 ng/ml in 37,3% of the studies (20). In the study of Ogus et al carried out between January-December with 3242 cases, mean value of vitamin D was found to be 22,80±13,27 ng/ml and vitamin D deficiency was reported in 47%, vitamin insufficiency in 28% and normal vitamin D levels in 25% of cases (21). In the study of Mansoor et al in Karachi region, mean vitamin D level was found to be 41,1±9,6 nmol/l (16,44 ng/ml) and vitamin D deficiency was detected in 69,9% of and vitamin D insufficiency in 21,1% of cases (22). In the present study, serum 25(OH)D level was found to be sufficient in 13,6% of cases, insufficient in 24,1%, mildly deficient in 37,5%, moderately deficient in 21,3% and severely deficient in 3,6%.

There are studies indicating that vitamin D levels change with seassons and deficiency becomes more prevalent especially in winter months (23-26). In the study of Colak et al, mean level of serum vitamin D levels was found to be 18,05±13,81 (3-100) ng/ml, the prevalence of deficiency and insufficiency of vitamin D being 67,10% and 83,90% respectively. In autumn and winter months, the levels of vitamin D were found to be similar and lower compared to those in spring and summer months (27). In study of Hekimsoy et al carried out in Aegean region, mean vitamin D levels in 391 patients over the age of 20 were found to be 16,90±13,09 ng/ml in winter months and the distribution of values were as follows: under 20 ng/ml in 74,90% of cases between 20-30 ng/ml in 13,80% and over 30 ng/ml in 11,30% (28). In the study of Ucar et al in the region of Ankara with 513 cases, it was reported that vitamin D deficiency was most marked in spring months and that the rate of vitamin D deficiency was 51,8% and the rate of insufficiency was 20,7% (11). In the study of Grygorieva et al on 7418 cases in Ukraine, serum vitamin D levels were reported ot be highest in autumn and lowest in spring (29). Similarly, in the study of Osredkar et al in Slovenia, vitamin D levels were were found to be significantly lower in winter months than in summer months (30). In the study of Muhittin A et al on 9890 female subjects, vitamin D levels were found to be significantly higher in summer and autumn seasons (31). Likewise, in the present study, vitamin D levels were found to be high during summer and autumn and low in winter and spring months.

Changes occur in vitamin D metabolism with advancing age. The number of vitamin D receptors decrease in organs playing part in metabolism of vitamin D. Hence, resistance develops in intestine against vitamin D, resulting in the reduction of absorbtion of calcium from intestines. As a consequence of the decrease in 1 alpha-hydroxylase activity in kidney, activation of vitamin D is reduced (32). Contrary to expectations, as in the study of Muhittin A et al, in the current study, vitamin D levels were found to be higher in cases over the age of 50 than younger ones. This may be attributed to the fact that older cases present to health institutions more frequently and hence have their vitamin D levels measured more commonly, resulting in more common supplementations.

The most important strength of the present study is that it is the study with largest population carried out in Turkey to date.

Consistent with similar studies performed previously in Turkey, serum 25(OH)D levels were found to be sufficient merely in 13,6% of cases. The high prevalence of vitamin D eficiency in our country may be associated with factors such as different life styles, use of sun screens, differences in nutrition patterns, staying in closed places, style of dressing and other environmental factors. Limitation of the present study is that as it is a retrospective study, we do not have information regarding the level of sun exposure, whether they have received vitamin D supplements, style of clothing, the use of sun screens, BMI, the presence of systemic diseases and regular use of drugs. And it is not known which medical speciality requested the vitamin D blood levels.

In conclusion, vitamin D deeficiency is a common problem in our country as in the rest of the world. Serum vitamin D levels may be influenced from seasonal changes, being lower during winter months. Although routine screening of serum vitamin D levels is not recommended, it may be suggested that strategies for improvement of vitamin D status may be developed in all age groups in additon to risk groups such as pregnant women.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the University of Health Sciences Turkey, Kartal Dr Lütfi Kırdar City Hospital Ethics Committee (24.04.2024 dated and 2024/010.99/3/6 no).

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Short term effectiveness of local autological platelet-rich plasma (PRP) injection in the treatment of women with stress urinary incontinence

Stres idrar kaçırma olan kadınların tedavisinde lokal otolog plateletten zengin plazma (PRP) enjeksiyonunun kısa dönem etkililiği

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ABSTRACT

Aim: It was aimed to evaluate the short-term efficacy of periurethral autologous plasma rich plasma(PRP) as alternative to surgical treatment in women with stress urinary incontinence(SUI).

Materials and Methods: 36 patients, diagnosed with SUI and stress-dominant mixed incontinence were enrolled. Urodynamic studies were conducted to ascertain the diagnosis. PRP was administered to the patients at the beginning and at the end of the first month. The efficacy of the treatment was evaluated using quality of life questionnaires and the cough-stress test(CST) administered to the patients at the beginning, the first and the third month.

Results: In the ICIQ-SF questionnaire, mean score prior to surgery was 15.36±3.53, decreasing to 10.53±3.52 by the end of the third month($p<0.001$). A similar trend was observed in the UDI-6 questionnaire, which decreased from 11.33±3.64 to 8.25±3.34 at the end of the third month($p<0.001$). A similar trend was observed in the IIQ-7 test, with a decrease from 12.50±4.95 to 8.94±4.34, and a significant improvement was detected in all questionnaires compared to pre-procedure($p<0.001$). Of the 35 patients who initially exhibited positive CST results, 14(40%) demonstrated negative results by the conclusion of the third month and a substantial discrepancy was identified($p<0.001$).

Conclusion: It has been hypothesized that PRP application may serve as an alternative to invasive surgery in the short-term treatment of SUI incontinence. While PRP appears to be an appropriate treatment option due to its cost-effectiveness, minimal application time, and reduced adverse effect profile, further research is required with a larger patient cohort and extended follow-up periods.

Key Words: Stress urinary incontinence, PRP, periurethral injection

ÖZ

Amaç: Bu çalışmada stres üriner inkontinanslı (SUI) kadınlarda cerrahi tedaviye alternatif olarak periüretral otolog plazmadan zengin plazma (PRP) uygulamasının kısa vadeli etkinliğini değerlendirme amaçlandı

Gereçler ve Yöntem: Çalışmaya ürodinami ile stres uriner inkontinans ve stres ağırlıklı mix uriner inkontinans tanısı konulan 36 hasta alındı. PRP başlangıçta ve birinci ayın sonunda olmak üzere iki sefer uygulandı. Tedavinin etkinliği hastalara işlem başlangıcında, işlem sonrası 1. ayda ve 3. ayda yaşam kalitesi anketleri ve öksürük stres testi (CST) ile değerlendirildi.

Bulgular: ICIQ-SF (International Consultation on Incontinence Questionnaire Short Form) anketinde ameliyat öncesi ortalama 15,36±3,53 olan skor 3. ay sonunda 10,53±3,52'ye geriledi ($p<0,001$). UDI-6 (urogenital distress inventory) anketinin başlangıç değerinin 11,33±3,64'ten 3. ay sonunda 8,25±3,34'e düştüğü görüldü ($p<0,001$). IIQ-7 (incontinence impact questionnaire) testinde 12,50±4,95'ten 8,94±4,34'e düşüş gözlendi ve tüm anketlerde işlem öncesine göre anlamlı bir iyileşme tespit edildi. Başlangıçta CST pozitif olan 35 hastanın 3. ay sonunda 14'ü (%40) negatif olup, bu fark anlamlı olarak değerlendirildi ($p<0,001$).

Sonuç: SUI kısa süreli tedavisinde PRP uygulamasının invazif cerrahiye alternatif olabileceği görülmüştür. PRP uygun maliyetli, kısa uygulama süresi ve daha az yan etki profili ile uygun bir tedavi gibi görünse de daha fazla hastaya ve daha uzun süreli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Stres üriner inkontinans, PRP, periüretral enjeksyon

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INTRODUCTION

According to the International Continence Society (ICS), stress urinary incontinence is defined as the involuntary leakage of urine with strenuous activities such as coughing and laughing (1). It is the most common type of urinary incontinence and affects 30-40% of adult women worldwide (2). The most common predisposing factors for SUI are advanced age, obesity, menopause, multiparity, and birth trauma (3). It can impair the quality of life in affected individuals and cause embarrassment due to urinary incontinence. Urinary incontinence is not only a medical problem, but also a major problem due to the financial burden it creates in the economies of countries. In the United States, the annual cost is $32 billion, which is more than the country's budget for dialysis and coronary bypass. The cost of diapers alone is $6 billion, and considering that it doubles every year, it becomes clear how big the financial burden we face (4).

Conservative approaches such as lifestyle changes, pelvic floor muscle exercises, use of a vaginal incontinence pessary and duloxetine "a serotonin-norepinephrine uptake inhibitor (SNRI)" (is not licensed for use) are the first line of treatment for SUI (3). If conservative treatments fail, surgical repairs such as mid-urethral sling and colposuspension should be considered to restore urethral competence (5). These procedures are widely used and provide an acceptable cure rate and continuity (6). However, especially after the FDA's warnings about the use of vaginal mesh and its complications, women turned away from surgery and sought alternative treatment. For this purpose, the use of a periurethral bulking agent, which is a less invasive and simpler approach, has gained popularity (7).

Periurethral injection methods are micro-invasive surgical methods that are easily applied by creating an alternative to invasive surgical methods in the treatment of SUI. They have short hospital stays and anesthesia is not used much. More reliable materials are used, and complications are less frequent. Nevertheless, in spite of the aforementioned benefits, the method is not without its drawbacks. For instance, it necessitates shorter, more time-effective and repetitive applications when compared with surgical methods. These applications were first tested by Murless in 1938. Murless aimed to increase bladder outlet resistance by injecting sodium morhuate obtained from the cod liver into the anterior wall of the vagina, but some important complications prevented its use. Subsequently, in the following years, many materials started to be used in periurethral injection treatments (8).

The aim of periurethral injection treatments is to increase the surface width and to prevent incontinence by increasing the closing pressure of the urethra by applying it to the urethral mucosa in patients with intrinsic sphincter insufficiency and minimal urethral mobility, which are the causes of SUI. It has also been reported that these materials help make the sphincter stronger by increasing the length of the muscles in this area (9,10).

The ideal injection materials used in the treatment of SUI should be biocompatible, non-immunogenic and hypoallergenic. In addition, it is imperative that the material does not result in migration or cause post-procedure pain. The ideal properties of such materials would be the capacity to induce minimal fibrosis, ease of transportation and storage, and prolonged action (11,12).

Platelet-rich plasma (PRP) is an autologous blood product with high platelet concentration, rich in various cytokines, chemokines and growth factors, which are obtained from the person's blood by centrifugation method and contribute to tissue regeneration (13). It is used with increasing popularity in many fields of medicine due to its angiogenic, regenerative and anti-inflammatory effects that increase tissue healing (14). In the field of urogynecology, it is used in vesicovaginal fistulas, cystocele, interstitial cystitis and SUI. It is thought that PRP treats SUI by contributing to ligament reconstruction in pubourethral ligament defects, which are a factor in the pathophysiology of SUI (15).

The objective of this study was to evaluate the effectiveness of periurethral PRP application in treating patients and reducing symptoms as an alternative to surgery in patients with SUI.

MATERIAL-METHOD

The study which was conducted at Mustafa Kemal University Faculty of Medicine, Gynecology and Obstetrics Clinic, between September 2021 and August 2022, was of a prospective, single-center nature. The study was approved by the local ethics committee (dated 26/08/2021 and numbered 2021/15) prior to its commencement. The study included patients suffering from stress incontinence and stress-dominant mixed incontinence who had not experienced improvement through conservative treatment (lifestyle changes, pelvic floor exercises etc.). Patients with detrusor overactivity, as indicated by urodynamic study results, neurogenic bladder dysfunction, low platelet count, hypofibrinogenemia, chronic liver disease, anticoagulant medication use, follow-up for malignant disease, acute and chronic infection, and pelvic organ prolapse were excluded from the study. The study was conducted in accordance with the principles of the Helsinki Declaration. Prior to participation, all participants were furnished with comprehensive information

regarding the study. Written informed consent was obtained from all patients prior to their participation in the study.

During this period, 48 patients attending the outpatient clinic with the complaint of stress incontinence were invited to participate in the study. All patients underwent gynaecological examinations and urodynamic study. The urodynamic parameters were then recorded. The results of the study revealed that 21 patients were diagnosed with pure stress incontinence, 15 patients with mixed urinary incontinence, 8 patients with detrusor overactivity, and 4 patients with neurogenic bladder. Thirty-six patients with urodynamically demonstrated stress incontinence and stress-dominant mixed incontinence were included in the study.

A total of 10 ml of blood was collected from the patients who were participants in the study. This blood was then placed into a PRP tube and subjected to centrifugation at 2800 rpm for a period of 6 minutes. Subsequent to centrifugation, 5 ml was extracted from the platelet-rich layer using a 27-gauge sterile special injector. The patients were then taken to the gynecological table in the lithotomy position. Local anaesthesia was administered subsequent to the sterilization of the application area. The length of the urethra was measured with the aid of an implanter, and 1.5-2-1.5 ml of PRP was applied to the middle urethral region 1 cm below the urethral meatus, at a depth of 1,5 cm, at the 3-6-9 o'clock positions, respectively. Catheterization was not employed in the treatment of the patients following the procedure, and they were discharged on the same day. The same procedure was repeated for the patients at the end of the first month. The impact of incontinence on quality of life was measured using the International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF), the Urogenital Distress Inventory (UDI-6) and the Incontinence Impact Questionnaire (IIQ-7). These questionnaires were administered to the patients before the first procedure, after the second procedure, and at the end of the third month. At the conclusion of the third month, the stress cough test was performed, and the continence status was recorded.

IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was utilized for the purpose of statistical analysis and calculations. The statistical significance level was set at $p<0.05$.

RESULTS

The present study comprised 36 patients with a mean age of 48.03 years (±9.93 years). The mean BMI of the patients was determined as 24.72±14.21 kg/ m². Urodynamic studies were conducted on the patients. The results of the study revealed that 21 patients were diagnosed with SUI, while 15 patients were diagnosed with stress-dominant mixed incontinence. The urodynamic parameters are presented in Table 1.

Table 1. Urodinamy Parameters

Qmax	20.92±6.67
Postvoidal residual volume	20.03±27.00
First sense of bladder filling	102.69±56.26
First desire to void	204.75±66.61
Strong desire to void	332.89±100.47
Max Cystometric Capacity	468.56±110.46

The mean value of the ICIQ-SF PREOP was found to be 15.36±3.53, the mean value of the ICIQ-SF 1st month was 12.53±3.48, and the mean value of the ICIQ-SF 3rd month was 10.53±3.52. All three assessments demonstrated an improvement in symptoms among patients. A statistically significant difference was found between the three time-dependent measurements of ICIQ-SF values ($p<0.001$). Subsequent examination of the ICIQ-SF scores indicated a substantial improvement in symptoms, though it should be noted that complete cure was not observed in any patient. The ICIQ-SF score evaluation categorized patients as follows: mild (1-5 points); moderate (6-12 points); severe (13-18 points); and very severe (19-21 points). The improvement in symptoms is demonstrated in Figure 1. This improvement was particularly pronounced in the group that was evaluated as severe and very severe before the procedure. In the third-month evaluation, only one of 18 patients with severe symptoms was included. Symptom evaluation remained in this patient, and improvement in symptoms was observed in 94.4% ($p<0.001$) of the patients.

The UDI-6 questionnaire is scored on a scale of 0-18 points, with a decrease in score indicating an improvement in quality of life. The UDI-6 values in the patients under the study were 11.33±3.64 before the procedure, they were 9.50±3.32 at the 1st month and 8.25±3.34 at the 3rd month. A statistically significant difference was found between the time-dependent measurement of UDI-6 values ($p<0.001$). Consequently, a marked enhancement in patients' quality of life was evident by the conclusion of the third month. The IIQ-7 test is a tool employed in the assessment of physical activity, social activity, social relationships, and emotional health. A decrease in scores is indicative of an improvement in quality of life. In the present study, the IIQ-7 questionnaire was administered to patients prior to PRP injection, followed by subsequent assessments at the 1st and 3rd months post-procedure. The obtained scores were 12,5-10,19 and8,94, respectively. This decline was deemed to be statistically significant ($p<0.001$). A cough test was performed on all patients included in the study prior to the procedure and at the

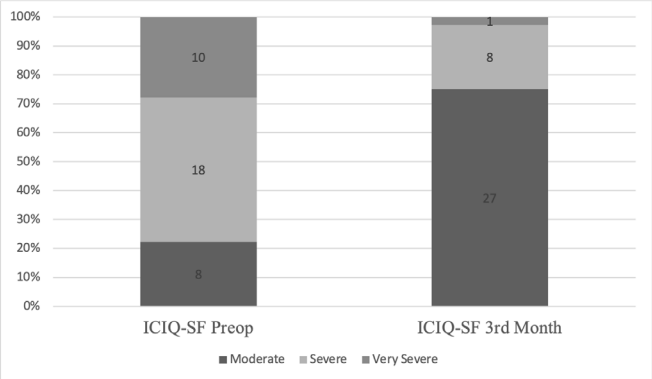

Figure 1. Distribution of Symptom

3-month controls following the procedure. Of the 36 patients with urodynamically confirmed SUI, 35 exhibited positive results in the initial cough stress test. At the 3-month follow-up, 14 of these 35 patients (40%) demonstrated a negative response. This outcome was deemed to be statistically significant ($p<0.001$).

DISCUSSION

SUI is defined as the involuntary leakage of urine with effort, sneezing or coughing (1). The etiology of SUI is multifactorial, with two main underlying causes: urethral hypermobility and intrinsic sphincter insufficiency (16). A wide range of treatment options, including conservative, medical, surgical and periurethral injection procedures are available for the management of SUI. A wide range of materials is utilized in periurethral injection treatments. The objective of these interventions is to augment the surface area and to mitigate incontinence by enhancing the urethral closing pressure through the application to the urethral mucosa in patients with intrinsic sphincter insufficiency and minimal urethral mobility (9). In recent years, PRP has been utilized for this purpose. The objective of this utilization is twofold: firstly, to observe the effect of platelet growth factors on the structure of platelets, and secondly, to ascertain the effect of these factors on the mechanical support of the injection area. According to the integral theory, the most important factor in SUI cases is the pubourethral ligament (17). Nikolopoulos et al. predicted that PRP might be appropriate for the restoration of the pubourethral ligament in 2016 and supported this hypothesis with animal models (18). The use of bulking agents to increase the mechanical support of the periurethra in the treatment of SUI, thereby providing the restoration of pelvic anatomy and reducing urethral hypermobility is not new in the treatment of SUI.

In the present study, 36 patients received two periurethral PRP injections, administered with one-month intervals. Patients were evaluated for symptoms at the 1-month and 3-month time points..

The findings from the two quality of life questionnaires and the cough stress test were then evaluated, and it was determined that there was a significant improvement in the patients' condition in the short term.

Periurethral injections are an alternative method that has recently gained popularity, especially among patients who are reluctant to undergo surgery. In a multicenter prospective study, Marlene et al. administered periurethral injections to 291 patients and found that 74 patients were cured and symptoms improved in 164 patients, according to symptom evaluation (19).

In a study by Chiang et al., they applied periurethral PRP 4 times at 1-month intervals to patients with urodynamically proven intrinsic sphincter insufficiency; refractory to medical treatment or anti-incontinence surgery. They evaluated the patients urodynamically, UDI-6, IIQ-7 scores and observed improvement in all three parameters (20). Conversely, the study demonstrated enhancements in the patients' quality of life, as evidenced by the results of the quality-of-life questionnaires. Moreover, a decline in symptoms was observed when the patients were subjected to a cough test. In another study by Tahoon et al. applied PRP to 20 patients with SUI; performed ICIQ-SF, UDI 6, IIQ7, pad test and urodynamics in 1st and 3rd months. The present study revealed that complete recovery was observed in six patients at the third-month evaluation, with an improvement in symptoms noted. It was determined that the value, which was 5.35 in the pad test, decreased to 2.5 (21). When these studies are evaluated in conjunction with our own, it is evident that periurethral PRP treatment is an effective, cost-effective and minimally invasive procedure.

The present study is not without its limitations. First, the use of subjective data such as quality of life questionnaires, for the evaluation of patients' symptoms and the absence of control urodynamics, constitute limitations of the present study. Second, our study did not evaluate the duration of PRP effect. The relatively brief follow-up period may have precluded the observation of a sustained effect, which could be attributed to placebo.

CONCLUSION

Among the periurethral injection agents, PRP, which has recently been the focus of research, is a popular bulking agent due to its cost-effectiveness, ease of access, short-term administration and minimal side effects. The present study found that periurethral injection of PRP in SUI patients reduced symptoms and increased their quality of life. While these findings suggest that PRP injection could be a viable treatment option for stress urinary incontinence,

further research is necessary to ascertain the necessity and duration of subsequent injections, which would require studies with a more substantial patient population and extended follow-up periods.

Ethics Committee Approval: The study was approved by the local ethics committee (dated 26/08/2021 and numbered 2021/15) prior to its commencement.

Informed Consent: Written informed consent was obtained from all patients prior to their participation in the study.

Conflict of Interest: There is no evidence of any potential conflict of interest relevant to this article.

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The relationship between endometrioma and systemic inflammation indexes

Endometrioma ve sistemik inflamasyon indeksleri arasındaki ilişki

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ABSTRACT

Aim: Recent studies have examined systemic inflammatory markers like C-reactive protein (CRP) and fibrinogen, but the role of comprehensive indices such as the systemic immune inflammation index (SII), systemic inflammation response index (SIRI), and pan-immune inflammation value (PIV) in endometrioma remains unclear. This study aimed to evaluate whether isolated endometrioma stimulates systemic inflammation by assessing SII, SIRI, and PIV.

Material and Methods: A retrospective case-control study was conducted involving 213 patients with endometrioma and 207 controls with no gynecological or systemic diseases. Data collected included age, CA-125, CA 19-9, platelet, neutrophil, lymphocyte, monocyte counts, and inflammatory indices (SII, SIRI, PIV). Statistical analysis was performed using the Student's t-test.

Results: No significant differences were found between the endometrioma group and the control group in terms of SII (970±146.6 vs. 753±471, p=0.121), SIRI (1.73±1.21 vs. 1.39±1.02, p=0.107), or PIV (551±420 vs. 419±313, p=0.100). CA-125 and CA 19-9 levels were significantly higher in the endometrioma group compared to controls (p=0.003 and p=0.020, respectively).

Conclusion: The study did not find significant evidence that isolated endometrioma induces systemic inflammation based on SII, SIRI, and PIV. The findings suggest that endometrioma may primarily cause localized inflammation rather than systemic effects. Limitations include the retrospective design and relatively small sample size, which may affect the generalizability and causality of the results. Further prospective studies with larger cohorts are needed to fully understand the systemic inflammatory implications of endometrioma.

Keywords: Endometriosis, ovarian cysts, inflammation, biomarkers

ÖZ

Amaç: Son çalışmalar C-reaktif protein (CRP) ve fibrinojen gibi sistemik inflamatuar belirteçleri incelemiştir, ancak sistemik immün inflamasyon indeksi (SII), sistemik inflamasyon yanıt indeksi (SIRI) ve pan-immün inflamasyon değeri (PIV) gibi kapsamlı indekslerin endometriomadaki rolü belirsizliğini korumaktadır. Bu çalışmanın amacı, izole endometriomanın sistemik inflamasyonu uyarıp uyarmadığını SII, SIRI ve PIV'yi değerlendirerek değerlendirmektir.

Gereç ve Yöntemler: Endometriomalı 213 hastayı ve jinekolojik veya sistemik hastalığı olmayan 207 kontrolü içeren retrospektif bir vaka-kontrol çalışması yapıldı. Toplanan veriler arasında yaş, CA-125, CA 19-9, trombosit, nötrofil, lenfosit, monosit sayıları ve inflamatuar indeksler (SII, SIRI, PIV) yer aldı. İstatistiksel analiz Student's t-testi kullanılarak yapılmıştır.

Bulgular: Endometrioma grubu ile kontrol grubu arasında SII (970±146.6 vs. 753±471, p=0.121), SIRI (1.73±1.21 vs. 1.39±1.02, p=0.107) veya PIV (551±420 vs. 419±313, p=0.100) açısından anlamlı fark bulunmadı. CA-125 ve CA 19-9 düzeyleri endometrioma grubunda kontrol grubuna kıyasla anlamlı derecede yüksekti (sırasıyla p=0.003 ve p=0.020).

Sonuç: Bu çalışmada, izole endometriomanın SII, SIRI ve PIV'e dayalı sistemik inflamasyona neden olduğuna dair anlamlı kanıt bulunmamıştır. Bulgular, endometriomanın sistemik etkilerden ziyade öncelikle lokalize inflamasyona neden olabileceğini düşündürmektedir. Retrospektif tasarım ve nispeten küçük örneklem büyüklüğü, sonuçların genellenebilirliğini ve nedenselliğini etkileyebilecek kısıtlamalar arasındadır. Endometriomanın sistemik enflamatuvar etkilerini tam olarak anlamak için daha geniş kohortlarla yapılacak prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Endometriozis, ovaryan kistler, enflamasyon, biyobelirteçler

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INTRODUCTION

A cyst formed by the transformation of epithelial cells on the surface of the ovary into endometrial tissue (coelomic metaplasia) or by the inward progression of ectopic endometrial tissue on the surface of the ovary (progressive invagination) forms a mass in the pelvic region. This cyst is a structure known as an endometrioma and called a pseudocyst. Endometrioma is a benign cyst and may be asymptomatic or with symptoms such as dyspareunia, pelvic pain, dysmenorrhoea. Endometriosis is a progressive disease characterised by inflammatory processes in which endometrial tissue may invade the pelvic organs and peritoneum beyond the uterine cavity. This condition usually leads to pelvic pain and infertility. Recent studies investigating the mechanism of inflammation in endometriosis patients have generally focused on inflammatory cells (1). Inflammatory cells such as neutrophils and macrophages, which are related with the primary immune response in endometriosis patients, have been found to show higher chemotactic activity in both proliferative and luteal biopsies compared to normal endometrium (2). On the other hand, it has been found that neutrophil activation responds to certain activation signals only in stage III and IV endometriosis patients, and this is related with the proinflammatory effects of endometriotic tissue (3).

It is a common view that endometrioma creates a more localised inflammation rather than systemic inflammation like endometriosis. In a study, it was observed that the inflammatory environment of ovarian endometriosis remained strongly localised and had less systemic effect (4). In another study in which serum levels of systemic inflammatory parameters were compared in endometriosis and endometrioma, it was found that ovarian endometriosis did not induce a systemic inflammatory response (5). Contrary to the results of these studies, studies showing that endometrioma triggers a systemic inflammatory response have also been performed. In one study, C reactive protein, platelet and fibrinogen levels were found to be higher in the group with endometrioma compared to the control group and it was reported that high coagulation and systemic inflammatory response were triggered due to shortening of thrombin time and prothrombin time (6).

Recently, new indicators such as systemic immune inflammation index (SII), systemic inflammation response index (SIRI) and pan-immune inflammation value (PIV), which are obtained from blood cell counts and considered as comprehensive inflammatory markers, have attracted interest. (7). Calculation of these inflammatory markers is both easy and cost-effective. These inflammatory parameters based on peripheral lymphocyte (Lym), neutrophil (NE) and platelet (PLT) counts have been recognised as a better index to reflect local immune response and systemic inflammation (8). In addition, these markers have been shown to have a high prognostic value in many cancer types, cervical cancer (9), pancreatic cancer (10) and colorectal cancer (11). In a study on systemic inflammatory index in patients with endometriosis, it was considered to be a potentially simple and cost-effective approach to predict disease (12).

The primary aim of our study was to evaluate whether isolated endometrioma stimulates systemic inflammation mechanisms with SII, SIRI and PIV, which have been the subject of recent studies. The main focal points of this study are that the relationship between endometrioma and systemic inflammation is not yet fully understood and the studies of the above-mentioned parameters, which are considered to be related to systemic inflammation, are limited in the literature on endometrioma.

MATERIAL METHODS

The aim of this retrospective case-control study was to investigate whether systemic inflammatory mechanisms are involved in patients with endometrioma. SII, SIRI and PIV levels, which are inexpensive and easy to calculate markers, were investigated in patients diagnosed with endometrioma in Gynaecology and Obstetrics outpatient clinics. The study was conducted in the Department of Obstetrics and Gynecology and included patients diagnosed with endometrioma between 1 November 2022 and 1 August 2024. The study population consisted of all patients diagnosed with endometrioma during the study period. In patients diagnosed with endometrioma, one or more symptoms such as chronic pelvic pain, dysmenorrhea, and dyspareunia were present. Pelvic pain was observed during vaginal examination in patients who had previously given birth or were non-virgins. Ultrasound performed on these patients (transvaginal for non-virgins and suprapubic abdominal ultrasound for virgins) revealed homogeneous cystic structures with a “frozen glass” appearance. The cyst wall was smooth and well-defined, typically with a unilocular structure. The size of the identified endometriomas ranged from 4 cm to 10 cm. The diagnosis of endometrioma was established based on clinical findings, laboratory results (elevated CA-125 levels), and typical cystic features on ultrasound. Patients in the control group were included in the study provided that they had no gynaecological and systemic disease. Patients were excluded if they were under 18 years of age, had pre-existing systemic diseases, history of malignancy, active smoking, alcohol or illicit drug use, HIV, HCV or HBV infection or any pre-existing chronic disease or organ transplantation history.

Data for the study were collected retrospectively from the medical records of eligible patients. These data included patients’ age, ca 125 value, ca 19-9 value, platelet value, neutrophil value,

lymphocyte value, monocyte value and systemic inflammatory index value, systemic inflammation response index value, pan immune inflammation value calculated from these values. According to the calculation formula, SII (Platelet count × Neutrophil count / Lymphocyte count), SIRI (Monocyte count × Neutrophil count / Lymphocyte count) and PIV (Monocyte count × Platelet count × Neutrophil count / Lymphocyte count) were calculated using absolute neutrophil count (×10^9/L), monocyte count (×10^9/L), lymphocyte count (×10^9/L) and platelet count (×10^9/L), respectively.The study included 213 patients with endometrioma and 207 control patients without any gynaecological or systemic disease. The statistical method used in the evaluation of the data was Student-T test.

RESULTS

When the patients were grouped as endometrioma and control group, the mean age of the endometrioma group was 36.5±8.47, while the mean age of the other group was 34.1±11.4 and the difference between them was not significant (p=0.77). CA 125 values were 280±74.5 in the endometrioma group and 26.0±22.5 in the other group and this difference was statistically significant (p=0.003). CA 19-9 values were 80.2±26.0 in the endometrioma group and 15.3±16.2 in the other group and this difference was statistically significant (p=0.020). Platelet values were 311000±83300 and 302000±58500 in the endometrioma and other groups, respectively, and this difference was not significant

Table 1. Comparison of endometrioma (group 1) and other control group (group 2)

	GROUP	AGE	CA 125	CA 19-9	PLT	NEU	MON	LYM	SII	SIRI	PIV
NUMBER OF PATIENT	1	213	213	213	213	213	213	213	213	213	213
	2	207	207	207	207	207	207	207	207	207	207
MEAN	1	36.5	280	80.2	311000	5.81	0.568	2.18	970	1.73	551
	2	34.1	26.0	15.3	302000	5.08	0.542	2.23	753	1.39	419
STANDARD DEVIATION	1	8.47	74.5	26.0	83300	5.24	0.188	0.751	146.6	1.21	420
	2	11.4	22.5	16.2	58500	2.32	0.164	0.690	471	1.02	313
P VALUE		0.77	0.003	0.020	0.22	0.145	0.180	0.646	0.121	0.107	0.100

PLT: Platelet, NEU: Neutrophil, MON: Monocyte, LYM: Lympocyte, SII:systemic immune inflammation index, SIRI: systemic inflammation response index, PIV: pan-immune inflammation value

Table 2. Comparison of demographic characteristics of endometrioma and control group

VARIABLES	ENDOMETRIOMA GROUP (n=213)	CONTROL GROUP (n=207)	P VALUE
GRAVIDY			0.225
0	61 (%28.6)	45 (%21.7)	
1	73 (%34.2)	86 (%41.5)	
≥2	79 (%37.1)	76 (%36.7)	
PARITY			0.427
0	51 (%24.9)	57 (%27.5)	
1	105 (%49.3)	97 (%46.9)	
≥2	57 (%26.8)	53 (%25.6)	
ABORTUS			0.386
0	148 (%69.5)	162 (%78.2)	
1	42 (%19.7)	29 (%14.0)	
≤2	23 (%10.8)	16 (%7.7)	
SMOKING	5 (%2.3)	4 (%1.9)	0.763
CONTRACEPTION			0.952
IUD	89 (%41.7)	81 (%39.1)	
COC	36 (%16.9)	49 (%23.7)	
Condom	53 (%24.9)	48 (%23.2)	
Other	35 (%16.4)	29 (%14.0)	

IUD: Intrauterin Device, COC: Combined Oral Contraceptives

(p=0.22). Neutrophil values of both groups were 5.81±5.24 and 5.08±2.32 , respectively, and this difference was not significant (p=0.145). Monocyte values were 0.568±0.188 and 0.542±0.164 in both groups, respectively, and the difference between them was not significant (p=0.180). Lymphocyte values were 2.18±0.751 and 2.23,±0.690, respectively, and this difference was not significant (p=0.646). SII values were 970±146.6 and 753±471 in the endometrioma and control groups, respectively, and this difference was not statistically significant (p=0.121). SIRI values were 1.73±1.21 and 1.39±1.02 in the two groups, respectively, and the difference between them was not significant (p=0.107). PIV values were found to be 551±420 and 419±313, respectively, and this difference was not statistically significant (p=0.100) (Table1).

There was no significant difference between endometrioma and control groups in terms of gravida, parity, abortion, smoking and contraceptive methods as reported in Table 2.

DISCUSSION

Endometrioma is a type of cyst formed by endometrial cells with haemorrhage and fluid accumulation, which develops in the ovarian regions as a complication of endometriosis pathology. It is usually associated with clinical symptoms such as pelvic pain, dysmenorrhoea and infertility and can cause various health problems in the long term if left untreated. There are studies emphasising that endometrioma is associated with systemic inflammation. In a study conducted by Ding et al., it was demonstrated that increases in C-reactive protein (CRP), platelet and fibrinogen levels, shortening of thrombin time and prothrombin time together with high coagulation and systemic inflammatory response were triggered in women with ovarian endometrioma (6). In another study conducted by Wu et al. (13) on patients with endometrioma, they found that this group had a hypercoagulable state due to altered procoagulant factors and high percentage of activated platelets in the peripheral blood and that this was closely related with systemic inflammation. In another study by Chmaj-Wierzchowska et al., urocortin, ghrelin and leptin levels were higher in the patient group with endometrioma compared to the control group, and the relationship between this and systemic inflammation was mentioned (14). In contrast to endometriosis, the prevailing view is that endometrioma causes inflammation at the site of localisation. The available data on the effects of endometrioma on systemic inflammation generally reveal that endometrioma causes a more localised inflammation and has no significant effect on systemic inflammation. Opøien et al. (5) reported that there was no significant difference in serum cytokine levels between patients with and without endometriosis, indicating that ovarian endometriosis does not cause systemic inflammation and that they did not observe cytokine changes indicating inflammation in precursor follicles adjacent to endometriomas. In a different study by Yland et al. (4) it was stated that the inflammatory effect of endometriomas was strongly localised and had a more limited systemic effect, and that the effect on infertility could not be explained only by increased inflammation.

In recent years, new indicators such as SII, SIRI and PIV, which are derived from blood cell counts and considered as comprehensive inflammatory indicators, have attracted attention. SIRI is known to show the balance between inflammatory response and immune status (15).

In our study, no significant difference was found in terms of systemic inflammation parameters in the endometrioma patient group compared to the control group. It was concluded that endometrioma does not cause systemic inflammation and the effects of inflammation may be localised and localised. This study provides valuable information regarding the prognostic value of systemic inflammation parameters in endometrioma patients. In particular, the findings that endometrioma does not cause systemic inflammation and that the effects of inflammation may be localised contribute to the limited studies available in the literature. It also sheds light on the few previous studies on systemic inflammation in endometrioma patients. SII, SIRI and PIV studies in endometrioma patients are also few in the literature. However, this study has some important limitations and weaknesses. Firstly, the retrospective design of the study has the potential to introduce direct biases related to data collection and patient selection. Retrospective studies are usually observational and limited in terms of controlling for interactive factors. This may cast doubt on the accuracy and validity of the findings of the study.

CONCLUSION

This study provides valuable information regarding the predictive value of systemic inflammatory markers in endometrioma. However, it is important to recognise its limitations. As a retrospective study, it is open to inherent biases related to data collection and patient selection. The relatively small sample size may also limit the generalisability of the findings. Furthermore, the study design does not allow firm conclusions to be drawn about the causality between the observed markers and systemic inflammation of the specific endometrioma.

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Kliniğimizde son beş yıl içerisindeki histerektomi olmuş hastaların endikasyonları ve histerektomi şeklinin karşılaştırılması

Comparison of the indications and hysterectomy types of patients in our clinic in the last five years

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ÖZ

Amaç: Histerektomi kadın hastalıkları ve doğum kliniklerinde, çeşitli endikasyonlarla yapılan en sık ameliyatlardan biridir. Jinekoloji pratiğinde abdominal, vajinal ve laparoskopi olmak üzere temelde üç farklı teknik bulunmaktadır. Son yıllarda minimal invaziv yöntemlere öncelik verilmesi önerilmektedir. Bu çalışmanın amacı kliniğimizde 2014-2019 yılları arasında yapılan histerektomi ameliyatlarının analizini yapmak ve literatür eşliğinde tartışmaktır.

Gereç ve Yöntemler: Çalışmamıza 2014-2019 yılları arasında Bezmialem Vakıf Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim dalına başvuran ve çeşitli endikasyon ve yöntemle histerektomi ameliyatı uygulanmış 963 kadın hasta dahil edildi. Bu hastaların endikasyonları ve histerektomi tipleri retrospektif olarak değerlendirildi.

Bulgular: Hastaların ortalama yaşı 52,84±9,33'tü. Toplam 5 yılda hastaların %50,5'ine (n=486) total abdominal histerektomi, %12,9'una (n=124) vajinal histerektomi, %36,7'sine (n=353) laporoskopik histerektomi uygulandığı saptandı. Yıllara göre histerektomi şeklinin değişiklik gösterip göstermediği Khi-Kare testi ile analiz edildiğinde istatistiksel olarak anlamlı şekilde abdominal histerektominin azaldığı, buna karşın laparoskopik histerektominin artığı saptandı(p<0,001).

Tartışma: Bu tek merkezli retrospektif çalışmada 2014-2019 yılları arasında 5 yıllık süreçte histerektomi yöntemleri ve endikasyonları incelendi. Literatür ile uyumlu olarak kliniğimizde en sık histerektomi endikasyonu myoma uteri olarak saptandı. Çalışma sonuçları minimal invaziv yöntemin benimsenip, ciddi şekilde artışı desteklemiştir. Çalışmamızda literatür ile uyumlu olarak 2014 yılından 2019 yılına gelindiğinde abdominal histerektominin yerini laporoskopik yöntem dramatik bir şekilde bırakmıştır. Son yıllarda kliniğimizde minimal invaziv yöntemler ile ilgili eğitimin artması, cerrahların tecrübesinin artışı ve aynı zamanda hastaların talebindeki artış bu değişimin en önemli nedenleri olduğunu düşünüyoruz.

Anahtar Kelimeler: Abdominal histerektomi, laparoskopik histerektomi, vajinal histerektomi

ABSTRACT

Aim: Hysterectomy is one of the most common operations performed in obstetrics and gynecology clinics. There are basically three different techniques in gynecology practice: abdominal, vaginal and laparoscopy. In recent years, it is recommended to give priority to minimally invasive methods. The aim of this study is to analyze the hysterectomy surgeries performed in our clinic between 2014-2019 and to discuss them with literature.

Material and Methods: Our study included 963 female patients who applied to the obstetrics and gynecology department of Bezmialem Foundation University, Faculty of Medicine, and underwent hysterectomy with various indications and methods between 2014 and 2019. The indications and hysterectomy types of these patients were evaluated retrospectively.

Results: The mean age of the patients was 52.84±9.33 years. Total abdominal hysterectomy was performed in 50.5% (n=486) of the patients, vaginal hysterectomy was performed in 12.9% (n=124) and laparoscopic hysterectomy was performed in 36.7% (n=353) of the patients in a total of 5 years. When analyzed by Chi-Square test whether hysterectomy type changed according to years, it was found that abdominal hysterectomy decreased statistically, whereas laparoscopic hysterectomy increased (p<0.001).

Discussion: In this single-center retrospective study, hysterectomy methods and indications were examined over a 5-year period between 2014 and 2019. Consistent with the literature, the most common indication for hysterectomy in our clinic was found to be myoma uteri. The results of the study supported the adoption of the minimally invasive method and the increase significantly. In our study, consistent with the literature, from 2014 to 2019, abdominal hysterectomy was replaced by the laparoscopic method dramatically. In recent years, we think that the increase in education about minimally invasive methods in our clinic, the increase in the experience of surgeons and the increase in the demand of patients are the most important reasons for this change.

Keywords: Abdominal hysterectomy, laparoscopic hysterectomy, vaginal hysterectomy

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GİRİŞ

Histerektomi kadın hastalıkları ve doğum kliniklerinde yapılan en sık operasyonlardan biridir (1). Anormal uterin kanama, adenomyozis, myoma uteri, adneksiyel kist ve kitleler, servikal ve endometriyal displazi, pelvik organ prolapsusu ve jinekolojik maligniteler bu ameliyatın başlıca endikasyonlarıdır (2). Prevelansını ülkelere, popülasyona göre değişim göstermesi nedeniyle tespit etmek zordur. Uygulanacak olan histerektomi tekniği ameliyat endikasyonu, hastanın genel sağlık durumu ve tercihi, cerrahın deneyimine göre değişmektedir. Jinekoloji pratiğinde abdominal, vajinal ve laparoskopi olmak üzere temelde üç farklı teknik bulunmaktadır. Son yıllarda minimal invaziv yöntemlere öncelik verilmesi önerilmektedir. Vajinal histerektomi, cerrahi travmanın daha düşük olması, daha hızlı iyileşme olması nedeniyle avantajlı görünmektedir (3). Benign endikasyonlarla yapılan histerektomi ameliyatlarında laparoskopik cerrahi önerilmektedir. Hastada batın anatomisini bozabilecek büyük myom, adneksiyel kitle ve malignite varlığında abdominal histerektomi tercih edilmektedir (4). 1989 yılında Reich ve ark. laparoskopik asiste vajinal histerektomi ise abdominal histerektomi yerine tercih edilebilecek bir diğer histerektomi yöntemi olarak tanımlamışlardır (5). Son yıllarda bu teknikler arasında hastaların daha hızlı taburcu olması, sosyal hayata daha hızlı ve kolay dönüş, daha iyi kozmetik sonuçlar olması nedeniyle laparaskopik histerektomi tercih edilmektedir (6).

Bu çalışmanın amacı kliniğimizde 2014-2019 yılları arasında yapılan histerektomi ameliyatlarının analizini yapmak ve literatür eşliğinde tartışmaktır.

MATERYAL METOD

Çalışmamıza 2014-2019 yılları arasında Bezmiâlem Vakıf Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalına Başvuran ve çeşitli endikasyon ve yöntemle histerektomi ameliyatı uygulanmış 963 kadın hasta dahil edildi. 01.01.2014 ile 01.01.2019 yılları arasında operasyon olan hastalar, 18 yaş üstü kadın hastalar, benign, prekürsör cerrahi gerekliliğe bağlı endikasyon ile histerektomi operasyonu olan hastalar çalışmaya dahil edildi. Postpartum dönemde histerektomi operasyonu olan hastalar, malignite tanısı olan hastalar hariç tutuldu. Total abdominal histerektomi uygulanan (n=486), vajinal histerektomi (n=124), laparoskopik histerektomi (n=353) hasta sonuçları retrospektif olarak değerlendirildi. Araştırmada sürekli değişkenler için ortalama ve standart sapma (SD) değerleri hesaplandı. Kesikli değişkenler medyan değerleri ile gösterildi. Değişkenlerin normalliği Kolmogorov-Smirnov (KS) testi ile analiz edildi. Üç grup değişkenleri medyan değerleri Kruskal-Wallis testi ile analiz edildi. Hipotezler çift yönlü olup, $p \leq 0.05$ ise istatistiksel olarak önemli farklığın olduğu kabul edilerek, tüm istatistiksel analizler R yazılımı/programlama (sürüm 3.6.2 (2019-12-12) - CRAN) kullanılarak değerlendirildi.

BULGULAR

2014-2019 yılları arasında 5 yılda çalışmamıza 963 kadın hasta dahil edildi. Hastaların ortalama yaşı 52,84±,33'tü. Hastaların %41'i (n=395) menopoz döneminde, %59'u (n=568) menopoz döneminde değildi. Çalışmaya dahil edilen hastalardan %5,5'u (n=56) nullipar, %11,7'si (n=113) primipar ve %82,8'si (n=794) multipardı. Doğum şekilleri incelendiğinde %76,3'ü (n=735) normal spontan doğum, %23,7'si (n=228) sezaryen doğum yapmıştı. Hastaların %89,5'inin (n=862) geçirilmiş laparotomi öyküsü yokken, %10,5'i (n=101) geçirilmiş laparotomi öyküsü mevcuttu. Histerektomi endikasyonları dağılımı; %27,1'i (n=261) myoma uteri, %5,3'ü (n=51) adenomiyozis, %17,9'u (n=172) anormal uterin kanama, %11'i (n= 106) endometriyal hiperplazi, %0,9'u (n=9) endometriozis, %18,7'si (n=180) pelvik organ prolapsusu, %4,4'ü (n=42) servikal displazi, %14,7'si (n=142) adneksiyel kitle şeklindeydi. Toplam 5 yılda hastaların %50,5'ine (n=486) total abdominal histerektomi, %12,9'una (n=124) vajinal histerektomi, %36,7'sine (n=353) laparoskopik histerektomi uygulandığı saptandı. Yıllara göre dağılım incelendiğinde 2014-2015 yılları arasında %91,8'i (n=145) abdominal histerektomi, %7,6'sı (n=12) vajinal histerektomi, %0,6'sı (n=1) laparoskopik histerektomiydi. 2015-2016 yılları arasında %78,1'i (n=107) abdominal histerektomi, %15,3'ü (n=21) vajinal histerektomi, %6,6'sı (n=9) laparoskopik histerektomiydi.. 2016-2017 yılları arasında %64,2'si (n=97) abdominal histerektomi, %10,6'sı (n=16) vajinal histerektomi, %25,2'sı (n=38) laparoskopik histerektomiydi. 2017-2018 yılları arasında %51,4'i (n=89) abdominal histerektomi, %20,2'sı (n=35) vajinal histerektomi, %28,3'ü (n=49) laparoskopik histerektomiydi. 2018-2019 yılları arasında %21,7'si (n=13) abdominal histerektomi, %13,3'ü (n=8) vajinal histerektomi, %65'sı (n=39) laparoskopik histerektomiydi. 2019-2020 yılları arasında %12,3'ü (n=35) abdominal histerektomi, %11,3'ü (n=32) vajinal histerektomi, %76,4'ü (n=217) laparoskopik histerektomiydi. Yıllara göre histerektomi şeklinin değişiklik gösterip göstermediği Khi-Kare testi ile analiz edildiğinde istatistiksel olarak anlamlı şekilde abdominal histerektominin azaldığı, buna karşın laparoskopik histerektominin artığı saptandı ($p<0,001$) (Tablo 1).

TARTIŞMA

Kadın hastalıkları ve doğum kliniklerinde histerektomi en sık yapılan operasyonlardan biridir. Bu tek merkezli retrospektif

Tablo 1. Histerektomi şeklinin yıllara göre dağılımı

		Histerektomi Şekli			
		TAH*	VAH**	L/S***	Total
YIL	2014	145	12	1	158
	(%)	91,8%	7,6%	0,6%	100%
	2015	107	21	9	137
	(%)	78,1%	15,3%	6,6%	100,0%
	2016	97	16	38	151
	(%)	64,2%	10,6%	25,2%	100,0%
	2017	89	35	49	173
	(%)	51,4%	20,2%	28,3%	100,0%
	2018	13	8	39	60
	(%)	21,7%	13,3%	65,0%	100,0%
	2019	35	32	217	284
	(%)	12,3%	11,3%	76,4%	100,0%
Total		486	124	353	963
		50,5%	12,9%	36,7%	100,0%

χ^2 = 418,2 p<0,001
*Total Abdominal Histerektomi
**Vajinal Histerektomi
***Laparoskopik Histerektomi

çalışmada 2014-2019 yılları arasında 5 yıllık süreçte histerektomi yöntemleri ve endikasyonları incelendi. Çalışma sonuçları minimal invaziv yöntemin benimsenip, ciddi şekilde artışı desteklemiştir. Endikasyonların incelendiği 1,7 milyon histerektomi operasyonunun dahil edildiği bir çalışmada, bu operasyonların %30 leiomyoma, %20 'si endometriozis %17,5'inin uterin prolapsus ve %18,2 malignite endikasyonları ile yapılmıştır(7). Atıgan ve ark. yaptığı çalışmadan 2015-2018 yılları arasında en sık histerektomi nedeni %38,6 oranı ile myoma uteri olarak bulunmuştur (8). Literatür ile uyumlu olarak kliniğimizde en sık histerektomi endikasyonu myoma uteri olarak saptandı.

American College Of Obstetrics And Gynecology (ACOG) histerektomi tipinin seçilmesinde hastanın anatomisinin önemi kadar cerrahın tecrübesinin de önemli olduğunu vurgulamaktadır. Büyük uterus varlığı, adneksiyel kitleler, hastanın geçirilmiş cerrahi öyküsü, malignite şüphesi abdominal histerektomiyi tercih haline getirmektedir (9). Ancak hastaların ameliyat sonrası dönemde ağrılarının daha fazla olması, iyileşme ve hayata dönüşün yavaş olması ve estetik kaygılar nedeniyle abdominal histerektomi yerini minimal invaziv yöntemlere bırakıyor gibi görünmektedir. Halen literatürdeki veriler doğal orifis olması, hastanın ameliyat sonrasında iyileşme sürecinin daha hızlı olması nedeniyle vajinal histerektomi yapılması önermektedir. Danimarka'da daha az invaziv olması, pelvik taban desteği erişim açısından, benign endikasyonlarda vajinal histerektomi tercih edilmesi gereken bir prosedür olarak kabul edilmektedir (10). Yapılan bir çalışmada vajinal ve laparoskopik histerektominin abdominal histerektomiye göre daha avantajlı olduğu hastaların iyileşme süresinin daha kısa olduğunu saptanmıştır (11) . Ayrıca Ottosen ve ark. Yaptığı çalışmada abdominal histerektomi ameliyatında vajinal yola göre daha fazla kan kaybı olduğu gözlenmiştir (12). Benzer şekilde ülkemizde yapılan bir çalışmada peroperatif kan kaybının laparoskopik histerektomide azaldığı gözlemlenmiştir (13). Son yıllarda ise laparoskopik histerektomi jinekoloji kliniklerinde birinci sırayı almıştır. Tayvan'da yapılan bir çalışmada laparoskopik histerektomi 2000'li yılların başında %35,9 iken, 2012 yılıa gelindiğinde %44'ün üzerine çıktığı gözlemlenmiştir (14). Hastanede kalış süresinin kısa olması, iyileşme süresinin daha hızlı olması hastaların laparoskopiyi tercih etmesine neden olmuştur. Laparoskopi ve laparotomik yöntemlerde komplikasyonlar incelendiğinde; çoğu çalışmada kanama miktarı, çevre organ zedelenmesi diğer yöntemlerle benzer bulunmuştur (Lumsden et al. 2000; Tsai et al. 2003).

Laparoskopik histerektomi 1989 yılında tarif edilmesine rağmen, 2003 yılında Amerika'da %11 oranın bu yöntem tercih edilmekteydi (17,18). Hem Amerikan jinekolojik laparoskopistler birliği hemde ACOG minimal invaziv yöntemi önerseler de bu oran 2010 yılına kadar ancak %20-30'a ulaşmıştır (19,20). Morrison ve Jacob yaptığı bir çalışmada 2006'dan 2010'a kadar minimal invaziv yöntemlerin %17,5'tan %44 üzerine çıktığını hatta aynı gün taburcu protokollerinin iyi tolere edildiği ve güvenli olduğu son ucuna varmışlardır (21). Kanada'da 10 yıllık süreçte benign endikasyonlarlka yapılan histerektomi operasyonlarında abdominal ve vajinal histerektomi tipinde düşüş, laparoskopik cerrahi de ise belirgin artış izlenmiştir (22). Yapılan başka bir çalışmada 2004 yılında benign endikasyonlarla yapılan laparoskopik cerrahi sadece %8 iken 2008 yılında %50'eye, 2012 yılında ise %72'ye yükselmiştir.

Yazarlar bu eğrideki yükselmeyi gönüllü mentorluk programı ile burs programı oluşturularak eğitimin artmasına bağlamışlardır (23). Güney Kaliforniya'da da 300'den fazla cerrah arasında yapılan program ve cerrahi mentörlük ile 5 yıllık süre içerisinden laparoskopi yöntemi %38'den %78'e yükseldiği gözlenmiştir (24). Çalışmamızda literatür ile uyumlu olarak 2014 yılından 2019 yılına gelindiğinde abdominal histerektominin yerini laparoskopik yöntem dramatik bir şekilde bırakmıştır. Minimal invaziv cerrahının avantajları iyi belgelenmiş olmasına rağmen jinekologların yavaş benimsemesinin en önemli nedeni; uzun öğrenme eğrisinin oluşu, asistanlık sürecinde yetersiz eğitim verilmesi olarak düşülmektedir (25).

Sonuç olarak 3. Basamak bir merkez olan kliniğimizde, histerektomi operasyonlarının yöntemlerindeki değişimi analiz ettiğimizde; minimal invaziv cerrahinin tercih edilme oranlarında belirgin artış gözlemledik. Bunun temel nedenleri; daha hızlı iyileşme, daha az postoperatif ağrı, hastanede kalış süresinde azalma ile birlikte kozmetik avantajları olmasıdır. Ayrıca cerrahların tecrübesindeki artış, asistan eğitiminin bir parçası olması nedeniyle de minimal invaziv yöntemlerin daha çok artacağını düşünüyoruz. Çalışmamızın bazı kısıtlılıkları mevcuttur. Bu yapılan operasyonların komplikasyonları, operasyon süreleri, hastaların hastanede kalış süreleri ve nihai patoloji sonuçları incelenmemiştir. Gelecekte bu verilerle daha kapsamlı çalışma yapılması literatüre ışık tutacaktır.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Tamoksifen kullanan meme kanserli kadınlarda endometrial hiperplastik değişikliklerin Tamoksifen kullanım süresi ve anormal uterin kanama ile ilişkisi

Relationship of endometrial hyperplastic changes with duration of tamoxifen use and abnormal uterine bleeding in women with breast cancer using tamoxifen

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ÖZ

Amaç: Bu çalışma, meme kanseri tedavisinde tamoksifen (TMX) kullanan kadınlarda endometrial hiperplastik değişiklikler, tamoksifen kullanım süresi ve anormal uterin kanama (AUK) arasındaki ilişkiyi araştırmayı amaçlamıştır.

Gereç ve Yöntemler: Ocak 2019 ile Şubat 2024 arasında cerrahi işlemler geçiren 178 meme kanseri hastasının patoloji sonuçları üzerine retrospektif bir inceleme yapıldı. Hastalar iki gruba ayrıldı: TMX tedavisi alanlar (n=104) ve almayanlar (n=78). Endometrial patoloji sonuçları, yaş, parite, menopoz durumu, Vücut Kitle Endeksi (VKE), ultrasonografi bulguları ve AUK semptomları değerlendirildi.

Bulgular: Tüm hastaların ortalama yaşı 49,7 ± 9.1 yıldı. TMX grubunun ortalama yaşı ve VKE, non-TMX grubuna kıyasla anlamlı derecede daha düşüktü (p<0.001). Endometrial ultrasonografi anormallikleri TMX grubunda anlamlı derecede yüksekti (p=0.001). AUK ile endometrial polipler arasında anlamlı bir ilişki yoktur. (p=0.594), ancak AUK ile malign endometrial patoloji arasında anlamlı bir ilişki gözlemlendi (p<0.001). TMX kullanan hastalarda 3-4 yıl kullanımda AUK'da istatistiksel olarak anlamlı bir artış gözlemlendi (p=0.001).

Sonuç: Kısa süreli TMX kullanımı (≤1 yıl) endometrial değişiklikler açısından nispeten güvenli görünmektedir. Ancak, 3 yılı aşan uzun süreli TMX kullanımı, özellikle AUK ve endometrial anormallikler açısından artmış bir riskle ilişkilidir. İleri yaş, menopoz sonrası durum, uzun süreli TMX kullanımı ve AUK varlığı, endometrial malignite gelişiminde dikkate alınması gereken önemli faktörlerdir.

Anahtar Kelimeler: Tamoksifen, meme kanseri, anormal uterin kanama, endometrium kanseri, hiperplastik değişiklikler

ABSTRACT

Aim: This study aimed to investigate the relationship between endometrial hyperplastic changes, duration of tamoxifen (TMX) use, and abnormal uterine bleeding (AUB) in women with breast cancer using tamoxifen.

Materials and Methods: A retrospective review was conducted on the pathology results of 178 breast cancer patients who underwent operative procedures between January 2019 and February 2024. Patients were divided into two groups: those who had received TMX treatment (n=104) and those who had not (n=78). Endometrial pathology results, age, parity, menopausal status, Body Mass Index (BMI), ultrasonography findings, and AUB symptoms were evaluated.

Results: The mean age of all patients was 49.7 ± 9.1 years. The TMX group had a significantly lower mean age and BMI compared to the non-TMX group (p<0.001). Endometrial ultrasonography abnormalities were significantly higher in the TMX group (p=0.001). There was no significant association between AUB and endometrial polyps (p=0.594), but a significant relationship was observed between AUB and malignant endometrial pathology (p<0.001). Patients using TMX for 3-4 years showed a statistically significant increase in AUB (p=0.001).

Conclusion: Short-term TMX use (≤1 year) appears to be relatively safe regarding endometrial changes. However, longer TMX use, particularly beyond 3 years, is associated with an increased risk of AUB and endometrial abnormalities. Older age, postmenopausal status, prolonged TMX use, and the presence of AUB are important factors to consider in the development of endometrial malignancy.

Keywords: Tamoxifen, breast cancer, abnormal uterine bleeding, endometrial cancer, hyperplastic changes

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GİRİŞ

Meme kanseri yıllık tanı alan kanser vakalarının %15.5'ini oluşturur, dünyada en sık görülen kanserdir. Kansere bağlı ölümlerde akciğer, kolon/rektum, karaciğer ve mide kanserinden sonra 5. sırada yer alır(1,2). TMX selektif östrojen reseptör modülarötürüdür (SERM) ve 1977 yılında World Health Organization (WHO) tarafından östrojen reseptör pozitif ilerlemiş meme kanseri tedavisinde kullanımının onaylanmasından sonra kullanılmaya başlanmıştır(3).

TMX meme üzerinde östrojen reseptörlerine bağlanarak tümör hücrelerindeki östrojen etkisini antagonize eder, bu şeklide tümörün büyüme ve gelişmesi yavaşlar(4). TMX pre ve postmenopozal, erken veya ileri evre hormon reseptör pozitif meme kanserinde günümüzde yaygın olarak kullanılmaktadır. Östrojen reseptör pozitif meme kanseri, meme kanseri vakalarının yaklaşık %80'ini oluşturmaktadır (4) .

Hormon reseptör (+) meme kanseri tanısı olan kadınlarda 15 yıllık gözlemde TMX kullanımı plaseboya göre rekürrens riskini %30 azaltmaktadır.(5,6).

Klasik (5 yıl) tedavi süresiyle kıyaslandığında uzun süreli (10 yıl) TMX kullanımı hastalıksız ve genel sağkalım süresini daha olumlu etkilemektedir(7).

TMX nin memede antiöstrojenik etkisine rağmen uterus üzerinde zayıf agonistik etkisine bağlı olarak doz ve süre bağımlı olarak endometrial hiperplastik değişiklikler (polip, hiperplazi vb) ve uterin kanser riskinde artışa neden olduğu pek çok çalışmada gösterilmiştir(8–12).

2011 yılında yapılan 21457 hastanın incelendiği bir metanalizde 5 yıl TMX kullanımının endometrium kanseri riskini hiç kullanmayanlara göre 2.4 kat arttırdığı saptanmıştır(13).

Meme kanseri tanısı alan hastalarda çeşitli ailesel germline mutasyonları (MLH1, MSH2,6, PTEN, BRCA1 ve BRCA2 mutasyonları vb), obesite , nulliparite, anovulasyon, TMX kullanımı gibi çeşitli nedenlerle over ve endometrium kanseri riski de artmaktadır.

Bu çalışmada da endometrial hiperplastik ve malign değişikliklerin (polip, hiperplazi, endometrium kanseri vb) ve AUK şikayetinin TMX kullanım süresi ile ile ilişkisi araştırılmıştır. Daha farklı bir deyişle TMX kullanmaya başlayan bir kadında ne zaman polip ve hiperplazi, ne zaman malignensi gelişmesini bekleriz ve bu değişiklikler ne zaman anormal uterin kanama şikayetine neden olur? sorularına cevap aranmıştır.

GEREÇ VE YÖNTEMLER

Mersin Üniversitesi Hastanesi Kadın Hastalıkları ve Doğum Kliniğinde Ocak 2019 ve Şubat 2024 tarihleri arasında operatif işlem yapılan meme kanseri tanılı 178 hastanın patoloji sonuçları retrospektif arşiv taraması şeklinde incelenmiştir. TMX tedavisi almış 104 hasta ve kullanmayan 78 hastanın endometrial patoloji sonuçları, yaş, parite, menopoz durumu, VKE, ultrasonografi bulguları ve AUK bulguları değerlendirilmiştir. Hastanemiz kayıt/dosya platformu NUCLEUS XCE üzerindeki veriler ve hastalarla birebir telefon görüşmeleri ile datalar kaydedilmiştir.

Hastaların yaşları, menopoz ve parite durumları, senkron ya da metakron bir kanser var mı, kronik hastalıklar (hipertansiyon, kalp hastalığı, diyabet, tiroid hastalıkları vb) kayıt edilmiştir. VKE değerleri boy ve kilo kullanılarak TMX kullanan ve kullanmayan grupta hesaplanmıştır.

Primer meme kanseri tanısı ve cerrahi işleme kadar geçen süre (TİAGS), TMX kullanıyorsa ya da kullanmışsa süresi (<1yıl, 1-2yıl, 3-4yıl, >5yıl ve üzeri), işlem sırasında TMX kullanımı (TİSK) durumu not edilmiştir

Hasta geliş şikayetinde anormal uterin kanama (AUK) olup olmadığı araştırılmış; kanama şikayeti varsa semptomatik, yoksa asemptomatik olarak değerlendirmeye alınmıştır.

Jinekolojik muayene bulgularında endometrium ultrason değerlendirmesi ve ek jinekolojik muayene bulguları çalışmada göz önünde bulundurulmuştur. Kliniğimizde menopozdaki hastalarda sınır endometrium kalınlığı 5 mm, premenopozal kadınlarda sınır endometrium kalınlığı 9 mm olarak kabul edilmektedir. Ultrason yapan kişinin gözlemine dayalı endometrium düzensizlikleri, polip görünümü, sıvı imaji kaydedilmiştir. Endometrium değerlendirmesinde muayene bulguları İnce (İ), Normal (N), Kalın (K), Düzensiz (D), Kalın ve Düzensiz (K +D), Polip (P), Rahim İçi Araç (RİA), Sıvı (S) şeklinde gruplandırılmıştır. Myometrium, overler, servikal ve vajinal ek jinekolojik muayene bulguları gruplara ayrılarak not edilmiştir

Operatif işlem olarak hastalara örnekleme (D&C, Pipelle ile biyopsi, Histeroskopik Biyopsi) ya da Histerektomi (Total Abdominal Histerektomi, Total Laparoskopik Histerektomi) işlemleri uygulanmıştır. (Radikal cerrahilere overler de dahil edildiğinden vajinal cerrahi tercih edilmemiştir.)

Patoloji sonuçları endometrium için Yetersiz Materyal, Benign (Sekretuar endometrium Proliferatif endometrium, Disordered proliferatif endometrium, atrofik endometrium, endometrial stroma vb), Polip, Endometrial Hiperplazi, Malign olarak gruplandırılmıştır.

Patoloji raporunda ek Jinekolojik patoloji sonuçları (Over kisti, Endometriozis,Adenomyozis, Ek Jinekolojik Malignensi ve Diğer jinekolojik patolojiler) değerlendirilmeye alınmıştır.

Verileri SPSS (Statistical Package for Social Sciences) 25.0 paket programı ile analiz kullanılmıştır. Tanımlayıcı analizlerde frekans verileri sayı (n) ve yüzde (%) olarak, standart sapma (sd), ortanca (1-3.çeyrek (IQR)) ile verilmiştir. Kategorik verilerin dağılımı Pearson Ki-kare Testi ve Fisher'ın kesin ki-kare testi ile değerlendirilmiştir. Sayısal verilerin dağılımı Kolmogorov Smirnov ve Shapiro Wilk testleri ile incelenmiştir. Bağımsız iki grupta normal dağılım göstermeyen veriler Mann Whitney U testiyle değerlendirilmiştir. Tüm testler için istatistiksel anlamlılık düzeyi p<0,05 olarak kabul edilmiştir. Değişkenlerin birbiri ile ilişkisi Pearson Korrelasyon analizi kullanılarak raporlanmıştır.

BULGULAR

Ocak 2019ve Ocak 2024 tarhleri arasında Mersin Üniversitesi Tıp fakültesi hastanesinde Kadın hastalıkları ve Doğum servisinde operatif işlem gören 5771 hasta kayıtları taranarak aynı zamanda meme kanseri tanısı olan 178 hasta çalışmaya dahil edilmiştir. Çalışma grubu tamoksifen kullanan hastalar n=104 (%58.4); kontrol grubu tamoksifen kullanmayan hastalar n=78 (%41.6) olarak belirlendi.

Tüm hastalarda, TMX kullanan ve kullanmayan hastalarda demografik ve klinik özelliklerin dağılımı Tablo 1'de verilmiştir. Tüm hastalarda yaş dağılımı 49.7 ± 9.1 yıl olarak belirlenmiştir. TMX kullanan hastalarda kullanmayan hastalara göre yaş anlamlı düzeyde düşük belirlenmiştir (p<0.001). TMX kullanan hasta grubunda VKE dağılımı anlamlı düzeyde düşük belirlenmiştir (p<0.001). TMX kullanan hasta grubunda kullanmayan hasta grubuna göre parite sayısı istatistiki olarak benzer saptanmıştır (p=0,096). TMX kullanan hastaların %54,8'i (n=57), kullanmayan hastaların %66.2'si (n=49) menopozda olarak belirlenmiştir. Gruplar arasında anlamlı bir farklılık tespit edilmemesine karşılık (p=0,126), endometrial malignensi tanısı menopozda olan hastalarda anlamlı olarak yüksek (p=0.022) tespit edilmiştir. Kronik hastalık bulunma durumu TMX kullanmayan hastalarda kullananlara göre daha yüksek saptanmıştır (p=0,002).

Tüm hasta grubunda, TMX kullanan ve kullanmayan hasta grubunda tamoksifen kullanımı, jinekolojik muayene, yapılan işlem ve patoloji sonuçlarının dağılımı Tablo 2'de sunulmuştur. TMX kullanan ve kullanmayan hastalarda AUK şikayeti, TİAGS (Tanı İşlem Arası Geçen Süre ve yapılan operatif işlem tipi benzer olarak bulunmuştur (p>0.05). TMX kullanmayan grupta hastaların %54,5'ine (n=48), TMX kullanan hastaların %51,1'ine (n=47) definitif histerektomi işlemi yapıldığı belirlenmiştir. TMX kullanan hasta grubunda Ek Jinekolojik Muayene bulgularından pelvik kitle saptanma oranı daha düşük tespit edilmiştir (p=0,04). Diğer ek jinekolojik muayene bulgu dağılımlarında istatistiki fark saptanmamıştır (p>0,05). TMX kullanmayan hasta grubunda endometrium incelemesinde ince olma oranı daha yüksek bulunmuştur (p=0,013). TMX kullanan ve kullanmayan hasta grupları arasında endometriumun Kalın (K), Düzensiz (D), Kalın ve Düzensiz (K +D), Polip (P), Sıvı (S) gibi anormal bulgular Endometrial Ultrason Anormallikleri olarak bir grupta

Tablo 1. Hastaların demografik ve klinik özelliklerinin dağılımı (n=178)

	TMX Kullanan	TMX Kullanmayan	Tüm Hastalar	P
Yaş	47.0 (±6.8)	53.4 (±10.6)	49.7 (± 9.1)	**0.001***
Parite	1.8 (1-3)	2.2 (2-3)	2 (1-3)	0.096*
VKI	25.1 (±2.2)	28.4 (± 5.2)	26.5(± 4.1)	**0.001***
Menopoz				
Var	57 (54.8)	25 (33.8)	72 (40.4)	0.126**
Yok	47 (45.2)	49 (66.2)	106 (59.6)	
Kronik hastalık				
Var	21 (20.2)	31(41.9)	52 (29.2)	**0.002****
Yok	83 (79.8)	43 (58.1)	126 (70.8)	
Meme dışı malignite				
Var	2 (%1.9)	2 (1.7)	4 (2.2)	1.00***
Yok	102 (98.1)	72 (97.3)	174 (97.8)	

*: Mann Whitney U testi, **: Pearson Ki-kare testi , ***: Fisher Exact Testi

Tablo 2. Tamoksifen Kullanımı, Jinekolojik Muayene, Yapılan İşlem ve Patoloji Sonuçlarının Dağılımı

	TMX Kullanan (n=104)	TMX Kullanmayan (n=74)	Tüm Hastalar (n=178)	P
AUK				
var	21 (20.2)	14 (14.6)	35 (19.7)	0.985**
yok	83 (79.8)	60 (81.1)	143(80.3)	
TİAGS	48.5(± 34.9)	45.3 (± 42.5)	47.1 (± 41.0)	0.063*
İşlem Tipi				
D&C	31 (29,8)	20 (27.0)	51 (28.7)	0.842**
Histeroskopi	20(19.2)	13 (17.6)	33(18.5)	
TAHBSO	53 (51.0)	41 (55.4)	94(52,8)	
Jinekolojik muayene				
Myom	19 (18.3)	3 (4.1)	22 (12.4)	0.09**
Over kisti	13 (12.5)	17 (23.0)	30 (16.9)	0.102**
Pelvik kitle	2 (1.9)	10 (13.5)	12 (6.7)	**0.04*** **
Servikal patoloji	1 (1.0)	5 (6.8)	6 (3.4)	0.083**
Vajinal patoloji	1 (1.0)	1 (1.4)	2 (1.1)	1.00***
Endometrial Ultrason				
İnce	14 (13.5)	22 (29.7)	36 (20.2)	**0.013****
Normal	25 (24.0)	22 (29.7)	47 (26.4)	0.499**
Kalın(K)	28 (26.9	13 (17.6)	41 (23.0)	0.200**
İrregüler(I)	15 (14.4)	7 (9.5)	22 (12.4)	0.447**
Kalın ve irregüler (K+I)	8 (7.7)	3 (4.1)	11 (6.2)	0.365***
P	13 (12.5)	4 (5.4)	17 (9.6)	0.112**
RİA	1 (1.0)	3 (1.7)	4 (2.2)	0.309***
Sıvı imajı (S)	3 (2.9)	4 (5.4)	7 (3.9)	0.452***
K+I+(K+I)+P+S	64(61.5)	27(36.5)	91(51.1)	**0.001****
Endometrial Patoloji				
Yetersiz	6 (5.8)	3 (4.1)	9 (5.1)	0.737***
Benign	69 (66.3)	50 (67.6)	119 (66.9)	0.865**
Polip	25 (24.0)	14 (18.9)	39 (21.9)	0.529**
Hiperplazi	2 (1.9)	1 (1.4)	3 (1.7)	1.000***
Malignensi	2 (1.9)	6 (8.1)	8 (4.5)	0.068***

*: Mann Whitney U testi, **: Pearson Ki-kare testi, ***: Fisher Exact Testi
+ TİAGS: Tanı-İşlem arası geçen süre
++K: Kalın, I:İrregüler, S: Sıvı, P: Polip

toplandığında tamoksifen kullanan hasta grubunda endometrial anormal görüntüleme anlamlı olarak yüksek bulunmuştur (p=0.001).

AUK ve Endometrial patoloji sonuçları arasındaki ilişki Tablo 3'te sunulmuştur. Patoloji sonucu polip olarak saptanan n=33 hastadan %18'inde (n=6) AUK şikayeti pozitif olarak saptanmıştır. AUK bulgusu ile endometrial polip patolojisi arasında anlamlı bir ilişki tespit edilememiştir (p=0.594). Endometrial patoloji sonucu malign olarak raporlanan n=8 hastadan %75'inde (n=6) AUK şikayeti pozitif olarak kaydedilmiştir. AUK ve malign endometrial patoloji sonucu arasında belirgin anlamlı bir ilişki tespit edilmiştir (P<0.001). AUK durumuna göre patolojik sonuçların karşılaştırılması Şekil 1'de verilmiştir.

Histerektomi yapılan hastalarda ek patolojik bulguların dağılımı Tablo 4'te verilmiştir. TMX kullanmayan hastalarda kullanan

Tablo 3. Anormal Uterin Kanama ve Endometrial patoloji sonucu ilişkisi

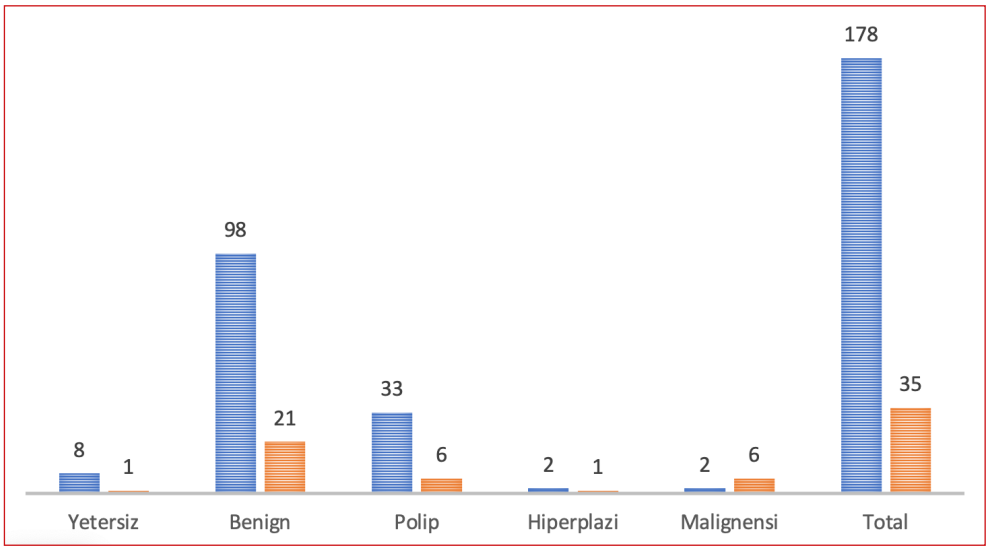
	Anormal Uterin Kanama (AUK)			
Endometrium Patoloji	**Yok**	**Var**	**Total**	**p**
Yetersiz	8 (5.6)	1 (2.9)	9 (5.1)	1.000**
Benign	98 (68.5)	21 (60.0)	119 (66.9)	0.447*
Polip	33 (23.1)	6 (17.1)	39 (21.9	0.594*
Hiperplazi	2 (1.4)	1 (2.9)	3 (1.7)	0.484**
Malignensi	2 (1.4)	6 (4.0)	8 (4.5)	**0.001****

*: Pearson Ki-kare testi , **: Fisher Exact Testi

Tablo 4. Histerektomi yapılan hastalarda ek jinekopatolojik bulgular

	TMX Kullanan (n=53)	**TMX Kullanmayan (n=41)**	**Tüm Hastalar (n=94)**	**P**
Over kisti	3 (5.7)	5 (12.2)	8 (8.5)	0.290***
Endometriozis	1 (1.9)	2 (1.3)	3 (3.2)	0.579***
Myoma Uteri	23 (43.4)	19 (46.3)	42 (44.7)	0.940**
Adenomyosis	14(26.4)	7 (17.1)	21 (22.3)	0.407**
Ek Malignensi	1 (1.9)	7 (17.1)	8 (8.5)	**0.020*****
Diğer patolojiler	8 (15.1)	7 (17.1)	15 (16.0)	1.00**

*: Mann Whitney U testi, **: Pearson Ki-kare testi, ***: Fisher Exact Testi



Şekil 1. Anormal Uterin Kanama (AUK) ve Endometrial Patoloji sonuçları karşılaştırması

hastalara göre Ek Jinekolojik Malignite oranı yüksek belirlenmiştir (p=0,02). Over kisti, Endometriozis, Myoma uteri, Adenomyozis ve Diğer patolojilerin saptanma oranları benzer bulunmuştur (p>0.05).

Hastaların TMX kullanım süresine göre Endometrial ultrason ve Endometrial patoloji ve AUK değerlendirme bulguları Tablo 5'te verilmiştir.

TMX kullanan hastalarda ilacın kullanım süresi 39.4 (12-57) ay olarak saptanmıştır.

İşlem sırasında TMX kullanma oranı %83.7 (n=87) olarak belirlenmiştir.

TMX kullanım süresi 1 yıldan az, 1-2yıl, 3-4 yıl, 5 yıldan uzun olmak üzere 4 gruba ayrıldığında %25'i (n=26) 5 yıl ve daha uzun süreli TMX kullanmıştır.

Tablo 5. Tamoksifen kullanım süresine göre klinikopatolojik özellikler

	Tamoksifen kullanım süresi					
	<1 yıl (n=14)	1-2 yıl (n=35)	3-4 yıl (n=29)	>5 yıl (n=26)	Total (n=104)	P
Endometrium US						
İnce	2 (14.3)	3 (8.6)	5 (17.2)	4 (15.4)	14 (13.5)	0.712**
Normal	8 (57.1)	8 (22.9)	5 (17.2)	4 (15.4)	25 (24.0)	0.028**
Kalın	2 (14.3)	10 (28.6)	10 (34.5)	6 (23.1)	28 (26.9)	0.566**
İrregüler	1 (6.7)	5 (46.7)	1 (6.7)	4 (40.0)	15 (14.4)	0.099**
Kalın ve İrregüler	0	4 (50.0)	2 (25.0)	2 (25.0)	8 (7.7)	0.759**
Polip	1 (7.1)	4 (30.8)	5 (38.5)	3 (25.0)	13 (12.5)	0.849**
RİA	0	1 (2.9)	0	0	1 (1.0)	1.000**
Sıvı	0	1 (2.9)	1 (3.4)	1 (3.8)	3 (2.9)	1.000**
K+I+(K+I)+P+S	4 (6,3)	23 (35,9)	19 (29,7)	18 (28,1)	64 (61.5)	0.057*
Endometrium Patoloji						
Yetersiz	1 (7.1)	0	1 (3.4)	4 (15.4)	6 (5.8)	0.048**
Benign	13 (92.9)	23 (65.7)	21 (72.4)	12 (46.2)	69 (66.3)	0.021*
Polip	0	12 (48.0)	7 (28.0)	6 (24.0)	25 (24.0)	0.067**
Hiperplazi	0	0	0	2 (7.7)	2 (1.9)	0.78**
Malignensi	0	0	0	2 (7.7)	2 (1.9)	0.78**
Polip + Hiperplazi	0	12 (44.4)	7 (25.9)	8 (29.6)	27 (26.0)	0.056**
TMX +AUK	1 (4.8)	1 (4.8)	13 (44.8)	6 (28.6)	21 (20.2)	0.001*
İşlemde TMX Kullanımı					87 (83.7)	

*: Pearson Ki-kare testi, **: Fisher Exact Testi
+K: Kalın, I:İrregüler, S: Sıvı, P: Polip

1 yıldan kısa sureli TMX kullanan hasta grubunda endometrium incelemesinde normal olma oranı daha yüksek bulunmuştur (p=0,022). Diğer endometrial ultrason değerlendirmelerinde TMX kullanım süresine göre anlamlı bir farklılık saptanmamıştır.

Patoloji sonuçlarına göre 5 yıldan uzun süreli TMX kullanan grupta endometrial örnekleme sonucu yetersiz materyal gelme oranı anlamlı olarak daha yüksek olarak belirlenmiştir (p=0.048).

1 yıldan kısa süreli TMX kullanan olgularda (n=14) premalign olabilecek polip ve hiperplazi gibi bulgular hiç tespit edimezken, 1-2 yıl TMX kullanan 12 hastada (%44.4) ve 3-4 yıl arası kullanan 7 hastada polip (%25.9), 5 yıl ve daha fazla TMX kullanan 8 hastada (%29.6) polip ve atipisiz hiperplazi tespit edilmiştir. Bu dönemdeki (Ocak 2019-Şubat 2024) meme kanseri nedeniyle Jinekoloji kliniğinde işlem gören hastaların hiçbirinde endometrial patoloji sonucu atipik hiperplazi olarak raporlanmamıştır.

Endometrial hiperplazi (n=2) ve endometrial malignensi (n=2) 5 yıl ve daha uzun süre TMX kullanan hastalarda tespit edilmiştir.

1-2 yıl TMX kullanan hastaların %4.8'inde (n=1), 3-4 yıl kullanan hastaların %45'inde (n=13), 5 yıl ve daha fazla kullanan hastaların%23'ünde (n=6) anormal uterin kanama şikayeti saptanmamıştır.

TMX kullanan hastalarda 3-4 yıl, tamoksifen kullanan grupta AUK bulgusu istatistiksel olarak anlamlı olarak artmıştır (p=0.001)

TARTIŞMA

TMX'nin meme üzerinde antiöstrojenik etkisine rağmen, kadın genital sistemi üzerinde östrojenik etkiye sahip olduğu yapılan pek çok çalışma ile gösterilmiştir. TMX kullanımına bağlı en sık görülen endometrial patoloji pek çok çalışmada polip olarak bildirilmiştir (14,15)

Çalışma gruplarında TMX kullanan hastaların yaş grubu anlamlı olarak daha düşük tespit edilmiştir (p<0.01). Premenopozal kadınlarda TMX kullanımının daha güvenli olması daha genç yaş grubundaki hastalarda TMX'nin daha fazla tercih edilmesinde etkili olabilir. TMX kullanan hastalarda endometrial malignite ile yaş arasında orta derecede pozitif korrelasyon tespit edilmiştir r= 0.417, p<0.001). Çalışmamızda TMX kullanan hastalarda endometrial

malignite 60 yaş üzerindeki hastalarda raporlanmıştır. Benzer çalışmalarda da yaş faktörünün önemi vurgulanmıştır (16). TMX kullanmayan hasta grubunda yaşla birlikte endometrial malignite artışı arasında anlamlı bir pozitif korrelasyon tespit edilmemiştir (r= 0.236, p=0.43).

Gruplar arasında menopozda olan ve olmayan hastalar benzer oranda tespit edilmiştir. Buna karşılık endometrial malignensi menopozdaki hastalarda anlamlı olarak daha yüksek tespit edilmiştir. ACOG (The American College of Obstetricians and Gynecologists) önerilerinde TMX kullanan premenopozal kadınlarda uterin neoplazi gelişimi açısından artmış bir risk saptanmadığı, yıllık rutin takiplerin yeterli olduğu bildirilmiştir (17). Bu açıdan TMX kullanan hastaların takiplerinde menopozda olan hastalar daha yakından takip edilmelidir.

Kronik hastalıklar TMX kullanan hasta grubunda anlamlı olarak daha düşük bulunmuştur. Bunun sebebi TMX kullanan gruptaki hastaların daha genç yaşta olması olabilir.

TMX kullanan grupta VKE anlamlı olarak daha düşük saptanmıştır. VKE gruplarına göre hastalar, (Az kilolu (VKE <18,5), Normal kilolu (VKE 19-24.5), Kilolu (VKE 25-29.5), Obez (VKE 30- 34.5) ve Aşırı kilolu (VKE >35), olarak gruplandırıldığında, TMX kullanan hastalarda polip ve hiperplazi gibi hiperplastik değişikliklerin normal kilolu (n=14) ve kilolu (n=13) hastalarda geliştiği gözlenmiştir. TMX kullanmayan hastalarda hiperplastik değişiklikler %87 (n=13) kilolu, obez ve aşırı kilolu hastalarda tespit edilmiştir. TMX kullanan hastalarda obesite ve yüksek VKE olması polip, hiperplazi ve malignite gelişimi açısından TMX kullanmayan hastalar kadar belirleyici bir faktör olmayabilir. Bu konuda daha ileri araştırmalara ihtiyaç vardır.

Endometrium değerlendirmesinde TMX kullanmayan hastalarda endometrium anlamlı olarak ince tespit edilirken, endometrial kalınlık artışı, irregülarite, polip ve sıvı imajı TMX kullanan grupta anlamlı yüksek olarak raporlanmıştır. TMX kullanımına bağlı anormal ultrason bulguları pek çok çalışmada dökümente edilmiştir (18–20). Bu çalışmada da benzer şekilde TMX kullanan hasta grubunda özellikle ilk 1 yıldan sonra artmış anormal endometrial ultrason bulguları saptanmıştır.

Patoloji sonuçlarına göre TMX kullanan grupta sonuçların %72.1'i (n=75) Yetersiz ya da Benign, %27.9'u (n=29) Polip+Hiperplazi+Malignensi olarak; TMX kullanmayan grupta sonuçların %71.6'sı (n=53) Yetersiz ya da Benign %28.4'u (n=21) Polip+Hiperplazi+Malignensi olarak raporlanmıştır. Çalışma gruplarında endometrial malignite oranı %4.5 olarak tespit edilmiştir ve gruplar arasında polip, hiperplazi ve malignite açısından anlamlı bir bir farklılık saptanmamıştır.

Polip ve hiperplazi gibi TMX kullanımına bağlı hiperplastik endometrium değişiklikleri olan hastaların %84'ünde (n=21) TMX kullanmayan ve polip ya da hiperplazi tespit edilen hastaların ise %93 (n=14) de AUK şikayeti tespit edilmemiştir. Endometrial malign patoloji sonucu olan 8 hastanın 6 sında AUK bulgusu pozitif olarak raporlanmıştır (%75, p=0.001). TMX kullanan hastaların ikisinde endometriumda Malign patoloji (Seröz Karsinom ve Musinöz Karsinom) olarak raporlanmış, her ikisinde de AUK şikayeti tespit edilmiştir. Tamoksifen kullanmayan grupta 6 olgunun endometrium patolojilerinde Karsinom Metastazı (n=2), Endometrioid Karsinom (n=4) olarak raporlanmıştır.

Endometriumun primer adenokanserlerinin hepsinde (n=4) AUK bulgusu mecutken, primer meme karsinomunun endometrium metastazlarında (n=2) ve overin primer seröz ve müsinöz kanserlerinin hiçbirinde (n=4) ve primer meme kanserinin over metastazlarının hiçbirinde(n=3) anormal uterin kanama şikayeti bulgusu saptanmamıştır.

Histerektomi spesmenlerinin patolojik incelemesinde TMX kullanmayan hasta grubunda istatistiksel olarak anlamlı yüksek ek jinekolojik malignite, ovaryan neoplazi (n=7) olarak raporlanmıştır. Bunlar primer meme karsinomu metastazı (n=3), seröz karsinom (n=3), musinoz karsinom (n=1) olarak raporlanmıştır. Ovarian neoplazi ile yaş arasında istatistiksel olarak anlamlı bir korrelasyon tespit edilemese de daha genç yaş grubundaki hastalarda olası bir malignensi gelişimine karşı overler daha dikkatli ve daha erken yaşta taranmalıdır (r= -0.50, p=0.510).

1 yıldan kısa süreli TMX kullanımında endometrial ultrason normal görüntüleme anlamlı olarak yüksek saptanmıştır (p=0.028). Ayrıca bu hasta grubunda patoloji sonuçları anlamlı yüksek Benign olarak kaydedilmiştir. (p=0.021). Endometrial kalınlık artışı, irregülarite, polip ve sıvı imajı ultrason muayene bulgularında TMX kullanım süresi ile anlamlı bir artış saptanmamıştır (p=0.057). Polip, Hiperplazi gibi TMX kullanımına bağlı olarak gelişebilecek hiperplastik endometrium değişiklikleri bir grupta toplandığında TMX kullanım süresi ile ilişkili anlamlı bir artış saptanmamıştır (p=0.051). Bu bulgulara göre 1 yıldan kısa süreli TMX kullanımı güvenli görünmektedir. Polip gelişimi özellikle 1 yıl kullanım sonrası artış göstermiş, daha uzun süreli kullanımda polip gelişimi benzer oranlarda saptanmıştır. Buna karşılık endometrial hiperpazi ve malignensi gelişimi 5 yıl ve daha uzun süreli kullanımda raporlanmıştır.

TMX kullanan hastalarda kullanım sürelerine göre gruplara ayrıldığında 3-4 yıl TMX kullanan grupta AUK bulgusu istatistiksel olarak anlamlı yüksek saptanmıştır (p=0.001). Polip gelişen hastalar daha çok 3. yıldan sonra semptomatik (AUK) olmaya başlamışlardır.

SONUÇ

Bu çalışmada endometrial ultrason ve patoloji bulguları değerlendirildiğinde 1 yıl ve daha kısa süreli TMX kullanımı güvenli olarak görünmektedir. 1-2 yıl TMX kullanımında hastaların yaklaşık yarısında endometrial polip tespit edilmiştir. Bu dönemde hastalar genellikle (%80) asemptomatik olarak değerlendirilmiştir. 3-4 yıl TMX tedavisi alan hastalarda AUK şikayeti daha sık gözlenmiştir. Malignite gelişimi açısından hastanın yaşı, menopoz durumu, TMX kullanım süresi ve AUK bulgusu önem kazanmaktadır. Özellikle 55 yaş ve üzerinde olmak, 5 yıldan uzun süreli TMX kullanmak, menopozda olmak, AUK bulgusu olması gibi parametreler dikkatle değerlendirilmelidir. Meme kanseri tanısı ile yapılan jinekolojik muayenede germline mutasyonları ile gelişebilecek ailesel over ve endometrium kanserlerinin daha erken yaşta ortaya çıkabileceği dikkate alınmalıdır. Primer meme kanserinin endometrium metastazlarında kanama bulgusu bulunmayabileceği göz önünde bulundurulmalıdır.

Katkılar: HY, HBA ve MY konsepti geliştirdi ve veri toplama sorumluluğunu üstlendi. HBA, ŞGG ve MÇK çalışmayı planladılar. HY, MÇK ve HBA sonuçları analiz etti. HBA ve MÇK, makale metnini yazdı ve şekil ile tabloları hazırladı. Tüm yazarlar, önemli entelektüel içerik açısından makaleyi gözden geçirdi ve nihai versiyonu onayladı.

Çıkar Çatışması Beyanı: Yazarlar arasında herhangi bir çıkar çatışması bulunmamaktadır.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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The clinical utility of neutrophil-based inflammatory indices (PIV, DNI, and NPAR) in the early prediction of cesarean scar pregnancy

Sezaryen skar gebeliğinin erken prediksiyonunda nötrofil bazlı enflamasyon indekslerinin (PIV, DNI ve NPAR) klinik yararı

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ABSTRACT

Aim: To assess the clinical utility of neutrophil-based inflammatory indices—pan-immune inflammation value (PIV), delta neutrophil index (DNI), and neutrophil percentage-to-albumin ratio (NPAR)—in the early prediction of cesarean scar pregnancy (CSP).

Materials and Methods: This retrospective case-control study was conducted at Ankara Bilkent City Hospital between January 2023 and March 2025. Thirty-six women diagnosed with CSP and sixty gestational age-matched women undergoing elective termination of early pregnancy were included. Inflammatory markers, including complete blood count parameters, DNI, NPAR, and PIV, were evaluated. Group comparisons were performed using appropriate statistical tests. Receiver operating characteristic (ROC) analysis was used to determine optimal cut-off values for predictive markers.

Results: CSP cases demonstrated significantly higher white blood cell (WBC) counts, neutrophil percentages (NEU%), DNI, and PIV values, along with significantly lower lymphocyte counts compared to controls ($p<0.05$). No significant difference was observed in NPAR values ($p = 0.591$). ROC analysis indicated moderate predictive performance for WBC, NEU (%), and PIV in predicting CSP. Optimal cut-off values were 8.40 (63.9 % sensitivity, 63.3% specificity, AUC: 0.707, p=0.001), 71.1 (61.1 % sensitivity, 60% specificity, AUC: 0.647, p=0.016), and 410.5 (61.1% sensitivity, 61.7% specificity, AUC: 0.647, p=0.016) for WBC, NEU (%), and PIV, respectively.

Conclusion: Elevated inflammatory indices such as WBC, NEU (%), DNI, and PIV may serve as adjunctive, accessible biomarkers for early CSP detection. Their integration with imaging modalities could enhance diagnostic accuracy, particularly in settings with limited access to advanced imaging. Larger prospective multicenter studies are warranted to validate these findings and explore their utility in clinical practice.

Keywords: Cesarean scar pregnancy, pan-immune inflammation value, delta neutrophil index, neutrophil percentage-to-albumin ratio, inflammatory biomarkers, early pregnancy diagnosis

ÖZ

Amaç: Sezaryen skar gebeliğinin (SSG) erken tahmininde, nötrofil bazlı enflamatuvar indekslerden olan pan-immün enflamasyon değeri (PIV), delta nötrofil indeksi (DNI) ve nötrofil yüzdesi-albümin oranının (NPAR) klinik yararını değerlendirmek.

Gereç ve Yöntemler: Bu retrospektif vaka-kontrol çalışması, Ocak 2023 ile Mart 2025 tarihleri arasında Ankara Bilkent Şehir Hastanesi'nde gerçekleştirilmiştir. SSG tanısı alan 36 kadın ile vaka grubuyla gebelik yaşı eşleştirilmiş ve erken gebeliği (<10. gebelik haftası) isteğe bağlı termine edilen 60 kadın kontrol grubu olarak çalışmaya dahil edilmiştir. Tam kan sayımı parametreleri, DNI, NPAR ve PIV dahil olmak üzere enflamatuvar belirteçler değerlendirilmiştir. Grup karşılaştırmaları uygun istatistiksel testler kullanılarak yapılmıştır. Tahmin edici belirteçler için optimal kesme değerlerini belirlemek için alıcı işletim karakteristiği (ROC) analizi kullanılmıştır.

Bulgular: SSG vakalarında, anlamlı olarak daha yüksek beyaz kan hücresi (WBC) sayıları, nötrofil yüzdeleri (NEU%), DNI ve PIV değerleri tespit edilirken anlamlı olarak daha düşük lenfosit sayıları gözlenmiştir ($p<0,05$). NPAR değerlerinde anlamlı bir fark gözlenmemiştir (p=0,591). ROC analizi, SSG prediksiyonunda WBC, NEU (%) ve PIV için orta düzeyde öngörücü performans göstermiştir. Optimal kesme değerleri sırasıyla WBC için 8,40 (duyarlılık %63,9, özgüllük %63,3, AUC: 0,707, p=0,001), NEU (%) için 71,1 (duyarlılık %61,1, özgüllük %60, AUC: 0,647, p=0,016) ve PIV için 410,5 (duyarlılık %61,1, özgüllük %61,7, AUC: 0,647, p=0,016) olarak hesaplandı.

Sonuç: WBC, NEU (%), DNI ve PIV gibi güçlü enflamatuvar indeksler, SSG'nin erken tespiti için yardımcı ve erişilebilir biyobelirteçler olarak kullanılabilir. Bu indekslerin görüntüleme yöntemleriyle entegrasyonu, özellikle ileri görüntüleme yöntemlerine erişimin sınırlı olduğu ortamlarda tanı doğruluğunu artırabilir. Bu bulguları doğrulamak ve klinik uygulamadaki yararlarını araştırmak için daha büyük, çok merkezli prospektif çalışmalar gereklidir.

Anahtar Kelimeler: Sezaryen skar gebeliği, pan-immün enflamasyon değeri, delta nötrofil indeksi, nötrofil yüzdesi-albümin oranı, enflamatuvar biyobelirteçler, erken gebelikte tanı

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INTRODUCTION

Cesarean scar pregnancy (CSP) is the term for a pregnancy that implants on or in a scar from a previous C-section. The incidence of CSP is increasing in line with the rising rates of C-sections and assisted reproductive techniques, occurring in approximately one in every 2000 pregnancies (1-3). Cesarean scar pregnancies, which can lead to various complications such as severe bleeding, uterine rupture, and hysterectomy, are considered a precursor to the placenta accreta spectrum (PAS) as they have similar histopathology (4-7). Due to relatively high morbidity rates and increased risk of maternal mortality in late pregnancy, termination of these pregnancies is recommended in the early weeks of gestation (8-10).

In CSPs, most pregnant women do not show symptoms at the time of admission to the clinic, but this may vary (e.g., vaginal bleeding, pelvic pain). Sonography is the primary diagnostic tool, but magnetic resonance imaging may be helpful in some cases where the evaluation is suboptimal (11, 12). The mechanisms underlying the formation of CSPs are varied, and theories in this regard include endogenous migration of the embryo through microdefects in the scar or the low oxygenated and inflammatory environment of the scar tissue attracting the fertilized oocyte to implant in this area (8, 13-15). Prior studies have reported that inflammatory processes underlie most obstetric pathologies and that inflammatory indices calculated from routine blood tests may be valuable in predicting these diseases or their adverse outcomes (16-19). Considering that the inflammatory environment, which is increased but reinforced by insufficient trophoblast invasion in vascularized cesarean scars, also plays a role in CSP development (11), the evaluation of systemic inflammatory indices may be important in predicting the disease in this pathology as well. Recent studies suggest that inflammatory parameters such as systemic immune-inflammation index (SII), systemic immune-response index (SIRI), neutrophil-lymphocyte ratio (NLR) (4, 8), monocyte count, monocyte-lymphocyte ratio (MLR) (11), and may be useful in predicting CSP in pregnant women. This study aimed to investigate the role of inflammatory parameters related to complete blood count (CBC), pan-immune inflammation value (PIV) (also known as aggregate index), delta neutrophil index (DNI), and neutrophil percentage-albumin ratio (NPAR) in predicting CSP.

MATERIALS AND METHODS

This retrospective case-control study was conducted at the Perinatology Clinic of Ankara Bilkent City Hospital between January 2023 and March 2025. Institutional review board approval was obtained from the Ethics Committee of the Republic of Turkey Ministry of Health Ankara City Hospital (Approval number: TABED 2-25-1118). All stages of the study adhered to the principles of the Declaration of Helsinki.

During the study period, a total of 36 women diagnosed with CSP by ultrasound and 60 healthy pregnant women who elective terminated their healthy intrauterine pregnancy (before the 10th gestational week) were included in the study as a control group (Figure 1). Multiple gestations, pregnancies with active bacterial or viral infections, and cases with maternal comorbidities associated with increased inflammation (malignancies, diabetes mellitus, cardiovascular or rheumatological diseases, etc.) were excluded from the study. Suspected active infection was excluded from the case group by relevant body fluid tests, and the control group reported no history of infection within one year.

The medical records of cases diagnosed with CSP during the specified period were retrospectively retrieved from the hospital database and included maternal age, body mass index (BMI), gravidity, parity, gestational age, number of previous C-sections, CBCs, albumin level, and inflammatory indices including DNI, NPAR, and PIV. The NPAR was calculated by dividing the neutrophil percentage value (NEU [%]) by the albumin (g/L). The PIV was calculated using this formula: neutrophil (NEU [10^9/L]) x platelet (PLT [10^9/L]) x monocyte (MON [10^9/L]) / lymphocyte (LYM [10^9/L]). The demographic and clinical characteristics, laboratory results, and inflammatory indices of the cases were compared with those of a gestational age-matched control group. Blood samples were collected from both study groups during hospitalization, and no medication, medical or surgical intervention was administered to any of the pregnant women prior to sampling.

All cases of CSP were in the first trimester of pregnancy, and the gestational age of these cases was calculated based on the date of the last menstrual period, the gestational sac (GS) (mm) diameter measured by US (average of the diameters measured along all three axis), or the crown-rump length (CRL) (mm) if the fetal pole was visible. In ultrasonography, CSP was diagnosed based on the presence of an empty uterine cavity, the location of the GS in the lower uterine segment and cesarean scar, the absence of very thin or no myometrial tissue between the GS and the bladder, and the presence of a closed cervix and empty cervical canal (20). The sonographic evaluations of all the cases were performed abdominally and vaginally using the Voluson E8 or E10 ultrasound equipment (GE Healthcare, Milwaukee, WI) by maternal-fetal medicine specialists (AT, FDO, OK, or DS) with more than five years of experience in obstetric ultrasonography.

A pregnancy implanted in well-healed cesarean scar tissue with

a myometrial thickness of ≥ 3 mm between the placenta and the bladder, growing toward the cervico-isthmic space or the uterine cavity, was defined as type 1 CSP (on-the-scar or endogenous implantation). Pregnancy implanted in the defective or "niche" part of incompletely healed scar tissue, where the myometrial tissue is very thin or absent and penetrates the uterine wall, sometimes reaching the uterine blood vessels, is defined as type 2 CSP (in-the-niche or exogenous implantation) (8, 21). In addition to being classified according to these definitions, cases of CSP were also evaluated in terms of clinical and ultrasonographic features, treatment approaches, and complications.

Statistical analysis

The study's sample size was calculated using G Power software (version 3.1; Heinrich-Heine- Universität Düsseldorf). The effect size of 0.80 was determined with a P-value of 0.05 and a power of 80%, and a minimum of 21 cases was planned for each group. Statistical Package for Social Sciences (SPSS version 26.0; Chicago, IL, USA) was utilized for data analysis. Median (interquartile range (IQR) or min.-max.) or mean±standard deviation represented continuous variables, while counts (percentages) measured categorical variables. The study assessed the normal distribution of variables through the Kolmogorov– Smirnov test. Two groups' normally distributed continuous variables were compared using the independent t test, while the Mann–Whitney U test was used for non-normally distributed variables. Pearson chi-square or Fisher's exact test was used to compare categorical variables. Receiver operating characteristic (ROC) curve analysis was performed to estimate optimal cut-off values, maximizing sensitivity and specificity according to the Youden index. A ROC analysis was performed to calculate the cut-off values of blood parameters or inflammatory indices that showed statistically significant differences in the case group for predicting CSP development. A p-value of less than 0.05 was deemed significant across all analyses.

RESULTS

A total of 112 194 pregnant women admitted to the outpatient clinic during the study period. The prevalence of CSP was 0.32 cases per 1000 pregnancies. The flowchart of the study population was shown in Figure 1. The median gestational age of CSPs was seven weeks. Cases were most commonly type 1 CSP (n=33, 91.7%), and most of them had a visible fetal pole (n=26, 72.2%). None of the cases of scar pregnancy were managed expectantly. The most used surgical procedures for treatment were, in order: dilation and curettage (D&C) only (n=18, 50%), and D&C performed after approximately 12 hours of compression of the CSP area using an intrauterine balloon tamponade (IBT) (n=16, 44.4%). Methotrexate treatment was administered intramuscularly (at a dose of 50 mg/m²) to four cases after D&C, while in one case it was injected directly into the GS. In two cases, uterine rupture occurred during IBT, so laparotomy was needed, and uterine repair was done after wedge resection. No hysterectomy was performed in any case, and blood transfusion was required in three cases (8.3%). Detailed data on clinical characteristics, treatment approaches, and related complications in CSP patients are presented in Table 1.

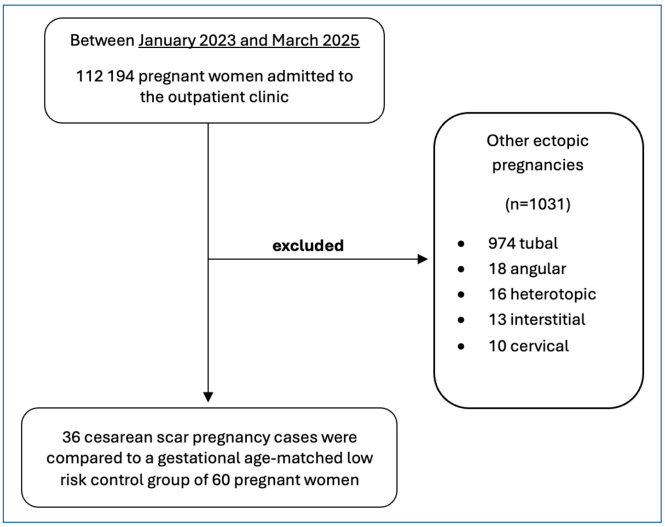

Figure 1. Flowchart of the study population

Table 1. Clinical characteristics, treatment approaches, and relevant complications in patients with CSP

Number of patients: 36	Values *
Gestational age (weeks)	7 (5-10)
Visible fetal pole	26 (72.2%)
Presence of fetal heartbeat	16 (44.4%)
Type of CSP	
On-the-scar (Type 1)	33 (91.7%)
In-the-niche (Type 2)	3 (8.3%)
Hypervascularization of scar area	10 (27.8%)
Scar area hematoma	6 (16.7%)
Expectant management	-
D&C	18 (50%)
IBT+D&C	16 (44.4%)
Methotrexate injection into GS	1 (2.7%)
Systemic methotrexate	4 (11.1%)
Hysterotomy with L/T	4 (11.1%)
Wedge resection	2 (5.5%)
Iatrogenic uterine rupture repairing	2 (5.5%)
Hysterectomy	-
Maternal Hgb (g/dL) values	
During hospitalization	12.57±1.07
Second hour after intervention(s)	11.42±1.30
Transfusion needed	3 (8.3%)
Length of hospital stay (days)	3 (1-10)

CSP, cesarean scar pregnancy; D&C, dilation and curettage; GS, gestational sac; Hgb, hemoglobin; IBT, intrauterine balloon tamponade; L/T, laparotomy.
* Statistical values are presented as mean ± standard deviation, median (min.-max.) or number (percentage).

Table 2. Comparison of demographic characteristics, first trimester blood parameters, and inflammatory indices between the study and control groups

	CSP (n=36)	Controls (n=60)	P value*
Age	34.86±5.9	28.77±4.83	**<0.001[a]**
BMI (kg/m²)	27.62±2.10	27.25±3.21	0.508[a]
Gravidity	3 (2)	2 (2)	**<0.001[b]**
Parity	2 (2)	1 (1)	**<0.001[b]**
Gestational age (weeks)	7 (2)	7 (2)	0.656[b]
Previous C-sections	2 (1)	0 (1)	**<0.001[b]**
First trimester blood parameters and inflammatory indices			
WBC (10⁹/L)	8.79 (1.99)	7.99±1.24	**0.001[b]**
NEU (10⁹/L)	5.85 (2.25)	5.89±1.22	0.550[b]
NEU (%)	71.95±4.64	68.87±5.34	**0.005[a]**
DNI	0.1 (0.1-3.4)	0.1 (0.1-0.4)	**0.043[b]**
LYM (10⁹/L)	1.53 (0.51)	1.84±0.56	**0.011[b]**
MON (10⁹/L)	0.40±0.10	0.38±0.09	0.347[a]
PLT (10⁹/L)	270.19±58.54	272.16±64.28	0.881[a]
Albumin (g/L)	42.52±4.12	41.35±4.11	0.178[a]
NPAR	1.70±0.21	1.68±0.22	0.591[a]
PIV	462.12 (284.71)	363.15±165.99	**0.016[b]**

BMI, body mass index; CSP, cesarean scar pregnancy; DNI, delta neutrophil index; LYM, lymphocyte; MON, monocyte; NEU, neutrophil; NPAR, neutrophil percentage-to-albumin ratio; PIV, pan-immune inflammation value (PIV=NEUxPLTxMON/LYM); PLT, platelet; WBC, white blood cells.
Values are presented as mean ± standard deviation, median (min.-max.), median (IQR) or as number (percentage).
* **P-values calculated using:** a Independent T test, b Mann–Whitney U test.
p<0.05 was considered statistically significant. Statistically significant data are indicated in bold.

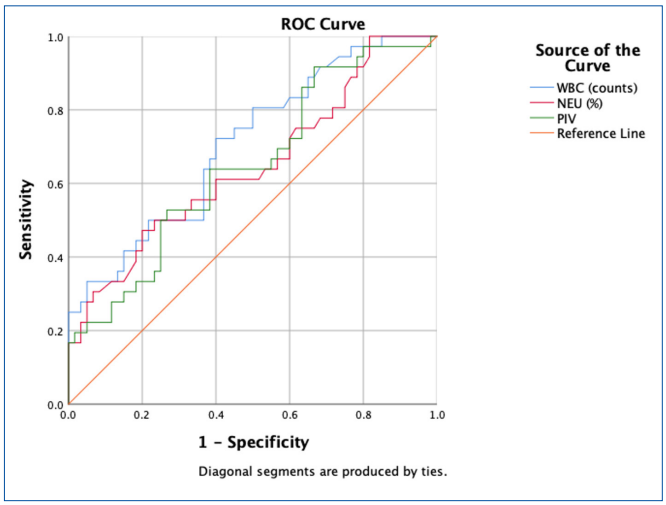

Figure 2. Receiver operating characteristic (ROC) curve of blood parameters and inflammatory indices in the prediction of CSP

NEU, neutrophil; PIV, pan-immune inflammation value (PIV=NEUxPLTxMON/LYM); WBC, white blood cells.

Statistically significant higher values for maternal age, gravidity, parity, number of previous C-sections, white blood cell (WBC) counts, NEU (%), DNI, and PIV were observed in the CSP group compared to controls (p<0.05, all). However, LYM counts were significantly lower in CSPs (p=0.011). There was no significant difference in NPAR values between groups (p=0.591). Data on the comparison of demographic characteristics, first trimester CBC parameters, and inflammatory indices of the study groups are presented in detail in Table 2.

A summary of ROC analysis demonstrating the optimal cut-off values of WBC, NEU (%), and PIV in the prediction of CSP was shown in Table 3. Optimal cut-off values were 8.40 (63.9 % sensitivity, 63.3 % specificity, area under the curve [AUC] 0.707, p=0.001), 71.1 (61.1 % sensitivity, 60 % specificity, AUC 0.647, p=0.016), and 410.5 (61.1 % sensitivity, 61.7 % specificity, AUC 0.647, p=0.016) for WBC, NEU (%), and PIV, respectively. The ROC curve for these analyses is shown in Figure 2.

DISCUSSION

This study evaluated the potential utility of systemic inflammatory markers derived from CBC in predicting CSP, a rare but serious form of ectopic pregnancy with increasing prevalence. We observed that several markers, particularly WBC count, NEU (%), DNI, and PIV, were significantly elevated in cases with CSP compared to gestational age-matched controls. Conversely, LYM counts were significantly lower in the CSP group, aligning with the concept of a systemic pro-inflammatory milieu in these patients. Additionally, our findings suggest that hematological indices obtained from routine

Table 3. Receiver operating characteristic (ROC) analysis table showing the cut-off values of blood parameters and inflammatory indices in the prediction of CSP

Variable	AUC	Std. error	Sensitivity	Specificity	Asymp. Sig*	95%CI		Cut-off value
						Lower	Upper	
WBC (10^9/L)	0.707	0.054	63.9%	63.3%	0.001	0.601	0.813	8.40
NEU (%)	0.647	0.059	61.1%	60%	0.016	0.531	0.763	71.1
PIV	0.647	0.058	61.1%	61.7%	0.016	0.534	0.761	410.5

AUC, area under the curve; CI, confidence interval; NEU, neutrophil; PIV, pan-immune inflammation value (PIV=NEUxPLTxMON/LYM); WBC, white blood cells.
*p<0.05 was considered statistically significant.

blood tests, particularly WBC, NEU (%), DNI, and PIV, can be used as easily accessible and cost-effective biomarkers in the evaluation of patients with suspected CSP in the early stages of pregnancy.

Elevated inflammatory indices in CSPs are likely due to local immune dysregulation at the implantation site. This dysregulation involves poor vascularization, hypoxia, and fibrotic changes, which trigger abnormal trophoblast invasion (7, 8). Studies have shown that hypoxic scar tissue may attract embryo implantation by upregulating cytokines and immune mediators (13). Our findings are consistent with these results, as increased NEU (%), DNI, and WBC counts reflect an innate immune activation profile similar to that observed in obstetric complications, such as PAS , which shares similar histopathological features with CSP, and preterm premature rupture of membranes (4, 19).

To our knowledge, this is one of the first studies to suggest that DNI and PIV could be useful for predicting CSP. The high DNI, representing the proportion of immature granulocytes, further supports this systemic inflammatory state and indicates that the bone marrow is actively producing and releasing granulocytic precursors, an observation commonly seen in acute inflammatory or infectious conditions (22). The high DNI value supports the hypothesis that CSP is associated with an increased innate immune response, possibly due to the spread of trophoblastic invasion to scar tissue. Karanfil Yaman et al. (23) demonstrated that increased DNI levels were significantly predictive of PAS in patients with placenta previa, further validating the role of neutrophil-derived indices in identifying aberrant trophoblastic invasion. These findings, along with those of Yakistiran et al. (24) in preeclampsia, underscore the potential of DNI as a shared biomarker across a spectrum of obstetric conditions involving defective placentation. Given the histopathological and pathophysiological overlap between CSP, PAS, and preeclampsia, our results suggest that DNI may be a useful early inflammatory marker indicative of these high-risk implantation anomalies. Its inclusion in risk stratification models could enhance early detection and intervention in CSP, especially when sonographic findings are ambiguous or unavailable. In addition, due to its multi-parameter nature, PIV, a comprehensive inflammatory marker, has shown statistically significant predictive value for CSP. This finding echoes recent investigations into the role of systemic inflammatory burden in obstetric pathologies, where higher PIV levels were associated with preeclampsia, chorioamnionitis, and gestational diabetes mellitus (19, 25, 26).

Contrary to expectations, NPAR values did not show a significant difference between the CSP and control groups. Although NPAR has been associated with the inflammatory process of many diseases in non-pregnant populations (27, 28), its predictive value in pregnancy may be limited due to other pregnancy adaptations that buffer physiological hypoalbuminemia and albumin fluctuations in early pregnancy (29, 30). However, in a recent study by Bicer et al. (31), NPAR was found to be elevated in preeclampsia and presented as an effective biomarker for predicting this condition.

The increasing incidence of CSP can be largely attributed to rising rates of cesarean delivery, advances in imaging techniques during early pregnancy, and assisted reproductive technologies (1-3). In this study, the prevalence of CSP was relatively lower when compared with the results of another study (4) recently conducted at our hospital (0.32 vs. 0.4 per 1000). This may be a reflection of government policies aimed at reducing the increasing rate of C-sections.

In this study, the moderate AUC values observed in ROC analysis for WBC (0.707), NEU% (0.647), and PIV (0.647) suggest these markers hold potential as adjunctive, rather than standalone, diagnostic tools in early pregnancy assessments. Clinically, the integration of hematologic markers with imaging could enhance early CSP detection, particularly in ambiguous cases or in low-resource settings where advanced imaging is unavailable. Given the morbidities associated with delayed diagnosis (uterine rupture, hysterectomy etc.) there is value in pursuing multimodal diagnostic pathways that incorporate cost-effective laboratory indices.

The fact that no hysterectomy was required in any of the CSP cases can be considered a major success in the treatment of this high-

risk condition. This outcome reflects the expertise and resources available at our tertiary referral center, where early diagnosis, personalized treatment planning, and multidisciplinary care are integral parts of the clinical decision-making process. The rapid use of ultrasonographic evaluation by experienced maternal-fetal medicine specialists, combined with the early implementation of personalized interventions such as IBT or methotrexate, contributed to the positive outcomes. This underscores the critical importance of early recognition and timely referral of cases suspected of CSP to well-equipped centers.

The strengths of this study include the analysis of a period of more than two years, the evaluation of new and comprehensive inflammatory indices in a specific disease group, and the comparison of blood parameters only during the first trimester hospitalization. Nevertheless, this study has several limitations. Its retrospective, single-center design and relatively small sample size restrict generalizability. Inflammatory indices are inherently non-specific and may be influenced by subclinical factors not fully captured in medical records. Additionally, evaluating inflammatory parameters based on blood samples taken before the GS is visible on ultrasound may be more appropriate for optimally assessing the utility of these indices in predicting CSP. Therefore, we believe that multicenter prospective studies encompassing the periconceptional period and involving large patient populations are needed.

CONCLUSION

This study provides new insights into the diagnostic landscape of CSP by identifying specific inflammatory markers that differ significantly between CSP cases and healthy early pregnancies. The observed alterations in WBC, NEU (%), DNI, and PIV indicate that systemic immune responses may be involved in the pathophysiological processes leading to aberrant implantation at the cesarean scar. Although these biomarkers are not disease-specific, their consistent elevation in CSP patients underscores their potential utility as part of an integrated diagnostic framework.

By focusing on routinely available hematologic indices, the study offers a practical approach to supplement existing imaging modalities. These findings pave the way for future research into risk stratification tools that could facilitate earlier recognition and management of CSP, especially in healthcare settings where access to specialized imaging or expert ultrasonography may be limited. Further prospective studies with larger, more diverse populations are needed to validate and expand upon these findings, ultimately improving clinical outcomes through timely diagnosis and intervention.

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Predictive role of triglyceride-glucose index in assessing endometriosis risk

Endometriozis riskini değerlendirmede trigliserid-glikoz indeksinin öngörücü rolü

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ABSTRACT

Aim: The aim of our study was to evaluate the predictive role of triglyceride-glucose index in assessing the risk of endometriosis.

Materials and Methods: Our study included 91 patients who were admitted to our gynecology clinic between february 2018 and 2024 and diagnosed with endometriosis and 260 patients in the control group. Body masss index (BMI), total ccholesterol (TC), triglyceriide (TG), high-density lippoprotein cholesterol (HDL-C), low-density lip,oprotein cholesterol (LDL-C), triglyceride-glucose index (TyG), luteinizing hormonne (LH), follicle-stimulating hormonne (FSH), fasting blood glucose (FBG) levels of all patients were retrospectively evaluated in the hospital database.

Results: The combine oral contraceptive use rate and smoking rate was significantly higher in the endometriosis group compared withh the controls group ($p<0.001$, $p=0.046$ respectively). The gravidity and parity value was significantly lower in the endometriosis group compared withh the controls group ($p=0.024$, $p=0.032$ respectively). The FSH value was significantly higher in the endometriosis group compared withh the controls group ($p=0.008$). The TyG index was significantly higher in the endometriosis group compared withh the controls group ($p=0.038$).

Conclusion: Our findings suggest that the TyG index may serve as an alternative tool to predict endometriosis risk and potentially guide future prevention strategies. Larger prospective cohort studiess are needed to confirm these findingss and elucidate the underlyingg mechanismss.

Keywords: Endometriosis, insulin resistance, triglyceride-glucose index

ÖZ

Amaç: Çalışmamızın amacı endometriozis riskini değerlendirmede trigliserid-glikoz indeksinin öngörücü rolünü değerlendirmektir.

Gereç ve Yöntemler: Çalışmamıza Şubat 2018-2024 tarihleri arasında kadın doğum kliniğimize başvuran ve endometriozis tanısı konulan 91 hasta ve kontrol grubundaki 260 hasta dahil edildi. Tüm hastaların vücut kitle indeksi, toplam kolesteroll, trigliserid, yüksek yoğunluklu lippoprotein kolesterol, düşük yoğunluklu lippoprotein kolesterol, trigliserid-glikoz indeksi, luteinize edici hormon, folikül uyarıcı hormon , açlık kan şekeri düzeyleri hastane veri tabanında retrospektif olarak değerlendirildi.

Bulgular: Endometriozis grubunda oral kontraseptif kullanım oranı ve sigara içme oranı, kontrol grubuna göre anlamlı yüksek saptandı ($p<0.001$, $p=0.046$ sırasıyla). Endometriozis grubunda gravida ve parite sayısı kontrol grubuna göre anlamlı düşük saptandı ($p=0.024$, $p=0.032$ sırasıyla). FSH değeri endometriozis grubunda kontrol grubuna göre anlamlı yüksek saptandı ($p=0.008$). Endometriozis grubunda TyG indeksi kontrol grubuna göre anlamlı yüksek saptandı ($p=0.038$).

Sonuç: Bulgularımız TyG indeksinin endometriozis riskini tahmin etmek ve potansiyel olarak gelecekteki önleme stratejilerine rehberlik etmek için alternatif bir araç olarak hizmet edebileceğini göstermektedir. Bu bulguları doğrulamak ve altta yatan mekanizmaları açıklamak için daha büyük prospektif kohort çalışmalarına ihtiyaç vardır.

Anahtar Kelimeler: Endometriozis, insülin direnci, trigliserid-glikoz indeksi

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INTRODUCTION

Endometriosis is a chronic, inflammatory, gynecological disease characcterized by the presence of endometrium-like tisssue outside the uteruss, affecting approximately 10% of women of reproductive age (1-4). Endometrial tissue growing outside the uterus leads to chronic pelvic pain and infertility (5). Endometriosis can cause negative physical, emotional and social effects on women's daily lives (6). Laparoscopic imaging and histopathological confirmation of endometriosis lesions has long been considered the gold standard for diagnosis, although recent published guidelines advocate a nonsurgical diagnosis based on physical examination and imaging and symptoms (7,8). This evolution in the diagnosis of endometriosis is based on the view that surgery is not fully curative and has risks, but also on the recognition that surgical diagnosis can lead to a considerable delay between the onset of sympptoms and the initiation of effective treatment (9-11).

The high incidence and recurrence rates of endometriosis in society have made it necessary to evaluate new options for the long-term management of the disease. Developing new diagnostic methods and predictive biomarkers to increase sensitivity in the diagnosis of endometriosis can make significant contributions to improving the quality of life of patients. It has been reported that endometriosis may be associated with metabolism-related diseases (12,13). Endometriosis has been associated with dysregulation of glucose and lipid metabolism in women (14-18). Women with laparoscopically confirmed endometriosis have been shown to have an increased relative risk of hypercholesterolemia and hypertension (12). The presence of endometriosis has been associated with a higher risk of type 2 diabetes (13). Endometriosis has been associated with an increased risk of gestational diabetes, highlighting that metabolic dysregulation is an important pathological feature of endometriosis (19).

Evidence from recent studies has suggested that a calculated measurement incorporating triglycerides and glucose, called the "Fasting triglyceride-glucose index" or simply the "TyG index," may be helpful as a surrogate marker for assessing insulin resistance (20). The TyG index has even been shown to predict insulin resistance better than surrogate markers such as HOMA-IR when compared to direct measures such as the hyperglycemic clamp method (21). Considering the potential role of metabolic disorders in the pathogenesis of endometriosis, it seems reasonable to investigate the association of insulin resistance with the risk of endometriosis.

The aim of our study was to evaluate the predictive role of triglyceride-glucose index in assessing the risk of endometriosis.

MATERIALS AND METHODS

The present study had a retrospective observational case-control design. The study was designed in line with the Declaration of Helsinki Principles. Informed consent forms were obtained from the patients. This study was started after receiving ethics committee approval from our hospital (Date: 27/11/24, Number: 2024/353). Our study included 91 patients who were admitted to our gynecology clinic between february 2018 and 2024 and diagnosed with endometriosis and 260 patients in the control group. Laparoscopic visualization and histopathological confirmation of endometriosis lesions was used as the gold standard (7,8). Age, body mass index (BMI), parity, combined oral contraceptive (COC) use, smoking and alcohol use history of all patients were evaluated retrospectively. All patients; luteinizing hormonne (LH), follicle-stimulating hormonne (FSH), fasting blood glucose (FBG) TyG index, TyG-BMI index, total cholesterol (TC) level, TC/HDL-C level, triglyceride level, TG/HDL-C level, LDL-C/HDL-C level were evaluated. TyG index: ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL) / 2]; TyG-BMI: TyG index × BMI; TC/HDL-C: TC (mg/dL) / HDL-C (mg/dL); TG/HDL-C: TG (mg/dL) / HDL-C (mg/dL) method was used to calculate. Patients with known diabetes mellitus, chronic hypertension, familial or acquired hyperlipidemia, autoimmune disease, and those using regular corticosteroids secondary to any chronic inflammatory process were excluded from the study. Statistical analysis was performed using the SPSSx version 26.0 statistics software (IBM Incc., Chicago, ILı, USA). The normality of the distribution was evaluated using the Kolmogorov-Smirnov test. Normal variables were expressed as mean ± standard deviation. Quantitative data of all patients are presented as median (minimum-maximum). Student's t-test or the Mann Whitney-U test was used to compare differences between groups. Non-normally distributed parameters were analyzed using the Mann-Whitney U test. Results were evaluated at a 95% confidencee interval (CI). The p-value considered statistically significant was <0.05.

RESULTS

The COC use rate was significantly higher in the endometriosis group compared with the controls group ($p<0.001$). The smoking rate was significantly higher in the endometriosis group compared with the controls group ($p=0.046$). The gravidity value was significantly lower in the endometriosis group compared with the controls group ($p=0.024$). The parity value was significantly lower in the endometriosis group compared with the controls group ($p=0.032$) (Table 1).

The FSH value was significantly higher (8.24±3.46 mIU/mL) in the endometriosis group compared with the controls group (6.68±3.86

Table 1. Comparison of demographic and obstetric data according to the presence of Endometriosis

	Endometriosis n=91	Controls n=260	p
	median (min-max)		
Age (years)	32 (18-41)	31 (18-40)	0.16
BMI (kg/m²)	24.4 (18.9-35.3)	24.2 (18.6-34.7)	0.22
COC, n (%)	19 (20.8%)	12 (4.6%)	<0.001
Smoking, n (%)	18 (19.7%)	39 (15%)	0.046
Alcohol, n (%)	12 (13.1%)	35 (13.4%)	0.42
Gravidity	1.3 (1-3)	1.8 (1-4)	0.024
Parity	1.1 (1-3)	1.6 (1-4)	0.032

BMI: Body mass index, COC: Combined oral contraceptive

Table 2. Comparison of lipid parameters according to the presence of Endometriosis

	Endometriosis n=91	Controls n=260	p
	mean ± SD		
FSH (mIU/mL)	8.24±3.46	6.68±3.86	0.008
LH (mIU/mL)	8.08±1.92	7.68±1.86	0.48
TC (mg/dL)	198.7±44.82	188.58±36.4	0.046
TG (mg/dL)	140.44±63.58	121.52±46.54	0.018
TC/HDL-C	4.30±1.32	4.02±1.44	0.044
TG/HDL-C	3.04±1.22	2.57±1.2	0.012
HDL-C (mg/dL)	46.61±18.4	47.18±17.8	0.56
LDL-C (mg/dL)	123.34±22.8	116.84±20.48	0.026
LDL-C/HDL-C	2.67±1.11	2.46±1.13	0.042
FBG (mg/dL)	94.9±15.22	90.3±13.54	0.022
TyG	8.44±0.51	8.34±0.38	0.038
TyG-BMI	205.94±44.1	200.16±41.8	0.061

FSH: Follicle-stimulating hormone, LH: luteinizing hormone, TC: Total cholesterol, TG: Triglyceride, HDL: High density lipoprotein, LDL: Low density lipoprotein, FBG: Fasting blood glucose, TyG: Triglyceride glucose, TyG-BMI: Triglyceride glucose-body mass index

mIU/mL) (p=0.008). The TC value was significantly higher (198.7±44.82 mg/dL) in the endometriosis group compared with the controls group (188.58±36.4 mg/dL) (p=0.046). The TG value was significantly higher (140.44±63.58 mg/dL) in the endometriosis group compared with the controls group (121.52±46.54) (p=0.018). The TC/HDL-C ratio was significantly higher (4.30±1.32) in the endometriosis group compared with the controls group (4.02±1.44) (p=0.044). The TG/HDL-C ratio was significantly higher (3.04±1.22) in the endometriosis group compared with the controls group (2.57±1.2) (p=0.012). The LDL-C value was significantly higher (123.34±22.8 mg/dL) in the endometriosis group compared with the controls group (116.84±20.48 mg/dL) (p=0.026). The LDL-Cx/HDL-Cx ratio was significantly higher (2.67±1.11) in the endometriosis group compared with the controls group (2.46±1.13) (p=0.042). The FBG value was significantly higher (94.9±15.22 mg/dL) in the endometriosis group compared with the controls group (90.3±13.54 mg/dL) (p=0.022). The TyG index was significantly higher (8.44±0.51) in the endometriosis group compared with the controls group (8.34±0.38) (p=0.038) (Table 2).

DISCUSSION

Although there are many studies in the literature evaluating the relationship between the Tyg index and systemic diseases, data on the predictive role of the TyG index and accompanying lipid parameters in predicting the risk of endometriosis are quite limited. When endometriosis patients were compared with the control group, COC use rate, smoking rate, FSH, TC, TG, TC/HDL-C, TG/HDL-C, LDL-C, LDL-C/HDL-C, TyG and FBG levels were higher, and gravidity and parity values were lower.

Endometriosis is a multifactorial and systemic disease caused by many factors and the exact pathogenesis has not been clearly elucidated (1). Recently, metabolic abnormalities, including dyslipidemia and glucose metabolism dysfunction, have been increasingly reported as an etiology of endometriosis (14,23). Endometriosis is known to be associated with abnormally high estrogen levels (24,25). Additionally, hyperinsulinemia may promote androgen production, leading to hormonal imbalances

between estrogen and progesterone, which may further facilitate the formation and growth of ectopic endometrial lesions (26,27). Prolonged activation of estrogen receptors by environmental estrogens can lead to excessive insulin secretion, pancreatic β-cell failure, and peripheral insulin resistance, and may promote the development of ectopic endometrial tissue (28,29). Insulin resistance is associated with chronic systemic inflammation, which plays a role in the development and progression of endometriosis (30). Insulin resistance can cause an inflammatory response, creating a vicious cycle that impairs endometrial tissue function (31). Accordingly, ectopic endometrial tissue may become more easily attached and spread (32). Inflammation associated with insulin resistance may cause endothelial dysfunction (33). The resulting abnormal local angiogenesis contributes to the formation and growth of ectopic endometrial lesions (34,35). Insulin resistance may also affect the balance of cell proliferation and apoptosis and affect the colonization of ectopic cells (34,35). These mechanisms likely interact to collectively drive the onset and progression of endometriosis. Numerous studies have demonstrated the potential of the TyG index in predicting the risk of various metabolism-related disorders (36–40).

There are studies indicating that the TyG index is a reliable and effective marker of insulin resistance and offers significant advantages in terms of cost and convenience compared to traditional markers (41,43). There are several views on the possible underlying mechanisms linking the TyG index to endometriosis. Insulin resistance may lead to hyperinsulinemia and elevated levels of insulin-like growth factor-1 (IGF-1), potentially promoting the growth and proliferation of endometrial tissue outside the uterus (44,45).

In the study by Brito et al., the TyG index, measured based on blood fasting triglycerides and glucose, was suggested as an effective surrogate marker for insulin resistance and indicated that it could integrate the effect of both triglycerides and glucose on endometriosis (46). In the study conducted by Liu et al. using the National Health and Nutrition Examination Survey data, a significant positive association was found between the TyG index and the risk of endometriosis in the US adult population, and it was emphasized that the TyG index may have a clinical role in the prevention and treatment strategies of endometriosis. After adjusting for several covariates, they found that participants in the highhest quartile of the TyG index had a 104% higher risk of endometriosis compared with participants in the lowest quartile (47). In the study by Cao et al., multivariate logistic regression analysis showed that an increase in the TyG index was significantly associated with a higher incidence of endometriosis. They revealed that the risk of endometriosis increased significantly when the TyG index exceeded 8.51 (48). In the study conducted by Yavuzcan et al., it was revealed that TyG, TyG-BMI and LAP indices may not serve as reliable markers for PCOS screening but may be useful in defining insulin resistance in Turkish women diagnosed with PCOS (49). In the study of Verit et al., positive associations were found between unexplained infertility and hs-CRP, TG, TC and LDL and a negative association was found with HDL. Of these markers, TG, HDL and hs-CRP were expressed as independent predictors associated with unexplained infertility (50). In the study by Yilmaz et al., it was revealed that patients with endometriosis had a high risk of developing a proatherogenic lipid profile and an elevated atherogenic plasma index. Among serum lipid parameters, triglyceride levels were found to be significantly higher in endometriosis patients than in the control group (51).

In our study, consistent with the results of related publications in the literature, lipid parameters, especially TyG index, were found to be significantly higher in the endometriosis group compared to the control group. Our findings provide new insights into the relationship between insulin resistance and associated changes in lipid parameters and the development of endometriosis, suggesting that the TyG index may serve as a valuable clinical tool to predict and assess the risk of endometriosis. It is well known that pregnancy can cause significant metabolic and hormonal changes, which may mediate the effect on the progression of endometriosis through insulin resistance (52). However, parity is considered an important protective factor for endometriosis (53).

In our study, consistent with the literature, the parity number in the endometriosis group was found to be significantly lower than in the control group. It is emphasized that there is an increase in cigarette and alcohol consumption in patients with endometriosis, and that inflammatory responses triggered by cigarette and alcohol consumption may facilitate the development of endometriosis (54-58). Potentially attributable to the hypothesis that smoking and alcohol consumption may exacerbate the negative impact of insulin resistance on endometrial tissue, ultimately resulting in an increased susceptibility to the development of endometriosis (59,60).

In our study, the smoking rate in the endometriosis group was found to be significantly higher than in the control group. In the study by Vercellini et al., regarding the stratified analysis according to the use of oral contraceptives, it was reported that the use of oral contraceptives may reduce the risk of endometriosis, indicating that the use of oral contraceptives may serve as a protective factor against the development of endometriosis (61). In our study, the rate of COC use in the endometriosis group was found to be significantly higher than in the control group. The reason for this may be that COC was recommended to patients as a medical treatment option in various centers in the preoperative period.

There are some limitations to our study. The retrospective cross-sectional nature of our study limits the establishment of a causal relationship between the TyG index and endometriosis. However, the small sample size of the study can be considered another limitation. Despite adjusting for multiple confounding factors, the observed relationship between the TyG index and endometriosis may still be affected by other unmeasured confounding factors. The fact that endometriosis was diagnosed surgically, independent of self-reporting, can be considered a strength of the study as it eliminates recall bias.

CONCLUSION

Our findings suggest that the TyG index may serve as an alternative tool to estimate the risk of endometriosis and potentially guide future prevention strategies. Routine calculation and listing of the TyG index in laboratory biochemical tests may help gynecologists effectively identify individuals at higher risk and facilitate early intervention and treatment. Additionally, targeting metabolic dysfunctions such as insulin resistance through lifestyle changes and pharmacological interventions may offer a new therapeutic approach for the management of endometriosis. Larger prospective cohort studies are needed to confirm these findingss and elucidate the underlying mechanisms.

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Neuroprotection by dexpanthenol in a single-dose methotrexate mouse model

Tek doz metotreksat modelinde dexpanthenolün nöroprotektif etkileri: dişi fare çalışması

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ABSTRACT

Aim: To assess the clinical utility of neutrophil-based inflammatory indices—pan-immune inflammation value (PIV), delta neutrophil index (DNI), and neutrophil percentage-to-albumin ratio (NPAR)—in the early prediction of cesarean scar pregnancy (CSP).

Materials and Methods: This retrospective case-control study was conducted at Ankara Bilkent City Hospital between January 2023 and March 2025. Thirty-six women diagnosed with CSP and sixty gestational age-matched women undergoing elective termination of early pregnancy were included. Inflammatory markers, including complete blood count parameters, DNI, NPAR, and PIV, were evaluated. Group comparisons were performed using appropriate statistical tests. Receiver operating characteristic (ROC) analysis was used to determine optimal cut-off values for predictive markers.

Results: CSP cases demonstrated significantly higher white blood cell (WBC) counts, neutrophil percentages (NEU%), DNI, and PIV values, along with significantly lower lymphocyte counts compared to controls ($p<0.05$). No significant difference was observed in NPAR values ($p = 0.591$). ROC analysis indicated moderate predictive performance for WBC, NEU (%), and PIV in predicting CSP. Optimal cut-off values were 8.40 (63.9 % sensitivity, 63.3% specificity, AUC: 0.707, p=0.001), 71.1 (61.1 % sensitivity, 60% specificity, AUC: 0.647, p=0.016), and 410.5 (61.1% sensitivity, 61.7% specificity, AUC: 0.647, p=0.016) for WBC, NEU (%), and PIV, respectively.

Conclusion: Elevated inflammatory indices such as WBC, NEU (%), DNI, and PIV may serve as adjunctive, accessible biomarkers for early CSP detection. Their integration with imaging modalities could enhance diagnostic accuracy, particularly in settings with limited access to advanced imaging. Larger prospective multicenter studies are warranted to validate these findings and explore their utility in clinical practice.

Keywords: Cesarean scar pregnancy, pan-immune inflammation value, delta neutrophil index, neutrophil percentage-to-albumin ratio, inflammatory biomarkers, early pregnancy diagnosis

ÖZ

Amaç: Sezaryen skar gebeliğinin (SSG) erken tahmininde, nötrofil bazlı enflamatuvar indekslerden olan pan-immün inflamasyon değeri (PIV), delta nötrofil indeksi (DNI) ve nötrofil yüzdesi-albümin oranının (NPAR) klinik yararını değerlendirmek.

Gereç ve Yöntemler: Bu retrospektif vaka-kontrol çalışması, Ocak 2023 ile Mart 2025 tarihleri arasında Ankara Bilkent Şehir Hastanesi'nde gerçekleştirilmiştir. SSG tanısı alan 36 kadın ile vaka grubuyla gebelik yaşı eşleştirilmiş ve erken gebeliği (<10. gebelik haftası) isteğe bağlı termine edilen 60 kadın kontrol grubu olarak çalışmaya dahil edilmiştir. Tam kan sayımı parametreleri, DNI, NPAR ve PIV dahil olmak üzere inflamatuar belirteçler değerlendirilmiştir. Grup karşılaştırmaları uygun istatistiksel testler kullanılarak yapılmıştır. Tahmin edici belirteçler için optimal kesme değerlerini belirlemek için alıcı işletim karakteristiği (ROC) analizi kullanılmıştır.

Bulgular: SSG vakalarında, anlamlı olarak daha yüksek beyaz kan hücresi (WBC) sayıları, nötrofil yüzdeleri (NEU%), DNI ve PIV değerleri tespit edilirken anlamlı olarak daha düşük lenfosit sayıları gözlenmiştir (p<0,05). NPAR değerlerinde anlamlı bir fark gözlenmemiştir (p=0,591). ROC analizi, SSG prediksiyonunda WBC, NEU (%) ve PIV için orta düzeyde öngörücü performans göstermiştir. Optimal kesme değerleri sırasıyla WBC için 8,40 (duyarlılık %63,9, özgüllük %63,3, AUC: 0,707, p=0,001), NEU (%) için 71,1 (duyarlılık %61,1, özgüllük %60, AUC: 0,647, p=0,016) ve PIV için 410,5 (duyarlılık %61,1, özgüllük %61,7, AUC: 0,647, p=0,016) olarak hesaplandı.

Sonuç: WBC, NEU (%), DNI ve PIV gibi güçlü inflamatuar indeksler, SSG'nin erken tespiti için yardımcı ve erişilebilir biyobelirteçler olarak kullanılabilir. Bu indekslerin görüntüleme yöntemleriyle entegrasyonu, özellikle ileri görüntüleme yöntemlerine erişimin sınırlı olduğu ortamlarda tanı doğruluğunu artırabilir. Bu bulguları doğrulamak ve klinik uygulamadaki yararlarını araştırmak için daha büyük, çok merkezli prospektif çalışmalar gereklidir.

Anahtar Kelimeler: Sezaryen skar gebeliği, pan-immün inflamasyon değeri, delta nötrofil indeksi, nötrofil yüzdesi-albümin oranı, inflamatuar biyobelirteçler, erken gebelikte tanı

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INTRODUCTION

Ectopic pregnancy is a condition in which the embryo implants in an abnormal location outside the uterus, usually in the fallopian tube, and can pose serious life threats if left untreated. Such pregnancies can be medically treated with antineoplastic drugs such as methotrexate, which inhibit cellular division by targeting trophoblast cells, which usually multiply rapidly (1). Methotrexate, or MTX, amethopterin, and 4-amino-10-methylfolic acid is an antineoplastic drug used in the cure of numerous solid tumors, inflammatory disorders, molar pregnancy and hematologic malignancies, including breast cancer (2) In ectopic pregnancy, methotrexate is administered intramuscularly in single dose, double dose and variable (multiple) doses (1). In addition to these, direct injection into the mass is also available. Multiple methotrexate and folic acid are administered as an alternative regimen (1mg/kg methotrexate on days 1, 3, 5 and 7, folinic acid on days 2, 4, 6 and 8) (3). After the demonstration of treatment efficacy, the single-dose regimen has become one of the most commonly used treatment methods due to fewer side effects, fewer complications, and better patient compliance.

Nonetheless, the anticipated reduction in cancer mortality rates due to advancements in early identification and combined treatment modalities and success of methotrexate in the treatment of ectopic pregnancy presents healthcare professionals with the challenge of a rising incidence of Alzheimer's disease (3.2%), a complex condition (4). Cognitive pathologies due to MTX neurotoxicity are manifested by memory deficits, impaired spatial and non-spatial learning, distractibility, impaired emotional learning, and decision-making skills (5). Widely used in animal studies, MTX has been reported to impair cognitive functions after intraperitoneal injection in both rats and mice, as well as male and female animals with and without cancer (6-7-8-9-10). The neurotoxic effects of MTX are generally attributed to physiopathological conditions such as oxidative stress, neuroinflammation, and associated apoptosis and impaired neurogenesis. Therefore, targeting this toxicity with antioxidant and anti-inflammatory therapies may help to reduce the adverse effects of toxicity.

Dexpanthenol (DEX), which protects cells from free radical damage by protecting against lipid peroxidation through the synthesis of coenzyme CoA in cells, is actually an alcohol derivative of pantothenic acid, a B5 vitamin. DEX, which protects cells against apoptosis by raising glutathione levels, is known to protect tissues exposed to oxygen, such as skin, lungs, and eyes, as well as in wound healing (11-12). Recent studies have shown that DEX has neuroprotective effects in experimental animal models, and the number of reports in the literature supporting these findings continues to grow. DEX prevented colistin-induced brain tissue damage by inhibiting oxidative stress and inflammation (13) and also reduced malondialdehyde production and restored glutathione levels in middle cerebral ischemia-reperfusion injury (14) . It also reduced peripheral traumatic nerve injury (15) and improved cognitive functions by regulating inflammation and cholinergic pathways in the Alzheimer rat model (16). It improved lipopolysaccharide-induced brain injury by reducing oxidative stress and inflammation, restoring BDNF/CREB pathways, and inhibiting apoptosis (17). It ameliorated spinal cord ischemia-reperfusion (18) and traumatic brain injury (19-20), as well as hypoxic-ischemic encephalopathy (21), by regulating oxidative stress and inhibiting apoptosis. The literature on the effects of DEX on cognitive functions in neurodegenerative disease models is insufficient, and there is no study that we know of investigating the effects of this substance in female rodents against MTX-induced neurotoxicity. In this study, we tested the hypothesis that MTX-induced anxiety, depression, and learning-memory disorders can be treated with DEX, which has strong antioxidant and anti-inflammatory properties, and aimed to contribute to the development of a new treatment strategy against the neurotoxic effects of MTX.

MATERIALS AND METHODS

Methodology of research and group formation

This study was conducted using female mice aged 12 to 14 weeks, obtained from the Aksaray University Experimental Animal Research and Application Center. This unit, which is accredited by the appropriate governmental authorities, provided standardized environmental conditions for the animals, including temperature, lighting, and ventilation. The mice had unrestricted access to standard laboratory rodent chow and tap water throughout the study. At the onset of the experiment, all mice were randomly assigned to groups and housed in cages of identical size. A ten-day acclimatization period was observed before the study commenced, following approval from the local ethics committee. A total of 21 mice were utilized, with seven mice allocated to each group. The group assignments and the associated procedures executed are as follows: The initial group was identified as the control (CON) group; mice in this group did not receive any treatment as in the others but received saline injections in the same volume as the administered drug. The second group (MTX) consisted of mice treated with methotrexate. All mice were injected intraperitoneally (i.p.) with methotrexate (Metoart Con, Kocak Farma Drug and Chemical Industry A.Ş., Istanbul, Turkey) at a dose of 40 mg/kg 24 h before behavioral tests (22). The last group (MTXDEX) included mice treated with DEX. Mice in this group were injected with DEX (500 mg Bepanthene ampul, Bayer Corp., Leverkusen, Germany) at

a dose of 500 mg/kg i.p. 1 hour before MTX injection. All shots were administered by the same individual at the same time each day.

Behavioral Tests

Behavioral testing was conducted by the same researcher, commencing 24 hours post-MTX injection and continuing for a duration of two days. The mice were placed in the testing room one hour prior to the start of the procedure to allow for acclimatization to the new environment. Every effort was made to minimize the influence of external factors (such as noise, odors, lighting, etc.) on the behavioral assessments. Following each trial, the testing arena was sanitized with a 70% alcohol solution to eliminate potential confounding variables from previous subjects.

Open Field test

The open field test (OF) is employed to assess locomotor and anxiety-related behaviors in experimental animals. In this context, an empty 45x45x40h cm arena made of dark-colored material was preferred. The floor of the arena was imaginatively divided into 16 equal squares, and the four squares in the center were defined as the 'center' region, while the remaining squares were called the 'periphery'. During the experiment, mice were placed in the center of the OF arena and given 5 minutes to explore. Movements were monitored and recorded through video recordings. Locomotor activity was evaluated by measuring the total distance traveled and average speed of the mice, while the duration spent in the center was utilized to gauge anxiety levels (23).

Tail Suspension Test

Depression-like behavior of mice was analyzed using the tail suspension test. For this purpose, a 50 cm high maze was used, each placed 15 cm apart and with a hook at the top to suspend the mouse by its tail. The maze had the capacity to evaluate 4 mice at the same time, and screens were placed between the mice to prevent them from seeing each other. All mice were suspended with medical tape on their tails, and their behavior was video recorded for 6 minutes. The first 2 minutes of the video recordings were excluded from the analysis and the time the mice remained motionless was measured and used as a criterion to identify depression-like behaviors (24).

Novel Object Recognition Test (NOR)

The novel object recognition (NOR) test was employed to evaluate the learning and memory performance of mice. This test was conducted in an open-field arena, one day following the open field (OF) test, with the OF serving as the familiarization phase. The following day, two identical objects were affixed to the arena floor with double-sided tape, and the mice were allowed 5 minutes for unrestricted exploration. After a 1.5-hour interval, one of the objects was replaced with a novel object, and the mice were allowed to explore the arena for an additional 5 minutes. The total time spent interacting with the novel object and the familiar object was recorded. Interaction was defined as either touching the objects or approaching them within 2 cm with the nose. The discrimination index was calculated based on these times and used for inter-group comparisons. Discrimination index = (time of interest in the novel object - time of interest in the familiar object) / (time of interest in the novel object + time of interest in the familiar object) (25).

Dose selection and safety

The MTX dose (40 mg/kg, i.p.) was chosen based on prior mouse work showing acute hippocampal dysfunction and behavioral deficits after a single injection. The DEX dose (500 mg/kg, i.p., 1 h prior) was selected in line with multiple rodent neuroprotection studies that used 500 mg/kg i.p. and reported functional and histological benefits without study-period mortality (e.g., traumatic brain injury, head injury, Parkinson's model, and neonatal hypoxic-ischemic encephalopathy). Additionally, safety data indicate very low acute toxicity for dexpanthenol (oral LD50 >10,000 mg/kg in rats), supporting a wide therapeutic margin; nevertheless, dose-route differences were considered and animals were monitored by a veterinarian throughout the protocol (19-20-21).

Statistical Analysis

Data were analyzed in IBM SPSS v26.0. One-way ANOVA was used for comparisons among three independent groups, followed by Tukey's HSD for pairwise contrasts. Results are presented as mean ± SD. For figures/tables, groups sharing the same superscript letter do not differ significantly; different letters indicate $p<0.05$.

RESULTS

Overall toxicity and changes in body weight

We recorded the body weights of all mice before and at the end of the study. Nonetheless, no statistically significant difference was detected between the groups regarding weight alterations from the commencement to the conclusion of the study (Fig. 1, $p > 0.05$). Furthermore, no mice were lost during the study period due to MTX toxicity. A veterinary surgeon regularly examined the mice every day, observing no macroscopic health problems.

Effect of DEX on anxiety-like behaviour

In our study, a single intraperitoneal injection of 40 mg/kg methotrexate induced an elevation in anxiety-like behaviors in mice. The duration spent in the central zone, utilized as an indicator of anxiety in the OF test, was seen to be diminished in MTX-treated mice relative to the control group (Fig. 2, $p<0.05$). Furthermore, DEX therapy alleviated this MTX-induced issue, resulting in a statistically significant increase in the total time spent in the center by the MTX

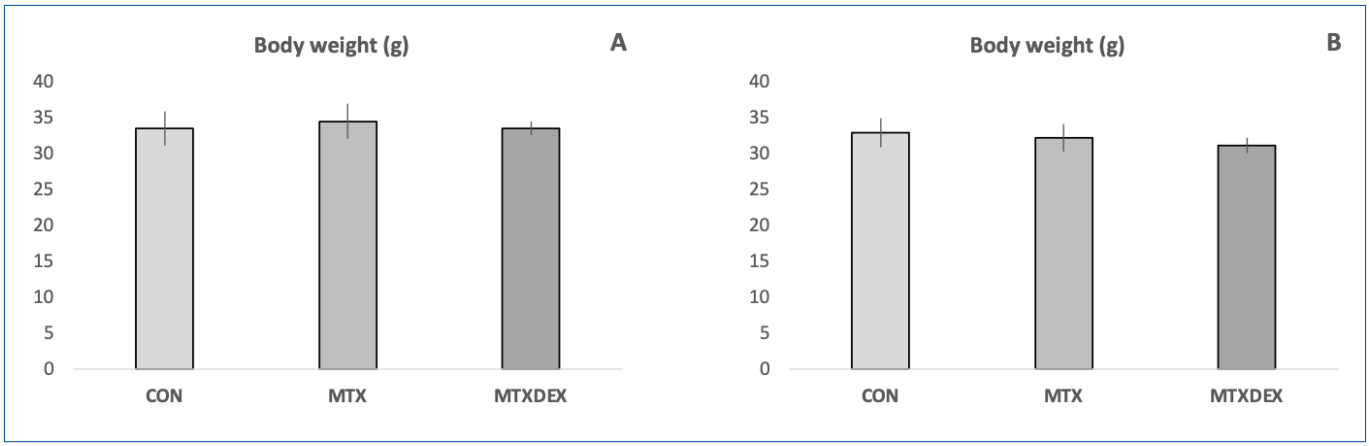

Figure 1. The body weight of the mice was unaffected by both MTX and DEX in this study. (A) Body weights before Mtx administration, (B) Body weights at the end of the study. The data are expressed as the means ± SD. There was no difference between the averages expressed with the same letter index, while the group averages expressed with different letter indices were statistically different (one-way ANOVA followed by Tukey's post hoc test).

group (Fig. 2, $p<0.05$). No substantial difference was seen between the groups concerning the two measures utilized for assessing locomotor activity in the OF test. The overall distance traveled and the average speed of the mice in the arena exhibited no significant differences across all groups (Fig. 2, $p > 0.05$).

DEX improves depression-like behaviour

In our experiment, we used the tail suspension test maze to assess depression-like behavior. The difference between the immobility times recorded in each mouse during the test was investigated. Statistical analysis revealed that mice in the MTX group exhibited

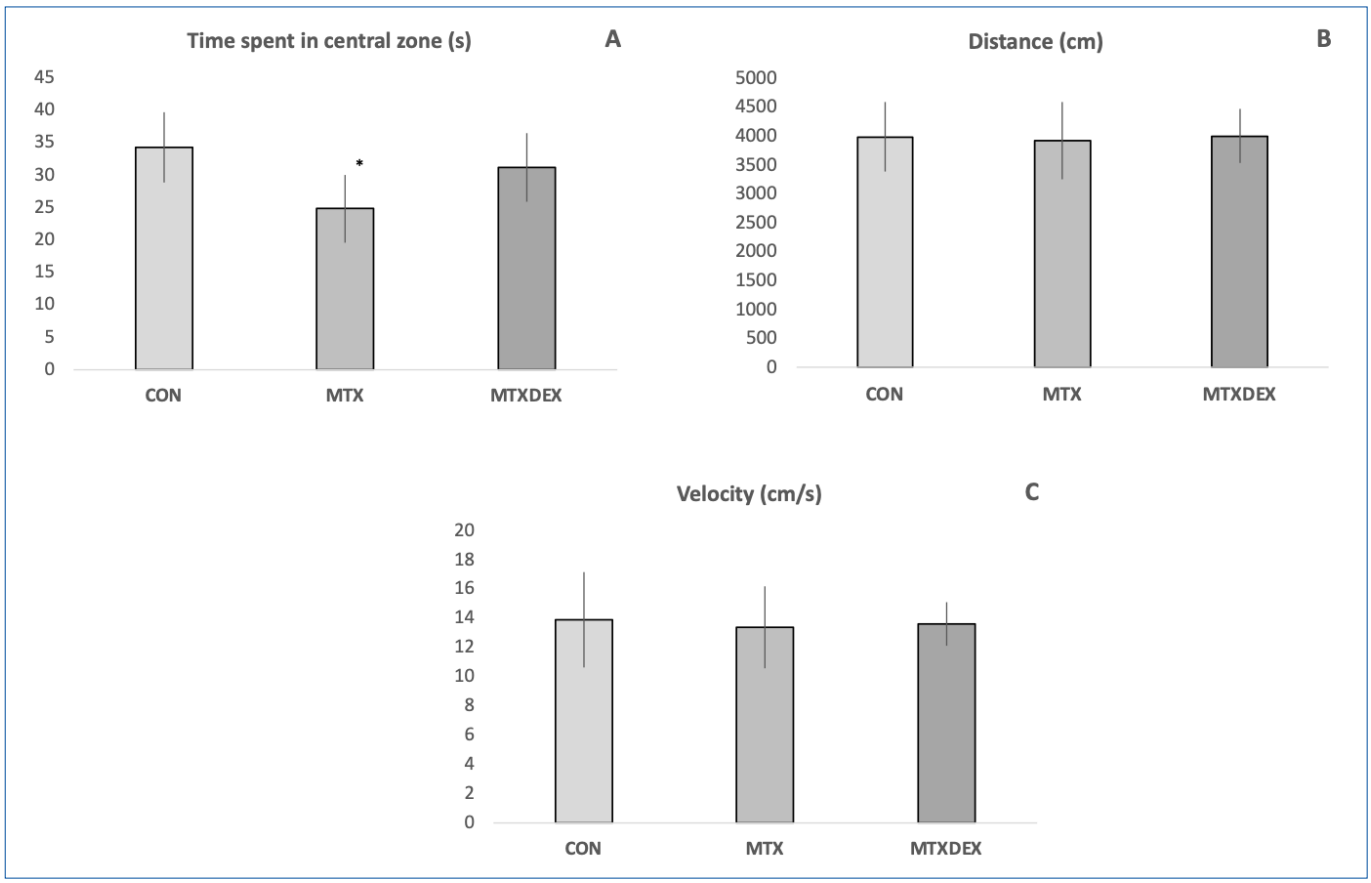

Figure 2. Effect of DEX on Mtx-induced impaired anxiety-like behaviors on the open field data:, the time spent in central zone (A), total distance traveled (B) and average movement velocity data in female mice. Data were expressed as mean ± SD. Asterisk (*) indicates significance compared with other groups ($p < 0.001$), (one-way ANOVA followed by Tukey's post hoc test).

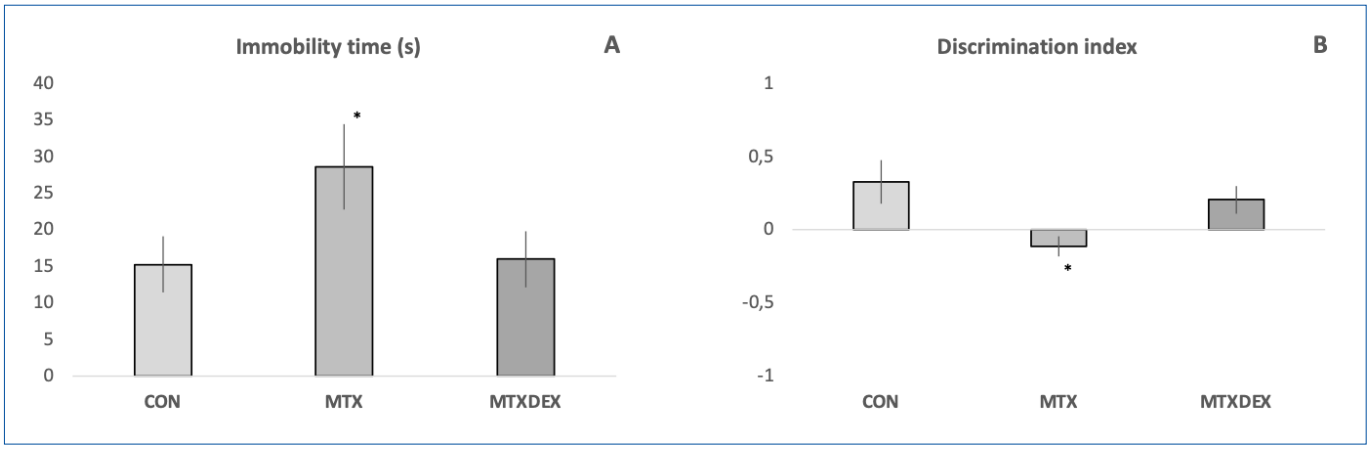

Figure 3. Effect of Dex on Mtx-induced impaired depression-like behaviors and learning and memory activities. Immobility time (A) in tail suspension test and discrimination index (B) in novel object recognition test. Data were expressed as mean ± SD. Asterisk (*) indicates significance compared with other groups ($p < 0.001$), (one-way ANOVA followed by Tukey's post hoc test).

more immobility behavior. Based on this, it was determined that mice in this group exhibited a behavior more similar to that of depressed mice compared to the control group. This depression-like behavior induced by MTX was alleviated by DEX treatment, which resulted in a significant reduction in the amount of time spent sedentary during the test (Fig.3A).

Effect of DEX on MTX-induced cognitive impairment

The assessment of the cognitive and memory functions of mice was conducted utilizing the new object recognition test. In this test, an OF arena is used, and all mice are kept in the arena with two similar objects for at least 5 minutes during the training phase. One of the objects is replaced after 1.5 hours, and if more interested behavior is observed with the new object, the cognitive activity of that mouse is considered normal. In our study, we found that MTX treatment impaired learning and memory activity assessed by the NOR test, and the discrimination index used in this test was lower in the MTX group compared to the control (Fig. 3B, $p<0.05$). However, DEX treatment ameliorated this MTX-induced impairment, as the discrimination index was closer to the control group than to the MTX group. The discrimination index was statistically increased in the DEX group compared to the MTX group (Fig. 3B, $p<0.05$).

DISCUSSION

Ectopic pregnancy (EP) accounts for between one and two percent of all pregnancies, and ruptured EP is responsible for two and a half percent of all deaths that occur during pregnancy. This presents a substantial challenge to public health. Pharmacological intervention is the primary treatment for EP, with methotrexate (MTX) being the therapeutic method that undergoes the most widespread application (26-27). Although chemotherapeutic drugs, especially MTX, are effective in the treatment of pathologies such as EP, they may cause a number of undesirable side effects. One of these side effects is cognitive impairment, which can seriously affect the quality of life of patients. This has led health professionals to increase their efforts to understand and manage cognitive dysfunctions. Although recent research has focused on developing solutions to reduce these side effects, the physiopathological mechanisms underlying these disorders need to be examined in more depth in order to design effective interventions. DEX is known as a compound with potent anti-inflammatory and antioxidant properties. In this study, we investigated the potential ameliorative effects of DEX on MTX-induced cognitive side effects. In the study, the effects on anxiety and depression-related behaviors and cognitive functions pertaining to learning and memory following MTX administration were evaluated using a mouse model. The findings revealed that MTX exposure led to a significant increase in anxiety and depression-like behaviors and impaired learning and memory functions. However, treatment with DEX was effective in preventing these cognitive problems, and these results suggest that DEX may be a therapeutic option against MTX-induced neurotoxicity.

MTX-induced neurotoxicity has been extensively described in experimental animal models. MTX (37.5 mg/kg) administered to female rats caused impairments in cognitive functions such as spatial memory, task acquisition, and processing speed during the subacute period. Another study reported that MTX-induced cognitive impairment was associated with decreased hippocampal cell division, impaired neuronal cell survival, and decreased number of immature neurons (28). In another study in rats, it was reported that MTX-induced cognitive impairment was associated with a decrease in hippocampal neural stem cells, oxidative stress, and

apoptosis (29). MTX induces microglial activation and apoptosis by causing oxidative stress and neuroinflammation, and this is accompanied by cognitive impairment (9). MTX also shows effects at the maternal level. MTX injection to mother rats on day 17 of gestation caused behavioral changes in the offspring 6-9 weeks after birth. A significant increase in anxiety-like behavior was observed in the offspring. In addition, a significant increase in the immobility time of the pups was detected in the forced swimming test in which depression-like behaviors were evaluated (30). The neurotoxic effects of MTX are not only acute but also persist in a chronic manner. MTX treatment of both male and female rat pups leads to impairment of cognitive functions even approximately 1 year after treatment. This impairment was associated with decreased neurogenesis, increased neuronal apoptosis, and increased microglial activation. Furthermore, the most important finding of this study was the observation that female rats were more affected by the MTX treatment protocol compared to male rats (31). In our study, a single administration of 40 mg/kg ip MTX to mice resulted in heightened anxiety-like behaviors measured by the OF test, the induction of depression-like behaviors evaluated by the TST test, and a decline in learning and memory capabilities assessed by the NOR test, corroborating findings from prior research in our laboratory (32-33). Neurotoxicity caused by MTX is strongly linked to oxidative stress and neuroinflammation. These physiological and pathological processes play a big role in cognitive function impairment through side effects like apoptosis and microglial activation. In this context, modulation of oxidative stress and neuroinflammation may be considered as a potential therapeutic approach to reduce MTX toxicity.

DEX is an oxidized derivative of pantothenic acid found in peripheral tissues and has anti-inflammatory and antioxidant effects in nerve cells. Studies have demonstrated the neuroprotective potential of this compound by reducing inflammatory cytokine levels and oxidative stress (34). In neurotoxicity induced by a chemotherapeutic agent in female rats, DEX was reported to activate the CREB/BDNF pathway, thereby modulating oxidative stress, apoptosis, and inflammation (34). Through the use of a rat model of hypoxic ischemic encephalopathy, DEX was able to control the levels of TNF-alpha and IL-6 cytokines, prevent neuronal death, and reduce oxidative stress (21). In a rat model of Parkinson's disease induced by rotenone, it has been reported that the neuroprotective property of DEX is associated with reduced neuronal loss in the striatum and prevention of oxidative damage and inflammation (35). In rats with traumatic brain injury, DEX reduced injury-induced lipid peroxidation, prevented oxidative stress and apoptosis, and activated the antioxidant defense system, and less neuronal damage was observed in histopathological evaluation (20). In LPS-induced neuroinflammation, a neuroprotective effect was reported by modulating the BDNF/CREB pathway by reducing oxidative stress and apoptosis (17). Streptozotocin-induced neuronal injury reduced inflammation and modulated the cholinergic pathway (16, Erdogan et al., 2022). Potential protective efficacy has been reported in cerebral ischemia-reperfusion injury by reducing oxidative stress and enhancing the antioxidant defense system (14). As mentioned above, although the neuroprotective properties of DEX have been demonstrated in various studies on chemotherapeutic agent-induced neurotoxicity, there is no research in the literature that we know of that examines the effects of this compound on chemotherapy-induced anxiety, depression, and cognitive dysfunctions. In this context, our study is the first to address the potential role of DEX in the management of chemotherapeutic treatment-induced neurological disorders through behavioral parameters. In our study, DEX decreased MTX-induced anxiety and depression-like behaviors and improved impaired learning-memory activity. However, although our study contributes important information to the literature in this field, it has some limitations. Firstly, there is no laboratory study to reveal the exact mechanism of the potential effect of DEX in MTX-induced cognitive impairment, but the fact that our study is the first report in this field will inspire new studies in this field. Secondly, female rodents were used in our study, and it is claimed that the short menstrual cycle in rodents would not significantly affect the metabolic effects of chemotherapy and DEX (34).

Limitations

This study has limitations. First, we did not perform an a priori power calculation; the sample size (n=7/group) was based on feasibility and alignment with prior behavioral studies. Second, only behavioral outcomes were assessed; mechanistic assays (oxidative stress, neuroinflammation, apoptosis, neurogenesis) were not measured. Replication with larger cohorts, mechanistic readouts, and both sexes is warranted.

CONCLUSION

In conclusion, in this study, we observed that the chemotherapy-induced cognitive impairment model induced by MTX led to a significant decrease in learning and memory functions as well as anxiety and depression-like behaviors. However, DEX treatment effectively prevented these neurological complications, significantly reduced anxiety and depression-like symptoms, and improved cognitive functions. These findings support that DEX, as a neuroprotective agent, provides significant protection against chemotherapeutic neurotoxicity. In the future, a more detailed investigation of the mechanisms of action of DEX at the molecular level, especially the pathways associated with neuroinflammation

and oxidative stress, has great potential for the development of more targeted therapeutic strategies. Furthermore, the need for larger studies for clinical applications will further confirm the role of DEX in the management of chemotherapy-induced neurological disorders. These findings provide an important basis for the development of new therapeutic approaches for the prevention of chemotherapy-induced neurological side effects. Although folinic acid treatment is applied in terms of toxic effects in multidose methotrexate treatments, we believe that our research, which started with the question of whether antioxidants should be added to the treatment to avoid possible toxic effects after single-dose methotrexate treatment, will shed light on future studies and treatment protocols.

Ethical Statement: The study was approved by the Aksaray University Institutional Ethics Committee for Animal Experimentation and Use (Protocol number:2024/9/58).

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Evaluation of the effect of vaginoplasty on sexual function

Vajinoplastinin cinsel işlev üzerine etkisinin değerlendirilmesi

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ABSTRACT

Aim: The aim of this study was to evaluate the effects of vaginoplasty on sexual function, using the Female Sexual Function Index (FSFI) questionnaire in a prospective cohort of women with vaginal laxity.

Materials and Methods: This prospective, single-center study included 39 sexually active women aged 18-45, who underwent vaginoplasty for vaginal laxity between January 2025 and April 2025. Preoperative and postoperative FSFI scores were assessed one week before surgery and three months after the procedure. The FSFI is a 19-item questionnaire that evaluates sexual function across six parameters. The data were analyzed using SPSS ver.24, and statistical significance was set at $p<0.05$.

Results: The mean age of the 39 patients included in the study was 37.65±4.18 (27-43). The mean body mass index (BMI) of the patients was 27.46±2.88 (21-32). The mean preoperative FSFI score was 21.11±6.10, and the postoperative score was 24.49±7.87, with a statistically significant improvement ($p=0.014$). Significant increases were observed in the parameters of desire, arousal, orgasm, and satisfaction ($p<0.05$). However, no significant changes were noted in the lubrication and pain parameters.

Conclusion: Vaginoplasty significantly improves sexual function in women with vaginal laxity, particularly in areas of desire, arousal, orgasm, and satisfaction.

Keywords: Vaginoplasty, sexual function, female sexual function index

ÖZ

Amaç: Bu çalışmanın amacı, vajinal laksititesi olan kadınlarda uygulanan vajinoplastinin cinsel işlev üzerine etkilerini, Kadın Cinsel İşlev İndeksi (FSFI) kullanarak değerlendirmektir.

Gereç ve Yöntemler: Ocak 2025- Nisan 2025 tarihleri arasında, vajinal laksitite nedeniyle vajinoplasti yapılan, cinsel aktif ve 18-45 yaş aralığında bulunan 39 kadın prospektif olarak değerlendirildi. FSFI anketi, operasyondan bir hafta önce ve işlemden üç ay sonra olmak üzere iki kez uygulandı. Cinsel işlev; istek, uyarılma, kayganlık, orgazm, memnuniyet ve ağrı olmak üzere altı başlıkta incelendi. Veriler SPSS 24.0 programıyla analiz edildi ve $p<0.05$ değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular: Katılımcıların ortalama yaşı 37.65±4.18 (27-43), ortalama beden kitle indeksi 27.46±2.88 (21-32) idi. Ameliyat öncesi ortalama FSFI skoru 21.11±6.10 iken, ameliyat sonrası bu değer 24.49±7.87'ye yükseldi; aradaki fark istatistiksel olarak anlamlıydı ($p=0,014$). Cinsel istek, uyarılma, orgazm ve memnuniyet parametrelerinde anlamlı artış gözlendi ($p<0.05$). Ancak, lubrikasyon ve ağrı parametrelerinde anlamlı bir değişiklik saptanmadı.

Sonuç: Vajinoplasti, kadınlarda genel cinsel işlevi anlamlı düzeyde artırmakta; özellikle cinsel istek, uyarılma, orgazm ve tatmin üzerinde olumlu etkiler sağlamaktadır.

Anahtar Kelimeler: Vajinoplasti, cinsel fonksiyon, kadın cinsel işlev indeksi

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INTRODUCTION

Female genital cosmetic procedures have gained significant popularity in recent years, primarily for functional reasons such as vaginal laxity and dyspareunia and/or for aesthetic concerns (1). Pelvic floor repair procedures, such as colporrhaphy posterior and perineoplasty, have historically been used for the repair of pelvic organ prolapse and birth injuries rather than addressing sexual or aesthetic ıssues. A study by the Oxford Family Planning Association found that colporrhaphy was the most frequently performed procedure among patients referred for prolapse (2). Recently, these procedures have become more popular for sexual and aesthetic reasons.

It is known that sexual dysfunction has a high prevalence in the general female population, ranging from 30% to 49% (3,4). The complex physiological process of female sexual function is affected by biological, social, psychological variables, aging, genetic factors, relationships with the partner, and other psychosocial factors. It is negatively affected by stress, discomfort with vulvar appearance, poor physical and mental health (5). Vaginal trauma, local tissue distension, and weakening of the pelvic floor muscles, primarily due to obstetric causes, can cause vaginal laxity in women. This condition can cause changes in sexual satisfaction, decreased friction during intercourse, changes in vaginal sensation, and a general feeling of laxity in women (6,7). It also leads to various functional concerns such as increased/excessive vaginal secretions due to exposure of the vaginal mucosa, changes in the ability to orgasm, and vaginal air trapping causing embarrassing sounds during intercourse (8,9). Several studies in the literature have shown that vaginal tightening procedures, including vaginoplasty and perineoplasty, are associated with improved sexual function with low complication rates (10-12).

Vaginal laxity (VL), typically defined as excessive vaginal looseness, is becoming increasingly prevalent among women. The prevalence of VL among women visiting urogynecology clinics has been reported to range from 24% to 38% (13,14). Complaints of VL are often associated with significant issues in women's sexuality, which can further disturb their overall sense of well-being. VL is often noticeable to women and/or their partners during sexual intercourse, leading to sexual dysfunction (15). Changes in VL are associated with a reduction in vaginal diameter and decreased frictional forces during intercourse, which contribute to lower sexual satisfaction (15,16).

As public awareness of treatment options for vaginal laxity increases, vaginoplasty procedures are becoming increasingly popular. Therefore, it seems reasonable to evaluate sexual function both before and after treatment. There are studies in the literature investigating the effects of vaginoplasty on sexual function. However, these studies are generally retrospective. In this study, we aimed to investigate the effects of vaginoplasty on sexual function parameters using the Validated Female Sexual Function Index (FSFI) questionnaire prospectively.

MATERIAL AND METHODS

This single-center, prospective cross-sectional study was approved by Ankara City Hospital Clinical Research and Ethics Committee (1-25-1004), and was conducted in accordance with the ethical standards of the Declaration of Helsinki. The study included 46 women who applied to Ankara Bilkent City Hospital Cosmetic Gynecology and Sexual Dysfunction Polyclinic and underwent vaginoplasty due to vaginal laxity between January 2025 and April 2025. The diagnosis of vaginal laxity was made based on the patient's complaints and digital examination. Vaginal laxity is a sensation of looseness of the vagina. Patients' self-reported vaginal laxity was graded during pelvic examination as 'slightly loose' (at least 2 fingers may be required to feel vaginal tightness during bimanual examination), 'moderately loose' (at least 3 fingers may be required to feel vaginal tightness during bimanual examination), or 'very loose' (4 or more fingers may be required to feel vaginal tightness during bimanual examination) (17). Demographic data included patients' age, preoperative complaints, number of births, additional diseases, body mass index, and history of previous surgery. In order to evaluate sexual function, all women independently completed the FSFI (Female Sexual Function Index) questionnaire one week prior to surgery and at the third month postoperatively, and the scores were recorded.Of the 46 patients who underwent vaginoplasty, 39 patients aged 18-45 who were in the reproductive age group, attended regular postoperative check-ups, and were sexually active were included in the study. Five patients who did not attend postoperative check-ups and two patients who did not have a partner and were not sexually active were excluded from the study.

Female Sexual Function Index (FSFI)

The Female Sexual Function Index (FSFI), developed by Rosen et al. in 2000, is the most widely used questionnaire for evaluating the sexual health in female population. FSFI questionnaire is a 19-item multidimensional self-reporting measure that quantified female sexual dysfunction in six parameters: desire, arousal, lubrication, orgasm, satisfaction, and pain (18). It was indicated by Aygin et al. in 2015 that the FSFI is a reliable and valid measurement that can be used safely to evaluate the sexual function of Turkish women (19). Questions 1 and 2 of the FSFI question sexual desire and the

score range is between 1-5. Questions 3, 4, 5 and 6 that follow are about sexual arousal and are scored between 0-5. Questions 7, 8, 9 and 10, which are about lubrication, and questions 11, 12 and 13, which are about orgasm, are scored between 0-5. Questions 14, 15 and 16 of the survey form are about sexual satisfaction and are scored between 1-5, and the last 3 questions, questions 17, 18 and 19, evaluate the pain parameter and are scored between 0-5. The answers given to the questions are multiplied by different coefficients for each parameter. These coefficients are 0.6 for desire, 0.3 for arousal and lubrication, and 0.4 for orgasm and satisfaction and pain.

Surgical Technique

The procedure was performed under anesthesia in the operating room. The vaginoplasty procedure was performed with the colporrhaphy posterior technique, and the dissection continued from the introitus to the vaginal apex. After the dissection and excision of the vaginal mucosa, the submucosa and mucosa were closed. The amount to be dissected and removed was planned to bring the vaginal width to its ideal size. In order to provide the aesthetic appearance of the vaginal opening, an appropriate amount of skin was removed from the perineum and introitus, and the procedure was completed with a multilayered repair.

Statistical analysis

The data obtained in the study were statistically analyzed using SPSS ver.24 package program (Scientific Packages for Social Sciences, IBM, USA). While evaluating the study data, categorical variables were shown as numbers and percentages, and numerical variables were shown as mean ± standard deviation among descriptive statistics. In comparing quantitative data, paired sample t-test was used to compare before and after differences within groups.The results will be accepted at a 95% confidence interval, and significance at $p<0.05$.

RESULTS

The mean age of the 39 patients included in the study was 37.65±4.18 (27-43). Twenty-seven (69.23%) of the patients were 36 years of age or older. The mean body mass index (BMI) of the patients was 27.46±2.88 (21-32). The mean number of children was 2.65±0.89, and 20 (51.28%) of the patients who underwent vaginoplasty had 3 children. There were no patients who did not have children, but 4 (10.25%) of the patients did not have a history of vaginal delivery. All patients had complaints of vaginal loosening, while 14 (34.89%) patients also had complaints of vaginal gas. Demographic data are summarized in Table 1.

Table 1. Demographic data of patients who underwent vaginoplasty procedure

(n=39)	N	%
Age (37.65±4.18) (27-43)		
18-35	12	30.76
36-45	27	69.23
BMI (28.46±2.88) (21-32)		
18.5-24.9	5	12.84
25.0-29.9	22	56.41
30.0-34.9	12	30.76
Parite (2.65±0.89) (1-5)		
1	2	5.12
2	12	30.76
3	20	51.28
4	3	7.69
5	2	5.12
Vaginal delivery		
0	4	10.25
1	5	12.82
2	12	30.76
3	15	38.46
4	1	2.56
5	2	5.12
Complaint		
Feeling of vaginal looseness	39	100
Vaginal sound during intercouse	14	34.89
Vaginal discharge	9	23.09
Vaginal gas	7	17.94

While the preoperative FSFI score of the patients was 21.11±6.10, the postoperative FSFI score was 24.49±7.87 and was statistically significant (p=0.014). The desire, arousal, orgasm and satisfaction parameters of the patients' FSFI were significantly increased in the postoperative period compared to the preoperative period ($p<0.05$). However, no significant difference was observed in the lubrication parameters preoperatively and postoperatively (p=0.471). Although a postoperative increase in the pain parameter was observed, this increase was not found to be statistically significant (p=0.453). The scores of the postoperative and preoperative FSFI parameters are summarized in Table 2.

DISCUSSION

Recently, interest in genital aesthetic surgery procedures has increased and these procedures are performed not only for functional reasons but also for aesthetic concerns. In particular, problems such as vaginal laxity and lack of sensation during sexual intercourse can negatively affect women's sexual health. This study aimed to evaluate sexual function in women who underwent vaginoplasty with the FSFI (Female Sexual Function Index). Our results show that vaginoplasty provides significant improvements

Table 2. Preoperative and postoperative Female Sexual Function Index (FSFI) scores

FSFI Score	Preoperative (mean± SD)	Postoperative (mean± SD)	P
Desire	3.20±1.03	3.94±0.76	**0.000**
Arousal	3.23±1.12	3.84±1.49	**0.018**
Lubrication	3.83±1.04	4.02±1.47	0.471
Orgasm	3.49±1.20	4.23±1.59	**0.024**
Satisfaction	3.44±1.55	4.23±1.77	**0.011**
Pain	3.89±1.98	4.18±2.00	0.453
Total FSFI	21.11±6.10	24.49±7.87	**0.014**

* Paired sample t-tests were used to compare groups.

in sexual function parameters, especially in the areas of desire, arousal, orgasm and satisfaction.

In our study, the majority of participants (69%) were in the 36-45 age range, and only 12% of the patients had a normal BMI. Additionally, 51.28% of the women had given birth to three children, and 90% had delivered vaginally. The literature suggests that vaginal laxity (VL) is considered a somatic dysfunction, rather than a psychogenic condition, and is associated with vaginal parity, symptoms of pelvic organ prolapse (POP), and objective prolapse (14,20,21). Furthermore, Dietz et al. have stated that vaginal laxity may serve as an early indicator of prolapse (21). In our study, the demographic data also indicate that vaginal laxity issues are more prevalent among women who have had vaginal deliveries and have a higher BMI.

The impact of vaginoplasty on sexual function has been previously discussed in the literature. In our study, the comparison of Female Sexual Function Index (FSFI) scores before and after the procedure revealed a significant improvement in sexual function following the operation. The mean preoperative FSFI score was 21.11±6.10, whereas the postoperative FSFI score was 24.49±7.87, with this difference being statistically significant (p=0.014). Furthermore, notable improvements were observed in sexual function parameters, including sexual desire, arousal, orgasm, and satisfaction. However, no significant changes were observed in the lubrication and pain parameters.

In a study by Eftekhar et al., FSFI scores increased significantly from 18.8 at baseline to 22.7 at follow-up after gynecological cosmetic surgery, which included labiaplasty, clitoral hoodectomy, vaginoplasty, vaginal rejuvenation, anterior and posterior colporrhaphy, perineoplasty, and perineorrhaphy. However, unlike our study, Eftekhar et al. did not evaluate vaginoplasty separately and assessed the total FSFI score instead. They did not examine the individual FSFI parameters separately (22). In a prospective study of Ilter et al. evaluating the effects of vaginoplasty on sexual function, significant changes were observed in the total FSFI score, as well as in the scores for orgasm, satisfaction, and pain. However, no significant changes were noted in the parameters of desire, arousal, and lubrication (10). They reported that the postoperative questionnaire was completed at a mean follow-up time of 18 months. In contrast, our study evaluated short-term results at the third postoperative month, and we believe that these short-term findings are more meaningful when assessing the impact of vaginoplasty on sexual function, considering the complex physiological and psychological nature of sexual function. In our study, a statistically insignificant increase was observed in the postoperative pain parameter. We attribute this increase to the fact that the survey was conducted in the early postoperative period and we think that this pain will regress in the long postoperative period.

In a review by Newman et al. on vaginal laxity, it was noted that women with vaginal laxity often report a sense of vaginal looseness, which leads to decreased penile/vaginal coupling and friction, resulting in a loss of sexual pleasure, arousal changes, and orgasmic dysfunction (23). In our study as well, vaginoplasty appears to be a procedure that primarily reduces vaginal laxity and enhances parameters related to sexual satisfaction, while its effects on other functions, such as pain and lubrication, seem to be limited.

CONCULUSION

The results of our study demonstrate that vaginoplasty is an effective treatment option for women experiencing vaginal laxity and related sexual dysfunction. In our study, the vaginal tightening procedure was found to significantly improve sexual function, particularly in the areas of desire, arousal, orgasm, and satisfaction. However, no significant changes were observed in the parameters of lubrication and pain. Nevertheless, there are some limitations to our study. It is a single-center study, and larger, multicenter studies are needed for further validation. In conclusion, vaginoplasty provides a safe and effective option for improving women's sexual functions. However, it is crucial to carefully evaluate patients' expectations and offer appropriate psychological support before performing such procedure

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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A 12-year retrospective study of gynecological consultations from the emergency department: impact of time of presentation on clinical outcomes

Acil servisten yapılan jinekolojik konsültasyonların 12 yıllık retrospektif incelemesi: Başvuru zamanının klinik sonuçlara etkisi

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ABSTRACT

Aim: To evaluate the causes, clinical outcomes, and time-related variations (time of day, weekday/weekend) in gynecological consultations requested from the emergency department (ED) to the obstetrics and gynecology department of a tertiary university hospital between 2013 and 2024.

Materials and Methods: This retrospective, descriptive, single-center study analyzed 6,072 female patients referred from the ED for gynecological consultation. Data included demographics, chief complaint, vital signs, laboratory results, and consultation outcomes (discharge, hospital admission without surgery, urgent surgery). Temporal variables were categorized as night (00:00–08:00), daytime (08:00–17:00), evening (17:00–24:00), and weekday/weekend.

Results: The most common complaints were Pelvic pain (28.9%), abnormal uterine bleeding (23.2%), and delayed menstruation (16.5%). Ectopic pregnancy had the highest urgent surgery rate (29.2%), followed by ruptured ovarian cyst (13.5%). Admission rates were higher at night (14.9%) than during daytime (10.1%) or evening (8.7%). For abnormal uterine bleeding, the likelihood of admission at night was twice that of daytime (IRR=2.07; 95% CI: 1.38–3.11), and the likelihood of urgent surgery was more than eightfold higher (IRR=8.87; 95% CI: 1.64–47.99). On weekends, ruptured ovarian cysts were significantly more likely to require urgent surgery than on weekdays (IRR=2.97; 95% CI: 1.26–7.01).

Conclusion: Pelvic pain, abnormal uterine bleeding, and delayed menstruation are the leading causes of gynecological consultations from the ED. Ectopic pregnancy and ruptured cysts carry the highest surgical burden. Increased admission and surgical rates during night hours and weekends highlight the need for targeted resource allocation and continuous surgical readiness in managing acute gynecological conditions.

Keywords: Gynecological emergencies, emergency department, time effect, admission rate, urgent surgery

ÖZ

Amaç: Bu çalışmada, 2013–2024 yılları arasında üçüncü basamak bir üniversite hastanesinde acil servisten kadın hastalıkları ve doğum kliniğine yapılan jinekolojik konsültasyonların nedenleri, klinik sonuçları ve zaman faktörüne (günün saati, hafta içi/hafta sonu) göre değişimleri değerlendirilmiştir.

Gereçler ve Yöntem: Retrospektif, tanımlayıcı tasarıma sahip bu tek merkezli çalışmada acil servisten jinekoloji servisine konsültasyon talep edilen toplam 6.072 kadın hasta incelendi. Demografik veriler, başvuru şikayeti, vital bulgular, laboratuvar sonuçları ve konsültasyon sonrası sonuçlar (taburculuk, gözlem amacıyla yatış, acil cerrahi) kaydedildi. Zaman değişkenleri; gece (00:00–08:00), gündüz (08:00–17:00) ve akşam (17:00–24:00) ile hafta içi ve hafta sonu olarak sınıflandırıldı.

Bulgular: En sık başvuru nedeni pelvik ağrısı (%28,9), anormal uterin kanama (%23,2) ve adet gecikmesi (%16,5) idi. Ektopik gebelik en yüksek acil cerrahi oranına (%29,2) sahipti, bunu rüptüre over kisti (%13,5) izledi. Gece saatlerinde başvuranlarda gözlem amaçlı yatış oranı (%14,9) gündüz (%10,1) ve akşam (%8,7) saatlerine göre daha yüksekti. Anormal uterin kanama olgularında gece saatlerinde yatış olasılığı gündüze göre 2 kat (IRR=2,07; %95 GA: 1,38–3,11), acil cerrahi olasılığı ise 8 kat (IRR=8,87; %95 GA: 1,64–47,99) fazlaydı. Hafta sonunda rüptüre kistlerde acil cerrahi olasılığı hafta içine göre anlamlı olarak yüksekti (IRR=2,97; %95 GA: 1,26–7,01).

Sonuç: Acil servisten jinekolojiye yapılan konsültasyonlarda pelvik ağrısı, anormal uterin kanama ve adet gecikmesi önde gelen nedenlerdir. Ektopik gebelik ve rüptüre kistler cerrahi açıdan en yüksek riski taşımaktadır. Gece başvurularında ve hafta sonlarında belirli şikayetlerde yatış ve cerrahi oranları artmakta olup, bu bulgular kaynak planlaması ve 24/7 cerrahi hazır bulunurluğun önemini vurgulamaktadır.

Anahtar Kelimeler: Jinekolojik aciller, acil servis, zaman etkisi, yatış oranı, acil cerrahi

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INTRODUCTION

Gynecological emergencies encompass a broad spectrum of clinical conditions that can significantly impact the quality of life in both reproductive-age and postmenopausal women. Their presentation ranges from mild pelvic discomfort to life-threatening massive hemorrhage and hemodynamic instability, requiring prompt diagnosis and timely intervention. Emergency departments (EDs) play a critical role as the initial point of contact, responsible for initiating diagnostic processes and ensuring appropriate referral. International data indicate that approximately 5–10% of all female patients presenting to EDs are evaluated for gynecological reasons (1-3). While many of these cases can be managed conservatively and discharged, conditions such as ectopic pregnancy, ruptured ovarian cyst, pelvic inflammatory disease, and severe abnormal uterine bleeding may require urgent surgical intervention or hospital admission (4, 5).

The most common reasons for gynecological consultations from the ED include Pelvic pain, abnormal uterine bleeding, delayed menstruation, acute pelvic inflammation, postoperative complications, and urinary tract infections (6, 7). While some of these presentations are benign and self-limiting, others represent acute, potentially life-threatening pathologies that demand immediate intervention. Therefore, systematically evaluating the reasons for presentation, clinical outcomes, and the need for interventions is essential for patient safety and effective healthcare planning.

The timing of presentation is an important factor influencing patient management in emergency medicine. Variations in ED workflow, staffing levels, consultant availability, and the speed of laboratory and radiology services may occur across different time periods (day, evening, night) and between weekdays and weekends (8-10). Previous studies have suggested that delays in diagnosis and treatment may be more frequent during night shifts and weekends, potentially affecting clinical outcomes (11, 12). However, long-term, large-scale studies investigating the relationship between the timing of presentation and clinical outcomes specifically in gynecological emergencies remain scarce.

In Türkiye, comprehensive evaluations of gynecological consultations from the ED—particularly analyses focusing on time-of-day and weekday/weekend variations—are extremely limited. Such data could be valuable for optimizing workload management, staffing, and emergency response capacity in both ED and gynecology departments.

The present study retrospectively analyzed all gynecological consultations from the ED to the obstetrics and gynecology department of a university hospital between 2013 and 2024. The primary aims were to determine the frequency of presenting complaints, assess hospital admission, discharge, and urgent surgical intervention rates by complaint type, and examine variations in clinical outcomes according to time-of-day and day-of-week. The findings are expected to strengthen coordination between the ED and gynecology services and contribute to strategies aimed at improving the quality of patient care.

MATERIALS AND METHODS

Study Design and Setting

This retrospective, descriptive, single-center study was conducted at the Emergency Department (ED) of Düzce University Health Practice and Research Hospital, a tertiary care center in Türkiye. The study period covered all gynecological consultations requested from the ED between January 1, 2013, and December 31, 2024.

Ethical Approval and Informed Consent

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (2013 revision) and was approved by the Düzce University Faculty of Medicine Clinical Research Ethics Committee (Approval No: 2025/106, Date: 07.07.2025). Due to the retrospective nature of the study, individual informed consent was not required. All data were anonymized prior to analysis, and no personally identifiable information was used.

Study Population

A total of 6,215 consultations were initially screened. After exclusion of 143 cases due to incomplete or erroneous consultation records, direct obstetric emergencies without gynecology consultation, and repeated visits from the same patient (only the first encounter was included), 6,072 unique cases were analyzed.

Inclusion criteria were: (1) referral from the ED to the gynecology department within the defined period, (2) consultation requested for a gynecological pathology, and (3) complete demographic and presentation data. Exclusion criteria were: (1) incomplete or erroneous consultation records, (2) cases managed directly in the obstetrics service for labor or obstetric emergencies without gynecology consultation, and (3) repeated visits by the same patient.

Data Collection and Variable Definitions

Data for this study were obtained retrospectively from the hospital electronic medical records and the emergency department consultation registry. For each patient, demographic information including age, date, and time of presentation was recorded, along with obstetric history such as gravida, parity, and, if available, pre-

pregnancy body mass index. Clinical presentation data included the chief complaint, duration of symptoms, associated symptoms, precipitating factors, and whether the etiology was traumatic or non-traumatic. Vital signs at presentation—blood pressure, heart rate, and body temperature—were documented, as well as laboratory results, specifically initial hemoglobin and complete blood count values. The outcome of each consultation was categorized as discharge, hospital admission for observation or treatment without surgery, or urgent surgical intervention.

Admission for observation or treatment was defined as hospitalization in the gynecology ward without urgent surgery, while urgent surgical intervention referred to any operative procedure performed within 24 hours of consultation. Discharge indicated that the patient was released home without the need for further inpatient management. Presentations were also classified according to temporal variables. Time of day was divided into night (00:00–08:00), daytime (08:00–17:00), and evening (17:00–24:00) based on the ED registration time. Day of the week was categorized as weekday (Monday–Friday) or weekend (Saturday–Sunday).

Statistical Analysis

Statistical Analysis

All analyses were performed using SPSS for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data or median with interquartile range (IQR) for non-normally distributed data. Comparisons between two independent groups were made using Student's t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

Temporal differences (time-of-day and weekday/weekend) in clinical outcomes were evaluated using incidence rate ratios (IRRs) with 95% confidence intervals (CIs), calculated through Poisson regression models with robust standard errors.

Sample size estimation was performed using power analysis for proportional data when the total population size was unknown; with an effect size of 0.5, an alpha error of 0.05, and a 95% confidence interval, the minimum required sample size was calculated as 255 patients (13). The final sample of 6,072 patients provided ample statistical power. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 6,072 female patients referred from the emergency department (ED) to the gynecology service during the 12-year study period were analyzed. The distribution of initial complaints and corresponding outcomes are presented in Table 1. pelvic pain was the leading cause of consultation (28.9%), followed by abnormal uterine bleeding (23.2%) and delayed menstruation (16.5%). Ectopic pregnancy demonstrated the highest urgent surgery rate (29.2%), while pelvic inflammatory disease showed the highest admission rate for observation or medical treatment (33.2%). Ruptured ovarian cysts also accounted for a considerable proportion of surgical interventions (13.5%). In contrast, patients presenting with delayed menstruation were almost exclusively discharged, with no admissions or urgent surgeries recorded.

Analysis according to time of presentation is shown in Table 2. Admission for observation was highest during night hours (14.9%) compared to daytime (10.1%) and evening (8.7%). Discharge rates were highest in the evening (76.7%) and lowest at night (72.1%).

Table 1. Top 10 presenting complaints and patient outcomes.

Initial Complaint	Cases (n)	Admission for Observation n (%)	Discharge n (%)	Urgent Surgery n (%)
Pelvic pain	1757	7 (0.4)	1749 (99.5)	1 (0.1)
Abnormal uterine bleeding	1408	139 (9.9)	1261 (89.6)	8 (0.6)
Delayed menstruation	1003	0 (0.0)	1003 (100.0)	0 (0.0)
Pelvic inflammatory disease	365	121 (33.2)	244 (66.8)	0 (0.0)
Ectopic pregnancy	219	116 (53.0)	39 (17.8)	64 (29.2)
C-section post-operative pain	190	50 (26.3)	136 (71.6)	4 (2.1)
Urinary tract infection	132	34 (25.8)	87 (65.9)	11 (8.3)
Ruptured cyst	126	67 (53.2)	42 (33.3)	17 (13.5)
Postoperative complications	109	26 (23.9)	79 (72.5)	4 (3.6)
Bartholin cyst/abscess	98	62 (63.3)	35 (35.7)	1 (1.0)

Table 2. Patient outcomes by time of day.

Time Period	Admission for Observation n (%)	Discharge n (%)	Urgent Surgery n (%)
00:00–08:00	119 (14.9)	575 (72.1)	36 (4.5)
08:00–17:00	283 (10.1)	2122 (75.8)	85 (3.0)
17:00–24:00	215 (8.7)	1897 (76.7)	55 (2.2)

Table 3. Top 10 presenting complaints and patient outcomes by time of day (IRR, 95% CI; reference: 08:00–17:00).

Complaint	Outcome	Time Period	IRR (95% CI)
Abnormal uterine bleeding	Admission	00:00–08:00	2.07 (1.38–3.11)
Abnormal uterine bleeding	Admission	17:00–24:00	1.00 (0.70–1.44)
Abnormal uterine bleeding	Urgent Surgery	00:00–08:00	8.87 (1.64–47.99)
Abnormal uterine bleeding	Urgent Surgery	17:00–24:00	1.30 (0.18–9.17)
Bartholin cyst/abscess	Admission	00:00–08:00	4.50 (0.10–194.67)
Bartholin cyst/abscess	Admission	17:00–24:00	1.06 (0.02–50.43)
Bartholin cyst/abscess	Urgent Surgery	00:00–08:00	1.50 (0.07–30.48)
Bartholin cyst/abscess	Urgent Surgery	17:00–24:00	0.35 (0.02–8.08)
C-section post-operative pain	Admission	00:00–08:00	0.44 (0.02–8.10)
C-section post-operative pain	Admission	17:00–24:00	0.42 (0.04–3.88)
C-section post-operative pain	Urgent Surgery	00:00–08:00	3.05 (0.06–148.99)
C-section post-operative pain	Urgent Surgery	17:00–24:00	1.24 (0.03–61.51)
Delayed menstruation	Admission	00:00–08:00	4.69 (0.09–233.93)
Delayed menstruation	Admission	17:00–24:00	1.04 (0.02–52.13)
Delayed menstruation	Urgent Surgery	00:00–08:00	4.69 (0.09–233.93)
Delayed menstruation	Urgent Surgery	17:00–24:00	1.04 (0.02–52.13)
Ectopic pregnancy	Admission	00:00–08:00	0.93 (0.62–1.38)
Ectopic pregnancy	Admission	17:00–24:00	1.17 (0.90–1.52)
Ectopic pregnancy	Urgent Surgery	00:00–08:00	1.14 (0.65–2.00)
Ectopic pregnancy	Urgent Surgery	17:00–24:00	1.02 (0.64–1.63)
Pelvic pain	Admission	00:00–08:00	0.42 (0.02–8.05)
Pelvic pain	Admission	17:00–24:00	0.14 (0.01–2.70)
Pelvic pain	Urgent Surgery	00:00–08:00	8.76 (0.36–214.45)
Pelvic pain	Urgent Surgery	17:00–24:00	0.98 (0.02–49.14)
Pelvic inflammatory disease	Admission	00:00–08:00	1.02 (0.68–1.53)
Pelvic inflammatory disease	Admission	17:00–24:00	0.89 (0.64–1.23)
Pelvic inflammatory disease	Urgent Surgery	00:00–08:00	3.02 (0.06–150.36)
Pelvic inflammatory disease	Urgent Surgery	17:00–24:00	1.30 (0.03–64.91)
Postoperative complications	Admission	00:00–08:00	4.32 (1.48–12.61)
Postoperative complications	Admission	17:00–24:00	2.62 (0.94–7.26)
Postoperative complications	Urgent Surgery	00:00–08:00	2.38 (0.05–114.57)
Postoperative complications	Urgent Surgery	17:00–24:00	0.70 (0.01–34.69)
Ruptured cyst	Admission	00:00–08:00	0.90 (0.61–1.34)
Ruptured cyst	Admission	17:00–24:00	0.85 (0.56–1.29)
Ruptured cyst	Urgent Surgery	00:00–08:00	1.66 (0.58–4.74)
Ruptured cyst	Urgent Surgery	17:00–24:00	1.46 (0.48–4.43)
Urinary tract infection	Admission	00:00–08:00	1.23 (0.57–2.65)
Urinary tract infection	Admission	17:00–24:00	0.60 (0.32–1.13)
Urinary tract infection	Urgent Surgery	00:00–08:00	3.92 (0.08–188.52)
Urinary tract infection	Urgent Surgery	17:00–24:00	0.85 (0.02–42.08)

IRR: Incidence Rate Ratio; CI: Confidence Interval

Table 4. Patient outcomes by day type.

Day Type	Admission for Observation n (%)	Discharge n (%)	Urgent Surgery n (%)
Weekday	437 (10.5)	3140 (75.6)	128 (3.1)
Weekend	180 (9.4)	1454 (75.8)	48 (2.5)

Table 5. Effect of weekend presentation on patient outcomes (IRR, 95% CI; reference: weekday).

Complaint	Outcome	IRR (95% CI)
Pelvic pain	Admission	14.67 (0.76–283.46)
Pelvic pain	Urgent Surgery	0.70 (0.03–17.12)
Abnormal uterine bleeding	Admission	0.98 (0.69–1.38)
Abnormal uterine bleeding	Urgent Surgery	0.35 (0.04–2.80)
Delayed menstruation	Admission	1.76 (0.04–88.46)
Delayed menstruation	Urgent Surgery	1.76 (0.04–88.46)
Pelvic inflammatory disease	Admission	1.28 (0.95–1.72)
Pelvic inflammatory disease	Urgent Surgery	2.31 (0.05–115.50)
Ectopic pregnancy	Admission	0.96 (0.73–1.27)
Ectopic pregnancy	Urgent Surgery	1.02 (0.65–1.60)
C-section post-operative pain	Admission	0.19 (0.01–3.40)
C-section post-operative pain	Urgent Surgery	1.68 (0.03–83.39)
Urinary tract infection	Admission	1.10 (0.62–1.96)
Urinary tract infection	Urgent Surgery	1.56 (0.03–77.43)
Ruptured cyst	Admission	0.66 (0.40–1.08)
Ruptured cyst	Urgent Surgery	2.97 (1.26–7.01)
Postoperative complications	Admission	1.02 (0.51–2.01)
Postoperative complications	Urgent Surgery	1.61 (0.03–79.57)
Bartholin cyst/abscess	Admission	2.17 (0.05–102.82)
Bartholin cyst/abscess	Urgent Surgery	6.50 (0.29–148.19)

IRR: Incidence Rate Ratio; CI: Confidence Interval

Urgent surgery was most frequently performed during nighttime presentations (4.5%), followed by daytime (3.0%) and evening (2.2%).

Complaint-specific incidence rate ratios (IRRs) demonstrated significant associations between presentation time and clinical outcomes (Table 3). Abnormal uterine bleeding cases were significantly more likely to require admission (IRR = 2.07, 95% CI: 1.38–3.11) and urgent surgery (IRR = 8.87, 95% CI: 1.64–47.99) at night compared with daytime. Postoperative complications also showed a higher likelihood of admission during nighttime hours (IRR = 4.32, 95% CI: 1.48–12.61). No statistically significant differences were identified for ectopic pregnancy, pelvic inflammatory disease, ruptured cysts, or urinary tract infections.

The comparison of outcomes between weekdays and weekends is presented in Table 4. Admission rates were slightly higher on weekdays (10.5%) compared to weekends (9.4%). Discharge rates remained similar (~75%), while urgent surgery was somewhat more frequent on weekdays (3.1% vs. 2.5%).

Detailed complaint-specific analysis for weekday versus weekend presentations is summarized in Table 5. pelvic pain cases demonstrated a markedly higher likelihood of admission on weekends, although the wide confidence interval limited interpretation (IRR = 14.67, 95% CI: 0.76–283.46). Ruptured ovarian cysts were significantly more likely to require urgent surgery on weekends compared with weekdays (IRR = 2.97, 95% CI: 1.26–7.01). No other statistically significant differences were identified across presenting complaints.

As seen in Figure 1, the rates of admission for observation and emergency surgery were found to be higher in patients admitted

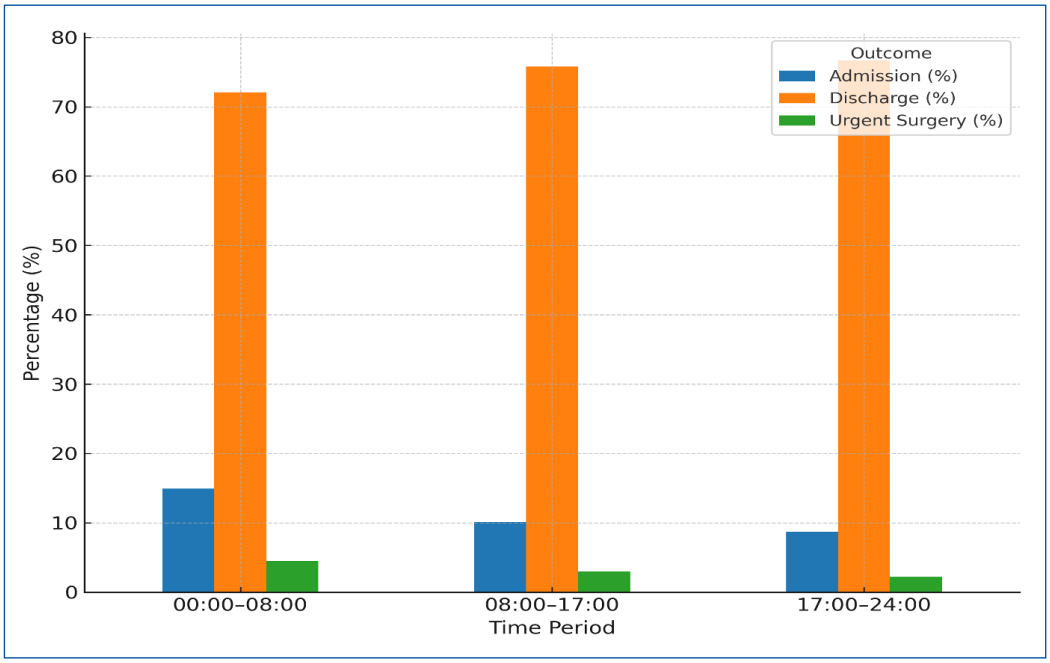

Figure 1. Patient outcomes by time of day

at night (00:00–08:00), while the discharge rate was highest in the evening (17:00–24:00).

DISCUSSION

This 12-year retrospective study provides a comprehensive evaluation of gynecological consultations requested from the emergency department (ED), bridging emergency medicine and obstetrics-gynecology perspectives. By analyzing over six thousand cases, this work offers robust insights into the distribution of presenting complaints, hospital admission patterns, surgical interventions, and the influence of temporal variables such as time of day and day of the week. The scale and duration of the study provide a valuable contribution to the literature, where large datasets on acute gynecological consultations remain limited (14, 15).

The predominance of pelvic pain, abnormal uterine bleeding, and delayed menstruation as leading consultation causes in our cohort is consistent with prior reports showing pelvic pain and bleeding to account for 20–40% of ED gynecological presentations (7, 16-18). Pelvic pain encompasses a wide range of differential diagnoses—from benign musculoskeletal pain to life-threatening emergencies such as ruptured ectopic pregnancy—and requires rapid triage to avoid delays in care (19). From an emergency medicine standpoint, such presentations demand prompt diagnostic imaging and laboratory work-up, while from a gynecological perspective, they necessitate careful consideration of reproductive implications and minimally invasive management where appropriate (20, 21).

Ectopic pregnancy demonstrated the highest surgical intervention rate in our study (29.2%), aligning with reported global ranges between 20% and 35% (22, 23). Despite advances in early diagnosis through high-resolution transvaginal ultrasonography and serum β-hCG monitoring, surgical management remains necessary in a substantial proportion of cases, particularly those presenting with hemodynamic instability or advanced tubal rupture (24). Ruptured ovarian cysts were the second most frequent surgical indication, reflecting the acute presentation and the importance of immediate surgical readiness in all operational hours (25). Pelvic inflammatory disease led to hospitalization in one-third of patients, underscoring the ongoing relevance of inpatient antibiotic therapy for severe cases—a practice supported by both the Centers for Disease Control and Prevention and European guidelines (26, 27).

Temporal analysis revealed that nighttime presentations (00:00–08:00) had significantly higher admission rates compared to daytime and evening hours. For abnormal uterine bleeding, the likelihood of admission at night was approximately twice that during the day, and the odds of urgent surgery were more than eightfold higher. These findings may be explained by reduced outpatient diagnostic and therapeutic options during night shifts, limited specialist availability, and a more conservative clinical approach when immediate follow-up cannot be guaranteed (28, 29). Postoperative complications also had increased odds of admission at night, likely reflecting a cautious approach toward patients with recent surgical histories (30). For other acute conditions—such as ectopic pregnancy, pelvic

inflammatory disease, or urinary tract infections—no significant time-of-day variation was observed, consistent with their inherently urgent nature requiring similar management regardless of presentation time (31).

The weekend effect—widely discussed in emergency and surgical literature—was less pronounced overall in our study but showed selective impact. Ruptured ovarian cysts had significantly higher surgical intervention rates on weekends, and pelvic pain was more likely to result in admission during this period. Possible explanations include reduced access to outpatient gynecology clinics, delays in elective surgical scheduling, and a greater reliance on immediate inpatient or operative management (32). For both emergency physicians and gynecologists, these findings reinforce the importance of maintaining 24/7 readiness for time-sensitive conditions, particularly those with a high probability of surgical intervention.

From a systems perspective, the integration of emergency medicine and gynecology protocols can improve efficiency, reduce unnecessary admissions, and ensure timely surgical access for high-risk cases. Structured triage algorithms incorporating time-of-day and day-of-week patterns, combined with cross-disciplinary communication, may optimize patient outcomes and resource utilization (33). Establishing standardized care pathways for common presentations—such as abnormal uterine bleeding, postoperative complications, and suspected ectopic pregnancy—could further enhance care quality (34).

This study has several limitations. Its retrospective design is inherently dependent on the completeness and accuracy of medical records, which may have introduced misclassification bias. Being a single-center analysis, findings may not be generalizable to institutions with different patient populations, referral systems, or resource availability. Clinical decision-making factors such as physician experience, patient preferences, and subtle clinical cues could not be captured. Variations in diagnostic imaging and laboratory access across the 12-year period may also have influenced management strategies. Additionally, our study focused exclusively on initial ED outcomes without long-term follow-up, precluding evaluation of recurrence rates or delayed complications.

CONCLUSION

In conclusion, pelvic pain, abnormal uterine bleeding, and delayed menstruation remain the leading causes of gynecological consultations from the ED, with ectopic pregnancy and ruptured ovarian cysts posing the highest surgical burden. Time-of-day exerts a measurable influence on admission and surgical rates, particularly for abnormal uterine bleeding and postoperative complications, while weekend presentation increases surgical intervention for ruptured cysts. These findings underscore the need for targeted resource allocation, continuous surgical readiness, and integrated emergency-gynecology care pathways to ensure timely, effective management of acute gynecological conditions.

Ethics Committee Approval: The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of Duzce University (Approval No: 2025/106, Date: 07.07.2025).

Conflict of Interest: The authors declare that they have no conflict of interest to disclose.

Author Contributions: BK and MB contributed to the study design and concept. BK, EY, and SMY collected the data. BK and EY performed the data analysis. BK and SMY prepared the first draft of the manuscript, and EY and MB reviewed and edited the manuscript. MB supervised the study. All authors read and approved the final version of the manuscript.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Evaluation of inflammatory response with complete blood count parameters in abdominal, vaginal, and laparoscopic hysterectomy techniques: A retrospective Cohort study

Abdominal, vajinal ve laparoskopik histerektomi tekniklerinde tam kan sayımı parametreleriyle enflamatuvar yanıtın değerlendirilmesi: Retrospektif Kohort çalışması

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ABSTRACT

Aim: The aim of our study was to evaluate the inflammatory response in abdominal hysterectomy (AH), vaginal hysterectomy (VH), and laparoscopic hysterectomy (LH) techniques using complete blood count (CBC) parameters and to demonstrate the role of the delta neutrophil index (DNI) in hysterectomy types.

Materials and Methods: The study included 251 patients. Patients were divided into three groups: AH, VH, and LH. Patient demographic characteristics, operational characteristics, and CBC results (white blood cell (WBC), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and DNI) were compared separately for the three groups before surgery, at 6 hours postoperatively, and at 24 hours postoperatively.

Results: The age and menopause rate of patients in the VH (n=84) group were higher than the LH (n=82) and AH (n=84) groups (P<0.05). The operative time was longest in the LH group and shortest in the AH group (P<0.05). The highest WBC, NLR, and PLR levels at postoperative 6th hour were in the AH group, and the lowest levels were in the VH group (P<0.01). There were no significant differences in serum DNI levels between the LH, AH, and VH groups preoperatively and at the 6th and 24th hours postoperatively.

Conclusion: We found the highest postoperative inflammatory response in the AH group and the lowest in the VH group, and contrary to many studies, we found that LH patients had an average inflammatory response. Although DNI increased in the postoperative inflammatory process, there was no difference between the AH, LH, and VH groups.

Keywords: Abdominal hysterectomy, vaginal hysterectomy, laparoscopic hysterectomy, WBC, NLR, PLR, DNI

ÖZ

Amaç: Çalışmamızın amacı, abdominal histerektomi (AH), vajinal histerektomi (VH) ve laparoskopik histerektomi (LH) tekniklerinde inflamatuar yanıtı tam kan sayımı (CBC) parametrelerini kullanarak değerlendirmek ve delta nötrofil indeksinin (DNİ) histerektomi tiplerindeki rolünü ortaya koymaktır.

Gereç ve Yöntemler: Çalışmaya 251 hasta dahil edildi. Hastalar AH, VH ve LH olmak üzere üç gruba ayrıldı. Hastaların demografik özellikleri, operasyonel özellikleri ve CBC sonuçları (beyaz kan hücresi (WBC), nötrofil/lenfosit oranı (NLR), trombosit/lenfosit oranı (PLR) ve DNİ), ameliyat öncesi, ameliyat sonrası 6. saatte ve ameliyat sonrası 24. saatte üç grup için ayrı ayrı karşılaştırıldı.

Bulgular: VH (n=84) grubundaki hastaların yaş ve menopoz oranı, LH (n=82) ve AH (n=84) gruplarına göre daha yüksekti (P<0,05). Ameliyat süresi LH grubunda en uzun, AH grubunda ise en kısaydı (P<0,05). Ameliyat sonrası 6. saatte en yüksek WBC, NLR ve PLR seviyeleri AH grubunda, en düşük seviyeler ise VH grubundaydı (P<0,01). LH, AH ve VH grupları arasında ameliyat öncesi ve ameliyat sonrası 6. ve 24. saatlerde serum DNİ seviyelerinde anlamlı bir fark yoktu.

Sonuç: Ameliyat sonrası en yüksek inflamatuar yanıtı AH grubunda, en düşük ise VH grubunda bulduk ve birçok çalışmanın aksine, LH hastalarının ortalama bir inflamatuar yanıta sahip olduğunu bulduk. DNİ ameliyat sonrası inflamatuar süreçte artmasına rağmen, AH, LH ve VH grupları arasında bir fark yoktu.

Anahtar Kelimeler: Abdominal histerektomi, vajinal histerektomi, laparoskopik histerektomi, WBC, NLR, PLR, DNİ

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INTRODUCTION

Surgical procedures have a significant impact on inflammatory processes in the body. Surgical trauma caused by surgery can trigger an inflammatory response, potentially leading to various postoperative complications. It is essential to understand and regulate this inflammatory process to enhance patient outcomes and minimize the risk of postoperative morbidity (1).

Among women, hysterectomy is the second most common surgical procedure after cesarean section. Despite its frequency, hysterectomy remains a major operation with possible long-term effects on women's health and quality of life (2). For benign uterine conditions, there are three approaches to hysterectomy: abdominal, vaginal, and laparoscopic. Regardless of the method used, hysterectomy is considered a substantial surgical intervention. Research has demonstrated that such significant surgical trauma results in immunological dysfunction in patients owing to oxidative stress (3). Surgical stress often leads to postoperative immunosuppression resulting from the intricate interplay of various hormones (particularly adrenal corticosteroids), cytokines, and acute-phase reactants. This immunosuppression can substantially increase the likelihood of postoperative infections and complications, potentially extending recovery time and hospital stay. The intensity and duration of immunosuppression may vary based on factors, such as the extent of surgical trauma, patient age, and pre-existing health conditions (4,5). Recent progress in minimally invasive techniques has improved outcomes and shortened recovery periods. Laparoscopic surgery is expected to cause less immune impairment than abdominal surgery due to its association with reduced tissue damage (6).

Several methods are available to evaluate the postoperative inflammatory response, including white blood cell (WBC) count, neutrophil count, platelet count, lymphocyte count, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and delta neutrophil index (DNI). These approaches are both simple and cost-effective (7). The delta neutrophil index is a measure of the proportion of immature granulocytes to neutrophils. Recent studies have indicated that the delta neutrophil index serves as an indicator of the inflammatory response and oxidative stress and plays a role in early prediction (8).

The aim of our study was to evaluate the inflammatory response in abdominal, vaginal, and laparoscopic hysterectomy techniques using complete blood count (CBC) parameters and to demonstrate the role of the delta neutrophil index in hysterectomy types.

METHODS

Total of 251 patients who underwent hysterectomy in the Gynecology and Obstetrics Clinic of our hospital, a tertiary center, between 2019 and 2024 were participated in this study. Ethics committee approval was obtained from the Ankara Bilkent City Hospital Ethics Committee No. 2. (Approval No: 24-639). Our study is a retrospective observational cohort study.

Female patients aged 18-70 years who underwent abdominal, vaginal and laparoscopic hysterectomy for benign gynecologic causes were included in our study. Benign gynecological causes were defined as abnormal uterine bleeding (AUB), endometrial pathologies, myoma uteri, and uterine desensus. Hysterectomy for postpartum hemorrhage, subtotal hysterectomy, hysterectomy for tubo-ovarian abscess, deep pelvic endometriosis, and hysterectomy for uterine or ovarian malignancies were excluded. In addition, patients with chronic inflammatory diseases, those already diagnosed with another organ malignancy, those with infections, corticosteroid users, anticoagulant users, diabetes and those with rheumatologic diseases were excluded.

The patients were divided into three groups: abdominal hysterectomy (AH), vaginal hysterectomy (VH), and laparoscopic hysterectomy (LH). Patients' age, body mass index (BMI), parity, gravida, operative indications, operation time, operative notes (with or without oophorectomy), and hospital stay were retrospectively investigated and recorded. CBC results (WBC, NLR, PLR, and DNI) of the patients before the operation, at the 6th hour after the operation and at the 24th hour after the operation were compared separately for the three groups. In our clinic, CBC checks are performed at the 6th and 24th hour after all hysterectomy operations, and patients without complications are discharged after 24 hours. These markers (WBC, NLR, PLR and DNI) are tested automatically as part of a standard complete blood count.

Statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to assess data normality. Normally distributed data are expressed as mean ± standard deviation. In contrast, non-parametric data were expressed as medians and interquartile ranges. One-way ANOVA and Kruskal–Wallis tests were used for intergroup comparisons. Repeated measures analysis of variance (ANOVA) were used to examine changes in data over time. The chi-squared test was used to compare categorical data. Statistical tests were considered significant at a P-value <0.05, whereas post-hoc correction tests were considered significant at a P-value <0.017 (0.05/3).

RESULTS

Of the 251 cases included in this study, 82 (32.7%) underwent LH, 85 (33.9%) underwent AH, and 84 (33.5%) underwent VH operations. While the mean age of all cases was 55.5 ± 9.0 years, the median values for gravida and parity were 3 (2) and 3 (1), respectively. The mean BMI value of all cases was 27.5 ± 3.5 kg/m^2. Of the patients, 127 (50.6%) were menopausal. When surgical indications were examined, surgery was performed for AUB in 125 cases (49.8%), pelvic mass in 40 cases (15.9%), and uterine decensus in 86 cases (34.3%). Uni- or bilateral salpingo-oophorectomy was performed in 140 (55.8%) patients. The mean operative time was 148.5 ± 44.3 minute. The postoperative hospital stay was 3 (2) days.

The demographic characteristics of the LH, AH, and VH groups are presented in Table 1. There were no significant differences between the groups in terms of gravida, parity, or BMI (P>0.05). However, the age and rate of menopausal patients in the VH group were higher than those in the LH and AH groups (P<0.05). There was no significant difference in the age and rate of menopausal patients between the LH and AH groups (P>0.017). From the perspective of surgical indications, while the most common indication in the LH and AH groups was AUB, all the patients in the VH group underwent surgery due to uterine desensus. There was a significant difference between the groups in terms of simultaneous uni- or bilateral salpingo-oophorectomy (P<0.05). The rate of simultaneous uni- or bilateral salpingo-oophorectomy was lower in the VH group than that in the LH and AH groups, whereas there was no difference between the LH and AH groups (P>0.017). However, there was a significant difference between the groups in terms of operation time (P<0.05). The operation time was longest in the LH group and shortest in the AH group. In contrast, there were no significant differences between the LH, AH, and VH groups based on postoperative hospital stay (P = 0.06).

The preoperative and postoperative serum CBC parameters of the LH, AH, and VH groups are presented in Table 2. Except for the postoperative 6th hour, which was significantly lower in the VH group than in the LH and AH groups (P<0.01), the LH, AH, and VH groups did not differ significantly based on the preoperative and postoperative 24th hour serum WBC levels (P>0.05). The change in WBC count over time revealed that the serum WBC count increased significantly at the 6th hour postoperatively in all the groups (P<0.01). The serum WBC count decreased significantly in the LH and AH groups at the 24th hour postoperatively than at the 6th hour postoperatively (P<0.01). Serum WBC count increased in the VH group at the 24th hour postoperatively than at the 6th hour postoperatively; however, this difference was not significant (P = 0.54). Overall, the change in the serum WBC count over time was significant in all groups (P<0.01) (Table 2).

The serum NLR did not differ significantly between the LH, AH, and VH groups preoperatively (P = 0.15). In contrast, serum NLR levels differed significantly between the LH, AH, and VH groups at 6th and 24th hours (P < 0.05). While serum NLR was significantly higher at

Table 1. Demographic characteristics of the total laparoscopic, abdominal, and vaginal hysterectomy groups.

Characteristics	LH group (n = 82)	AH group (n = 85)	VH group (n = 84)	P value
Age (years)	52.8 ± 7.3	50.6 ± 6.3	63.1 ± 7.8	<0.01
Gravida	3 (2)	3 (2)	3 (1)	0.10
Parity	2 (1)	3 (1)	3 (1)	0.15
BMI (kg/m^2)	27.5 ± 3.5	27.4 ± 4.2	27.6 ± 2.7	0.92
Menopause Yes No	 28 (11.2) 54 (21.5)	 21 (8.4) 64 (25.5)	 78 (31.1) 6 (2.3)	<0.01
Surgical indications AUB Pelvic mass POP	 67 (26.7) 13 (5.2) 2 (0.8)	 58 (23.1) 27 (10.7) 0 (0.0)	 0 (0.0) 0 (0.0) 84 (33.5)	-
Uni- or bilateral salpingo-oopherectomy Yes No	 70 (27.9) 12 (84.8)	 60 (23.9) 25 (10.0)	 10 (4.0) 74 (29.5)	<0.01
Operative time (min)	175.9 ± 53.6	125.7 ± 33.9	144.7 ± 25.6	<0.01
Postoperative hospital stay (day)	3 (2)	3 (1)	3 (2)	0.06

Data are presented as the mean ± standard deviation, median (interquartile range), or n (%).
* One-way ANOVA, Kruskal–Wallis, and chi-square tests were used for intergroup comparisons.
Abbreviations: AH, abdominal hysterectomy; AUB, abnormal uterine bleeding; BMI, body mass index; LH, laparoscopic hysterectomy; VH, vaginal hysterectomy.

Table 2. Preoperative and postoperative serum complete blood count parameters in the total laparoscopic hysterectomy, abdominal hysterectomy, and vaginal hysterectomy groups.

CBC Parameters		LH (n = 82)	AH (n = 85)	VH (n = 84)	P*
White blood cell count (x 10^3/μL)	Preoperatively	6.8 ± 1.9	6.9 ± 2.1	6.7 ± 1.7	0.75
	6th hour postoperatively	13.4 ± 3.8	14.2 ± 3.7	11.9 ± 4.1	<0.01
	24th hour postoperatively	11.0 ± 3.4	11.4 ± 3.3	12.1 ± 3.5	0.15
	Pα	<0.01	<0.01	<0.01	
Neutrophil-to-lymphocyte ratio	Preoperatively	2.5 ± 1.0	2.4 ± 1.1	2.2 ± 0.8	0.15
	6th hour postoperatively	16.5 ± 9.6	19.2 ± 9.1	10.6 ± 6.4	<0.01
	24th hour postoperatively	10.3 ± 7.5	7.9 ± 5.8	12.9 ± 6.8	<0.01
	Pα	<0.01	<0.01	<0.01	
Platelet-to-lymphocyte ratio	Preoperatively	159.9 ± 50.8	176.4 ± 68.6	139.8 ± 45.8	<0.01
	6th hour postoperatively	338.6 ± 173.7	416.2 ± 208.8	278.8 ± 101.4	<0.01
	24th hour postoperatively	271.5 ± 174.5	236.1 ± 128.5	232.9 ± 125.4	0.12
	Pα	<0.01	<0.01	<0.01	
Delta neutrophil index	Preoperatively	0.3 ± 0.5	0.4 ± 0.7	0.3 ± 0.6	0.54
	6th hour postoperatively	0.9 ± 1.2	1.4 ± 2.0	1.1 ± 1.7	0.23
	24th hour postoperatively	0.8 ± 1.4	0.6 ± 1.4	1.0 ± 1.6	0.22
	Pα	<0.01	<0.01	<0.01	

Data are presented as the mean ± standard deviation, median (interquartile range), or n (%).
*One-way ANOVA variance was used to compare the TLH, AH, and VH groups.
αRepeated-measures analysis of variance (ANOVA) was used to examine changes in complete blood count levels over time.
AH: Abdominal hysterectomy; LH: Laparoscopic hysterectomy; VH: Vaginal hysterectomy.

the 6th hour in the AH group than in the LH and VH groups (P < 0.01), serum NLR level was significantly lower at the 24th hour in the AH group than in the LH and VH groups (P < 0.01). The change in serum NLR levels over time revealed that serum NLR levels increased significantly at the 6th hour postoperatively in all the groups (P < 0.01). The serum NLR levels decreased significantly at the 24th hour postoperatively than at the 6th hour postoperatively in all groups (P < 0.01). Overall, the change in serum NLR over time was significant in all groups (P values < 0.01) (Table 2).

Except for the postoperative 24th hour, in which the difference between the LH, AH, and VH groups was not significant (P = 0.12), serum PLR levels were significantly lower in the VH group than in the LH and AH groups preoperatively and at 6th hour postoperatively (P < 0.01). The change in serum PLR levels over time revealed that serum PLR levels increased significantly at the 6th hour postoperatively in all groups (P < 0.01). The serum PLR levels decreased significantly at the 24th hour postoperatively than at the 6th hour postoperatively in all groups (P < 0.01). Overall, the change in serum PLR over time was significant in all the groups (P < 0.01) (Table 2).

There were no significant differences in serum DNI levels between the LH, AH, and VH groups preoperatively and at the 6th and 24th hours postoperatively (P = 0.54, 0.23, and 0.22, respectively). The change in serum DNI levels over time revealed that serum DNI levels increased significantly at the 6th hour postoperatively in all groups (P < 0.01). Serum DNI levels decreased significantly in the AH group at the 24th hour postoperatively than at the 6th hour postoperatively (P < 0.01). While serum DNI level decreased in the LH and VH groups at the 24th hour postoperatively than at the 6th hour postoperatively, these differences were not significant (P values were 0.52 and 0.60, respectively). Overall, the change in serum DNI levels over time was significant in all groups (P values < 0.01) (Table 2).

DISCUSSION

In our study, we evaluated the inflammatory response in abdominal, vaginal, and laparoscopic hysterectomy techniques using complete blood count parameters. In patients who underwent VH, higher age, a higher proportion of postmenopausal patients, fewer previous

surgeries, and fewer uni-or bilateral salpingo-oophorectomy were observed. The LH group had the longest operation time, while the AH group had the shortest. According to the results of the comparison of WBC, NLR, PLR, and DNI between the groups at preoperative, 6th hour postoperatively, and 24th hour postoperatively, all markers increased at 6th hour postoperatively compared to preoperative levels and decreased at 24th hour postoperatively compared to 6th hour postoperatively in all groups. However, all markers were higher in the AH group compared to the VH and LH groups at 6th hour postoperatively (although this increase was not significant in the DNI group, P=0.23). In the VH group, WBC, NLR, and PLR were lowest at 6th hour postoperatively. DNI levels did not differ significantly between the groups at preoperative, 6th hour postoperatively, or 24th hour postoperatively.

Abdominal, vaginal, and laparoscopic hysterectomy techniques have been used for a long time and have been compared many times in the literature. Although some studies do not report a higher mean age in VH patients (9), we found a higher mean age in the VH group in our study. We believe that this situation is also the reason why we identified more patients in menopause in the VH group. We also found that uterine descent was a frequent reason for hysterectomy in the VH group. Consequently, our findings can be explained by the development of uterine descent due to increased connective tissue weakness that occurs with older age in the VH group. Furthermore, consistent with the literature, we found that unilateral or bilateral salpigoophorectomies were less frequently performed in the VH group due to the difficulty of surgical technique (9).

Data on the comparison of operation times in hysterectomies are unclear. In one study, abdominal, vaginal, and laparoscopic hysterectomies were compared, and the shortest operation time was found in the VH group, while the longest operation time was found in the LH group (10). Several other studies have demonstrated similar results (11,12,13). These studies attributed the long surgical times in the LH group to lack of surgical experience and the time required for the assembly and setup of laparoscopic equipment. Additionally, a meta-analysis comparing vaginal hysterectomy and laparoscopic hysterectomy, which included 1,618 patients and 18 studies, reported shorter operative times in the VH group (14). In our study, we found the shortest operative time in the AH group and the longest in the LH group. We hypothesize that this is due to surgical experience, based on the ratio of hysterectomy types performed at our hospital.

Surgical trauma triggers a stress response and leads to an inflammatory response. After surgery, leukocyte and neutrophil counts increase, while lymphocytes and platelets decrease (3). Many studies have reported less tissue damage and immunological responses in laparoscopic surgeries compared to open surgeries (1,15, 16). WBC, NLR, and PLR are used as markers of inflammation (1). Özsürmeli et al. compared the changes in these inflammatory markers at the preoperatively and 24th hour postoperatively in patients undergoing LH and AH (1). They found that WBC, NLR, and PLR levels increased at 24th hour postoperatively in both groups. However, they reported that this increase was significantly higher in the AH group than in the LH group (1). Unlike them, in our study, we also investigated patients in the VH group in addition to the AH and LH groups. We also included the 6th hour postoperatively levels of WBC, NLR, and PLR. Our findings revealed that WBC, NLR, and PLR values increased at 6th hour postoperatively in all groups, then decreased at 24th hour postoperatively, but were still higher than preoperatively at 24th hour postoperatively. Although we could not demonstrate a clear significant difference between the groups in the postoperative 24th hour levels of these markers, the postoperative 6th hour levels were significantly different. We found that WBC, NLR, and PLR values at 6 hours postoperatively were highest in the AH group and lowest in the VH group. Although the AH group had the shortest operative time, the inflammatory response was highest in this group. This suggests that the role of surgical time in tissue damage is unimportant. Furthermore, despite being an open procedure, VH had the lowest inflammatory response. We believe that this is because, compared to AH and LH, VH has the least contact with other abdominal tissues such as the intestines, and therefore there are fewer cytokines and immunomodulators that can be secreted from these tissues.

DNI appears to be a marker that has been increasingly researched recently and whose importance is growing day by day. Some studies have reported that it is an indicator of inflammatory response (8), while others have suggested that it is a prognostic biomarker of the infectious process (17). However, definitive results have not yet been established. There are currently no studies in the literature comparing DNI between different types of hysterectomy. Therefore, our study is the first of its kind. Our findings show that DNI, like other markers, increases at 6th hour postoperatively and then decreases at 24th hour. However, DNI did not show a significant difference between the AH, VH, and LH groups. Therefore, we believe that the role of DNI in the inflammatory response is limited. The main limitation of our study is its retrospective nature, but the sufficient sample size and the reliability of our medical records are our strengths.

CONCLUSION

In conclusion, the highest postoperative inflammatory response was observed in the AH group, while the lowest response was

observed in the VH group. We found that LH patients had an average inflammatory response, and we believe that the findings of other studies indicating less tissue damage are open to debate. Therefore, further studies are needed in the future. Although DNI increased during the postoperative inflammatory process, there was no difference between the AH, LH, and VH groups.

Ethics Approval: Ethics committee approval was obtained from the Ankara Bilkent City Hospital Ethics Committee No. 2. (Approval No: 24-639).

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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Can we rely solely on fasting parameters instead of oral glucose tolerance test for gestational diabetes mellitus screening?

Gebelikte diyabet taramasında oral glukoz tolerans testi yerine sadece açlık parametreleri kullanılabilir mi?

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ABSTRACT

Aim: Gestational diabetes mellitus (GDM) poses significant risks during pregnancy. While the oral glucose tolerance test (OGTT) remains the diagnostic standard, its complexity and poor patient compliance highlight the need for simpler alternatives. This study evaluates whether fasting glucose and other metabolic parameters can effectively replace the OGTT for GDM screening in Turkish pregnant women, offering a more practical and efficient diagnostic approach tai-lored to this population.

Materials and Methods: This retrospective observational study was conducted between January 2020 and August 2022 in two maternity hospitals in the same region. A total of 192 women diagnosed with GDM and 384 healthy pregnant women were included in the study. A receiver operating characteristic (ROC) analysis was performed to determine the association between the biochemical blood parameters tested in the second trimester fasting plasma glucose, fasting insulin, and HbA1c and the diagnosis of GDM.

Results: The study included 576 pregnant women. The GDM group showed a higher pre-pregnancy BMI compared with the healthy controls ($p < 0.01$). There were statistical differences in the fasting plasma glucose (FPG), fasting insulin, and hemoglobin A1c (HbA1c) between the groups ($p = 0.001$, 0.001, and 0.01, respectively). In the ROC analysis, FPG demonstrated the highest area under the curve (AUC) value (0.920).

Conclusions: Although fasting plasma glucose and fasting insulin can detect a significant proportion of GDM cases, they are insuf-ficient as standalone tools, and the OGTT remains the diagnostic gold standard.

Keywords: Gestational diabetes; glucose tolerance test; fasting blood glucose; pregnancy; diagnostic screening

ÖZ

Amaç: Gestasyonel diabetes mellitus (GDM) gebelik sırasında önemli riskler oluşturmaktadır. Oral glukoz tolerans testi (OGTT) tanısal standart olmaya devam ederken, karmaşıklığı ve hasta uyumunun zayıf olması daha basit alternatiflere olan ihtiyacı vurgulamaktadır. Bu çalışma, açlık glukozu ve diğer metabolik para-metrelerin Türk gebe kadınlarda GDM taraması için OGTT'nin yerini alıp ala-mayacağını ve bu popülasyona özel daha pratik ve etkili bir tanı yaklaşımı sunup sunamayacağını değerlendirmektedir.

Gereç ve Yöntemler: Bu retrospektif gözlemsel çalışma, Ocak 2020 ile Ağustos 2022 tarihleri arasında aynı bölgede bulunan iki kadın doğum hastanesinde yürütülmüştür. Çalışmaya, GDM tanısı alan 192 kadın ile 384 sağlıklı gebe dahil edilmiştir. İkinci trimesterde ölçülen biyokimyasal kan parametreleri (açlık kan glukozu, açlık insülini ve HbA1c) ile GDM tanısı arasındaki ilişkiyi belirlemek için alıcı işletim karakteristik (ROC) analizi yapılmıştır.

Bulgular: Çalışmaya 576 gebe kadın dahil edilmiştir. GDM grubunda gebelik öncesi vücut kitle indeksi (VKİ) sağlıklı kontrollere kıyasla daha yüksekti ($p < 0.01$). Gruplar arasında açlık kan şekeri (AKŞ), açlık insülini ve hemoglobin A1c (HbA1c) açısından istatistiksel farklılıklar vardı (sırasıyla $p = 0.001$, 0.001 ve 0.01). ROC analizi sonucunda, AKŞ en yüksek eğri altında kalan alan (AUC) değerine sahipti (0.920).

Sonuçlar: AKŞ ve açlık insülini parametreleri GDM olgularının önemli bir kısmını belirleyebilse de tek başına yeterli değildir; OGTT'nin tanısal değeri korunmalıdır.

Anahtar Kelimeler: Gestasyonel diyabet, glukoz tolerans testi, açlık kan şekeri, gebelik, tanısal tarama

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INTRODUCTION

Gestational diabetes mellitus (GDM), defined as glucose intolerance first identified after 15 weeks of gestation (1), is a significant global health concern affecting approximately 17% of pregnancies worldwide, with prevalence varying by population and diagnostic criteria (2-4). Despite reported gestational diabetes mellitus (GDM) rates as high as 27.9% in Turkey, adherence to the gold-standard oral glucose tolerance test (OGTT) for diagnosis remains alarmingly low. Studies indicate that only 30–50% of eligible pregnant women in Turkey undergo OGTT, even in high-risk populations (5, 6). This contrasts sharply with higher adherence rates in countries like Australia (85–90%) (7) and the United Kingdom (75–80%) (8), where standardized screening protocols and robust healthcare systems facilitate implementation. Globally, adherence varies widely, with low- and middle-income countries reporting rates as low as 20–40% due to logistical, financial, or cultural barriers (9). The gap between Turkey's high GDM burden and low OGTT utilization underscores urgent needs for improved screening strategies and healthcare provider education (10-15).

GDM is associated with both short- and long-term fetomaternal complications, including cesarean delivery, birth trauma, neonatal intensive care admissions, and stillbirths (16-18). While screening and treatment mitigate acute morbidity, evidence of long-term benefits (e.g., reduced risks of diabetes, obesity, and metabolic disorders) remains inconclusive. Nevertheless, consensus guidelines emphasize postpartum glucose monitoring and lifestyle interventions for all GDM patients to curb future metabolic risks (19) .

In Turkey, the OGTT, though nationally recommended (12), faces declining uptake due to patient misconceptions (e.g., media-fueled fears of fetal harm) and practical barriers (17). The 2 h duration and fasting requirements represent major limitations that further deter compliance in the 75 g OGTT; however, although fasting is not required for the 50 g glucose tolerance test, it is a screening test and additional testing is required to diagnose. Although alternatives such as hemoglobin A1c (HbA1c) have been explored (20, 21), their diagnostic validity remains unestablished (21). Consequently, some clinicians resort to ad hoc monitoring of FPG, postprandial glucose, or fasting insulin, despite lacking robust evidence.

This study aims to evaluate the diagnostic utility of fasting parameters (FPG and fasting insulin) at 24–28 weeks' gestation as potential alternatives to the OGTT in Turkish pregnant women, addressing critical gaps in screening accessibility and reliability.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee of Giresun Training and Research Hospital (approval date: 14.05.2025 / number: 18) and was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants

Study Design, Patient Selection, and Diagnosis

This retrospective observational study was conducted between January 2020 and August 2022 at two maternity hospitals in Northeast Turkey: Trabzon Kanuni Training and Research Hospital and Giresun University Maternity and Children's Hospital. The study population comprised pregnant women aged 18–40 years who attended the antenatal clinic and underwent a 75 g OGTT during the late second trimester of pregnancy (24–28 weeks gestation), gestational age was initially calculated based on the last menstrual period and was verified using first-trimester ultrasound crown-rump length measurements for accuracy. Women with pre-existing medical conditions that could affect study participation, such as chronic hypertension, pre-gestational diabetes, thyroid disorders, and other endocrine abnormalities, were excluded. Additional exclusion criteria included high-risk pregnancies, such as those complicated by preeclampsia or multiple gestation, as well as known metabolic disorders. Women with incomplete clinical data or missing laboratory results were also excluded from the study.

Recorded maternal characteristics included age, gravidity, parity, pre-pregnancy BMI, and BMI at the time of OGTT evaluation. The gestational week at the time of OGTT was recorded instead of the date of the last menstrual period. In addition, family history of diabetes was noted for all participants.

Venous blood samples were collected from all participants after an overnight fast. Samples for FPG, fasting insulin, and HbA1c analyses were drawn into sterile, standardized 4 mL dipotassium EDTA tubes (Vacutainer® BD, USA). This volume ensured sufficient material for all planned assays while adhering to standard clinical protocols.

All pregnant women were screened at 24-28 weeks' gestation using the 75g OGTT test. Patients were diagnosed with GDM according to the International Association of Diabetes and Pregnancy Study Groups criteria: FPG ≥92 mg/dL (5.1 mmol/L) and/or 1-hour blood glucose ≥180 mg/dL (10.0 mmol/L) and/or 2-hour blood glucose ≥153 mg/dL (8.5 mmol/L) (if they met any of the conditions). In addition, patients with FPG ≥126 mg/dL (7 mmol/L) and/or 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) were diagnosed with overt diabetes (2). Patients who met the criteria were referred to as the GDM group. The optimum cut-off point for fasting insulin was 15.7 µU/mL (20) and for HbA1c ≥ 5.7 (22). Two groups were made

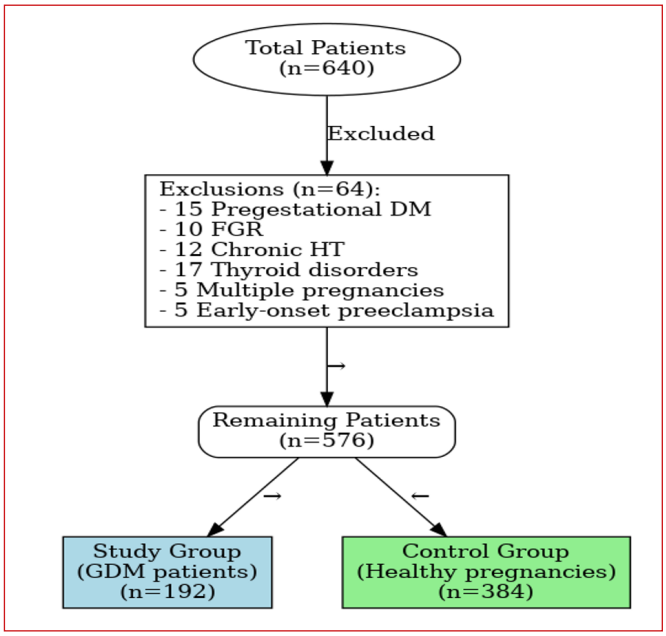

Figure 1. Patient Flow Diagram

according to their pre-pregnancy BMI. BMI 25 ≤ BMI <30 kg/m^2 was considered overweight and BMI ≥ 30 kg/m^2 was considered obese (23).

From an initial cohort of 640 patients, 64 were excluded based on the predefined exclusion criteria. Specifically, 15 patients had pregestational diabetes, 10 had fetal growth restriction, 12 had chronic hypertension, 5 had early-onset preeclampsia, 17 presented with thyroid disorders, and 5 had multiple pregnancies. Consequently, 576 pregnant women were included in the final analysis, comprising 192 diagnosed with GDM and 384 healthy controls (Figure 1).

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Chicago, IL, USA). Continuous variables with normal distribution were presented as mean ± standard deviation, while non-normally distributed variables were expressed as median with interquartile range. Categorical variables were reported as frequencies and percentages. The normality of distribution was assessed using the Kolmogorov–Smirnov test.

For comparative analyses, independent samples t-tests were used for normally distributed continuous variables, while the Mann–Whitney U test was employed for non-normally distributed data. Categorical variables were analyzed using Fisher's exact test or Pearson's chi-square test, as appropriate.

Diagnostic performance was evaluated through receiver operating characteristic (ROC) curve analysis, which assessed fasting insulin, OGTT glucose values, and HbA1c as predictors of GDM. The analysis provided area under the curve (AUC) measurements with 95% confidence intervals, along with optimal cut-off values, sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV).

A two-tailed p-value of ≤0.05 was considered statistically significant for all analyses. The sample size calculation was based on an effect size of 0.2, alpha error of 0.05, and power of 0.80, indicating that a minimum of 190 participants per group was required to achieve adequate statistical power.

RESULTS

The study involved 576 pregnant women, 192 with GDM and 384 with normal results. Table 1 shows the general characteristics and laboratory parameters between the groups. Pre-pregnancy BMI was higher in the GDM group than in the controls (31.4 ± 6.9 vs. 27.9 ± 4.6, p = 0.001).

Table 1. Comparison of demographic characteristics and laboratory parameters between GDM and non-GDM groups.

	GDM (n: 192) [a]	Non-GDM (n: 384)	*p*-Value
Maternal age	29.6 ± 5	28 ± 5	0.59
Pre-pregnancy BMI, kg/m^2	31.4 ± 6.9	27.9 ± 4.6	0.001
BMI at the time of OGTT	31.9 ± 15	28.3 ± 13	0.001
Gravida	2.2 ± 1.2	1.8 ± 1	0.001
Parity	1.1 ± 1.2	0.6 ± 0.8	0.001
OGTT fasting, mg/dL	96.9 ± 10	82.1 ± 5	0.001
OGTT 1 h, mg/dL	153 ± 41	124 ± 26	0.001
OGTT 2 h, mg/dL	134 ± 28	106 ± 19	0.001
Fasting insulin	21.6 ± 12	12.9 ± 5.6	0.001
HbA1c	4.8 ± 0.4	4.6 ± 0.3	0.01
Gestational age	25.2±4	26.3±2	0.56

Abbreviations: [a] Parameters with a normal distribution are presented as mean ± standard deviation; GDM, gestational diabetes mellitus; BMI, body mass index; OGTT, oral glucose tolerance test; $p < 0.05$ values were considered significant.

Table 2. General characteristics of the participants.

	GDM (n: 192)	Non-GDM (n: 384)	*p*-Value
Maternal age			
≥35 y (n, (%))	36 (18.75)	22 (5.8)	0.04
Pre-pregnancy BMI, kg/m²			
≥25 n, (%)	75 (39.5)	153 (39.9)	0.06
≥30 n, (%)	99 (52)	115 (30.5)	0.001
Insulin			
≥15.7 mikroU/mL (n, %)	104 (54)	81 (21.1)	0.001
HbA1c			
≥5.7 (n, %)	24 (12.7)	15 (4)	0.001
OGTT fasting			
≥92 n, (%)	128 (66.6)	0	0.001
OGTT 1 h			
≥180 n, (%)	30 (15.6)	0	0.001
OGTT 2 h			
≥153 n, (%)	28 (14.5)	0	0.001

Abbreviations: **GDM:** gestational diabetes mellitus; **BMI**: body mass index; **OGTT**: oral glucose tolerance test; $p < 0.05$ values were considered significant

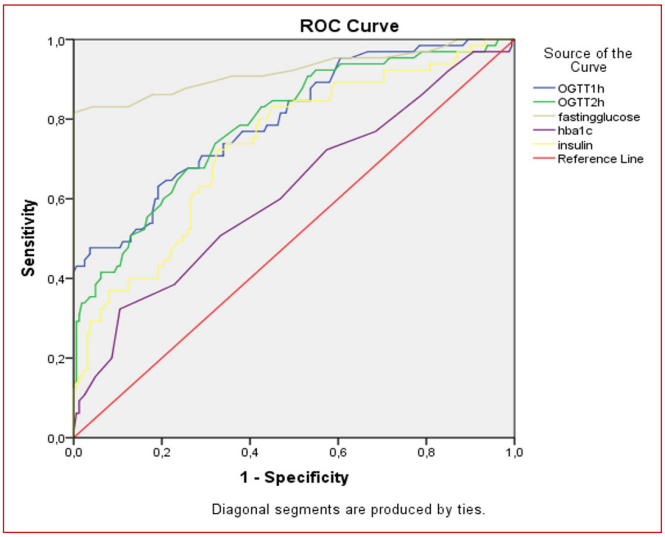

Figure 2. Comparison of Diagnostic Performances of Various Biomarkers Using ROC Curve Analysis

Abbreviations: ROC: receiver operating characteristic, OGTT: oral glucose tolerance test, OGTT1h: 1-hour glucose value from the Oral Glucose Tolerance Test, OGTT2h: 2-hour glucose value from the Oral Glucose Tolerance Test, HbA1c: Glycated hemoglobin

The GDM group exhibited significantly higher concentrations of fasting insulin, FPG, HbA1c, and glucose values at both the first and second hours of the OGTT, relative to the control group.

Table 2 shows categorized general characteristics of the participants. In the GDM group, 18.7% of the pregnant women were ≥ 35 years old and 52% had a BMI >30 (p = 0.04 and p = 0.001, respectively). In the GDM group, 54% had insulin ≥ 15.7 µU/mL and 12.7% had HbA1c ≥ 5.7, which were significantly higher than in the control group (p = 0.001 and p = 0.001, respectively). In the GDM group, 66.6% of cases were diagnosed based solely on FPG ≥92 mg/dL, without requiring OGTT values. An additional 15.6% were diagnosed through elevated 1-hour glucose levels (≥180 mg/dL), and 14.5% through elevated 2-hour glucose levels (≥153 mg/dL), according to the IADPSG diagnostic criteria.

An ROC analysis was performed to evaluate the diagnostic performance of the blood parameters used for identifying GDM. The AUC value for FPG was 0.920 when applying the standard

Table 3. ROC analysis of fasting insulin, fasting glucose, OGTT 1 h, OGTT 2 h, and HbA1c for the prediction of GDM.

	Cut-off Value	AUC (95% CI)	Sensitivity %	Specificity %	PPV%	NPV%
Fasting glucose	≥ 92	0.92 (0.871–0.971)	69%	100%	100	78.6
OGTT 1 h	≥ 180	0.79 (0.735–0.864)	32.5	100	100	78.6
OGTT 2 h,	≥ 153	0.78 (0.722–0.854)	32.5	100	100	78.4
Fasting insulin	≥15.7	0.73 (0.660–0.805)	50.7	75.4	45.2	79.4
HbA1c	>5.7	0.61 (0.534–0.701)	25	78	47	60

Abbreviations: AUC Area Under the Curve, **PPV**: Positive Predictive Value, **NPV**: Negative Predictive Value, **GDM**: Gestational Diabetes Mellitus, **OGTT**: Oral Glucose Tolerance Test, **HbA1c**: Glycated Hemoglobin

diagnostic cut-off of ≥92 mg/dL. At this threshold, the sensitivity and NPV of FPG were 69% and 78.6%, respectively. For fasting insulin, when a cut-off value of ≥15.7 µIU/mL was applied, the AUC was 0.730, with a specificity of 75.4%, sensitivity of 50.7%, PPV of 45.2%, and NPV of 79.4%. The results of the ROC analysis are shown in Figure 2, Table 3.

DISCUSSION

This retrospective observational study is one of the first clinical trials focus-ing on a GDM screening strategy based on fasting insulin and fasting blood glucose levels in second-trimester pregnant women in Turkey. Our findings showed that 54% of GDM patients could be diagnosed with fasting insulin and 66% with fasting blood glucose based on the cut-off values recommended in the literature.

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. This condition arises from progressive insulin resistance that develops during the second trimester, peaking in the late gestational period. When pancreatic β-cell function proves insufficient to compensate for this physiological insulin resistance, re-sultant hyperglycemia manifests, necessitating systematic screening between 24 and 28 weeks of gestation, as recommended by current clinical guidelines (1, 11, 15). Although simple ratios derived from fasting insulin and glucose have been widely used in epidemiological studies, none are recommended for routine assessment of insulin resistance in the clinical setting (24, 25). Serum fasting insulin concentration, triglyceride concentration, and the ratio of triglyceride to high-density lipoprotein (HDL) cholesterol concentrations are useful markers for identifying individuals with insulin resistance. The optimum cut-off point for insulin was determined as 15.7 µU/mL (21). In our study, fasting insulin levels were significantly higher in the GDM group compared to the controls. Moreover, more than half of the women with GDM had fasting insulin levels above the cut-off value, which was statistically significant compared with the control group.

National and international organizations recommend universal GDM screening instead of selective screening since 20% of individuals with GDM have no risk factors (1, 2, 12) . However, publications in the literature suggest that cost savings can be achieved by using the FPG at 24 to 28 weeks to screen pregnant women in low-income regions where universal screening cannot be applied. A study conducted in China showed that 38% of pregnant women with FPG between 79 mg/dL and 90 mg/dL had undiagnosed GDM, and 12% of patients with GDM were not detected(24). In the HAPO study, 50% to 75% of patients with GDM had FPG ≥ 92 mg/dL on the OGTT (25). Consistent with these findings, our study demonstrated that approximately two-thirds of GDM cases could be identified using FPG ≥ 92 mg/dL, while additional cases were detected with the 1-hour and 2-hour OGTT values. Based on the FPG alone, 34.6% of GDM patients could not be diagnosed. In a systematic review, when the FPG threshold used was 95.5 mg/dL, specificity was reported as 98% and sensitivity as 58%. In our study, the sensitivity and predictive values of FPG supported its diagnostic utility, although a proportion of cases would still remain undetected if used as the sole screening tool.

HbA1c, which is used to diagnose diabetes and monitor the efficacy of treatment (26, 27) , may be a helpful test for evaluating glycemic management during pregnancy (28, 29). There are no standardized values according to trimesters. Levels are lower in pregnant women due to physiologic changes during pregnancy (30). A study involving 607 Indian women found an AUC of 0.683 (95% CI: 0.601–0.765) for HbA1c in diagnosing GDM in the late second trimester of gestation (31). Similarly, a Turkish study including 339 women found an AUC of 0.697 (95% CI: 0.645–0.745) (32). In this study, a threshold of HbA1c ≥ 5.7% was used, although this value is conventionally applied to define prediabetes rather than overt diabetes (≥ 6.5%). The rationale for using this lower threshold was to evaluate its potential utility as an early marker for gestational diabetes mellitus (GDM), given that even mild elevations in HbA1c during pregnancy may indicate impaired glucose metabolism. Previous studies have also explored HbA1c cut-off values below the diagnostic threshold for diabetes to assess their predictive value for GDM (22), and our study aimed to contribute to this growing body of evidence. In our study, the AUC was 0.61 (95% CI: 0.534–0.701), which is consistent with other studies. When HbA1c ≥ 5.7% was used, the proportion of GDM patients identified was limited, although this finding remained statistically significant compared with controls. This reduced sensitivity may be attributed to physiological changes in pregnancy, such as shortened erythrocyte lifespan and altered hemoglobin glycation rates. While the specificity for GDM increased with higher HbA1c cut-off values, the sensitivity improved at lower cut-offs, though neither approach provided sufficient diagnostic accuracy.

The study's strengths include its retrospective design, multicenter nature, relatively large sample size, and potential clinical utility in settings with low patient compliance.

This study has several limitations. First, the findings may not be generalizable to all Turkish populations, as important factors such as socioeconomic status and lifestyle were not assessed. Second, clinical outcomes including birth weight, cesarean delivery rates, and neonatal hypoglycemia were not evaluated. Third, the fasting

insulin cut-off value was not population-specific, and pregnancy-related anemia may have influenced HbA1c measurements. Finally, the analysis was restricted to the 24–28 weeks' gestational window, without considering earlier or later time points.

CONCLUSIONS

This retrospective study demonstrates that while FPG and fasting insulin levels show reasonable diagnostic accuracy for GDM, they remain insufficient as standalone screening tools, missing approximately one-third of GDM cases. Our findings reinforce that the OGTT remains the gold standard for GDM diagnosis, particularly given the limitations of alternative biomarkers such as HbA1c, which exhibited poor sensitivity in our cohort.

The clinical implications are twofold: First, in resource-limited settings or for patients refusing the OGTT, FPG-based screening may identify a majority of GDM cases, though with significant false negative rates requiring careful patient counseling. Second, our results highlight the need for population-specific cut-off optimization and further research into composite screening algorithms combining fasting parameters with clinical risk factors.

Institutional Review Board Statement: The Ethics Committee of Giresun Training and Research Hospital approved the study protocol, which complied with the requirements of the Declaration of Helsinki (approval date 14.05.2025/ number 18)

Informed Consent Statement: The need for written informed consent was exempted because of the study's retrospective design.

Data Availability Statement: The datasets used and/or analyzed in this study are accessible from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

Author Contributions: Conceptualization, S.B.Y.; methodology, S.BY.; validation, S.BY.; formal analysis, S.BY. and N.B.A.; investigation, S.B.Y. and N.B.A.; resources, S.B.Y and N.B.A.; data curation, S.B.Y and N.B.A.; writing—S.B.Y.; writing—review and editing, S.B.Y. and N.B.A.; visualization, S.B.Y. and N.B.A.; supervision, S.B.Y. and N.B.A.; project administration, S.B.Y. and N.B.A.; funding acquisition, S.B.Y. and N.B.A. All authors have read and agreed to the published version of the manuscript.

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ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

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A cross-sectional study of *CHEK2* pathogenic variants: cancer risk spectrum and clinical insights

CHEK2 patojenik varyantlarına dair kesitsel bir çalışma: Kanser risk spektrumu ve klinik değerlendirmeler

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ABSTRACT

Aims: *CHEK2* is a tumor suppressor gene involved in DNA damage response and a moderate-risk gene for breast cancer. However, its role in other malignancies remains unclear, and the clinical impact of biallelic *CHEK2* mutations is not well understood. This study aims to expand the cancer risk spectrum of *CHEK2*, including rare tumors, and to provide insights into the phenotypes associated with biallelic mutations and Multiple Inherited Neoplasia Alleles Syndrome (MINAS).

Materials and Methods: We analyzed 40 individuals from 34 families carrying *CHEK2* mutations, identified via multigene panel testing for hereditary cancer syndromes. Next-generation sequencing was performed for the probands, and segregation analysis in affected relatives was conducted using Sanger sequencing. Clinical data, including cancer type, age at diagnosis, and family history, were obtained from medical records and clinical evaluations.

Results: We identified 16 distinct *CHEK2* mutations, with c.1427C>T (p.Thr476Met) being the most frequent. Breast cancer was the most common diagnosis (75%), followed by thyroid cancer and rare tumors, including pancreatic neuroendocrine and cerebellopontine angle tumors. Multiple primary cancers occurred in 15% of patients, and 10% had MINAS, harboring additional variants in genes like PTEN and BRCA2. Biallelic *CHEK2* mutations were linked to severe phenotypes, including bilateral breast cancer and adolescent-onset polyposis.

Conclusions: Our findings broaden the *CHEK2*-associated cancer spectrum, extending beyond breast cancer to include rare malignancies and complex presentations. The identification of biallelic mutations and MINAS underscores the need for comprehensive genetic testing and tailored surveillance. These insights are crucial for refining risk assessment, enhancing prevention, and improving clinical management for individuals harboring *CHEK2* mutations.

Keywords: *CHEK2*, MINAS, polyposis, FATWO, hereditary cancer syndromes

ÖZ

Amaç: *CHEK2*, DNA hasar yanıtında rol oynayan bir tümör süpresör gendir ve meme kanseri için orta derecede risk faktörü olarak kabul edilir. Ancak, diğer malignitelerdeki rolü belirsizliğini korumaktadır ve biallelik *CHEK2* mutasyonlarının klinik etkileri tam olarak anlaşılamamıştır. Bu çalışma, *CHEK2* ile ilişkili kanser risk spektrumunu genişletmeyi, nadir tümörleri tanımlamayı ve biallelik mutasyonlar ile Multiple Inherited Neoplasia Alleles Syndrome (MINAS) fenotipleri hakkında yeni bilgiler sunmayı amaçlamaktadır.

Gereç ve Yöntemler: Kalıtsal kanser sendromları şüphesiyle multigen panel testi yapılan ve *CHEK2* mutasyonu saptanan 34 aileye ait 40 birey analiz edilmiştir. Probantlar için yeni nesil dizileme (NGS) yapılmış, etkilenen aile bireylerinde segregasyon analizi Sanger sekanslama ile gerçekleştirilmiştir. Kanser tipi, tanı yaşı ve aile öyküsü gibi klinik veriler tıbbi kayıtlar ve klinik değerlendirmeler yoluyla elde edilmiştir.

Bulgular: Toplam 16 farklı *CHEK2* mutasyonu tanımlanmış, bunlar arasında en sık c.1427C>T (p.Thr476Met) mutasyonu görülmüştür. Kohortta en yaygın tanı meme kanseri olup (%75), bunu tiroid kanseri takip etmiştir. Ayrıca, pankreatik nöroendokrin tümörler ve serebellopontin açı tümörleri gibi nadir maligniteler de gözlenmiştir. Hastaların %15'inde birden fazla birincil kanser bulunurken, %10'unda PTEN ve BRCA2 gibi ek varyantlar içeren MINAS saptanmıştır. Biallelik *CHEK2* mutasyonları, bilateral meme kanseri ve adolesan yaşta başlayan polipozis ile ilişkilendirilmiştir.

Sonuç: Bulgularımız, *CHEK2* ile ilişkili kanser spektrumunu genişleterek meme kanserinin ötesinde nadir maligniteleri ve kompleks klinik tabloları içermektedir. Biallelik mutasyonlar ve MINAS, kapsamlı genetik testlerin yanı sıra bireyselleştirilmiş izlem ve yönetim stratejilerinin önemini ortaya koymaktadır. Bu çalışmanın bulguları, risk değerlendirmesinin iyileştirilmesi, önleyici yaklaşımların geliştirilmesi ve *CHEK2* mutasyonu taşıyan bireylerin klinik yönetiminin optimize edilmesi açısından kritik öneme sahiptir.

Anahtar Kelimeler: *CHEK2*, MINAS, polipozis, FATWO, herediter kanser sendromları

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INTRODUCTION

CHEK2 encodes the checkpoint kinase 2 protein (CHK2), a tumor suppressor involved in the DNA damage response (DDR) pathway as part of the ATM-CHK2-p53 complex (1). The DDR is a signal amplification cascade that detects DNA damage, induces cell cycle arrest, and initiates DNA repair. Similar to mutations in many other genes involved in DDR and DNA repair pathways, mutations in the *CHEK2* play an active role in carcinogenesis (2).

Initial studies identified *CHEK2* germline mutations as predisposing to a moderate risk for breast cancer (3). Among these mutations, c.1100delC has been extensively studied and is associated with a significant increase in breast cancer risk (4). A meta-analysis of patients with this mutation estimated a cumulative risk of 37% for developing breast cancer by the age of 70 (5). While the loss-of-function (LOF) variants, such as c.1100delC, are typically classified as pathogenic variants (PVs), the clinical significance of other *CHEK2* variants, particularly missense mutations, remains less-defined (6). The effect of these missense variants is variable and highly dependent on whether critical protein domains within the CHK2 protein are affected (6).

Genetic testing for *CHEK2* is now a standard part of routine diagnostic Next Generation Sequencing (NGS) panels for various inherited cancers, with *CHEK2* being one of the most frequently identified genes harboring germline mutations (7). Despite the established role of *CHEK2* mutations in increasing the risk for hereditary cancers, the full spectrum of associated cancer risks is not yet fully understood. *CHEK2* germline mutations have been reported in large cohort studies and case-based publications across a variety of cancer types (8, 9). In the past, these mutations were even linked to Li-Fraumeni syndrome (10); however, this terminology is no longer in use (11). Recent studies have reinforced the increased risks for breast and prostate cancers (6, 12), leading to current cancer screening guidelines primarily focusing on these two cancer types for individuals with *CHEK2* mutations (13). However, these guidelines do not routinely address other potential cancer risks, highlighting the need for systematic data collection to more comprehensively define the full range of cancer risks in *CHEK2* mutation carriers. Furthermore, the American College of Medical Genetics and Genomics (ACMG) emphasizes the necessity of additional research to inform clinical management strategies for individuals with *CHEK2* mutations (14).

In this study, we present the clinical and genetic characteristics of 40 affected individuals from 34 families with *CHEK2* variants, identified through multigene panel testing for suspected hereditary cancer syndromes. Among these patients, we report atypical presentations, including rare cancers and the presence of concurrent pathogenic variants in other hereditary-cancer-related genes, underscoring the variability in *CHEK2*-related cancer phenotypes and the challenges in clinical interpretation.

MATERIALS AND METHODS

The study cohort includes 40 affected individuals from 34 families who were referred to medical genetics department with a suspicion of hereditary cancer syndrome and were found to have variants in the *CHEK2*, each with various cancer diagnoses. The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the institutional ethics committee of Hacettepe University (SBA 24/850, 17th September 2024). Written informed consent was obtained from the affected individuals for molecular testing and publication. Clinical data were gathered from both medical records and in-person evaluations between 2021 and 2024, including age at diagnosis, cancer type, family history of cancer, and other relevant clinical features and histopathological findings.

For genetic analysis, genomic DNA was extracted from peripheral blood samples of the index cases and their affected family members using a QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. A targeted panel, consisting of the coding regions of at least 40 cancer predisposition genes *(APC, ATM, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, FANCC, FLCN, GALNT12, HOXB13, MEN1, MET, MLH1, MSH2, MSH6, MUTYH, NBN, NTHL1, PALB2, PMS2, POLD1, POLE, PTCH1, PTEN, RAD51C, RAD51D, RB1, RET, SMAD4, STK11, TP53, VHL)* was performed on the DNA samples of the index cases using next-generation sequencing (NGS) technology.

Variant filtering steps were performed using the Seq Genomize Variant Analysis Platform, and variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines. Pathogenic and likely pathogenic variants were reported. Each identified variant was visually inspected using the Integrative Genomics Viewer (IGV). Segregation studies were conducted by Sanger sequencing for the affected family members of index cases carrying *CHEK2* variants.

Statistical Analysis

Descriptive statistics were used to summarize the data. Categorical variables were presented as frequencies and percentages, while continuous variables were reported as medians and ranges. No inferential statistical analyses were performed.

RESULTS

Clinical characteristics of affected individuals

This study included 40 patients with *CHEK2* variants from 34 unrelated families. Detailed demographic, clinical, and molecular data of the affected individuals are presented in Table 1. The cohort predominantly consisted of female patients (90%), with 4 male patients (10%). The ages at diagnosis ranged from 17 to 72 years, with a median age at diagnosis of 46 years. Breast cancer

Table 1. Clinical and genetic characteristics of the cohort.

ID	FAM ID	Gender	Current Age (y)	Diagnosis	Age at Cancer Diagnosis (y)	Family History	*CHEK2* (NM_007194.4) Variant	Zygosity	Concurrent Variant
P1	F1	F	47	Breast Cancer	43	Paternal grandfather stomach Ca, Paternal niece ALL	c.1427C>T (p.Thr476Met)	HET	No
P2	F2	F	40	Breast Cancer	37	Father colorectal Ca (AaD: 54y), Maternal aunt leukemia (AaD: 54y)	c.16del (p.Asp6Metfs*55)	HET	No
P3	F3	F	45	Breast Cancer	41	Father lymphoma AaD: 65y)	c.592+3A>T	HET	No
P4	F4	F	50	Breast Cancer	45	Maternal aunt colorectal Ca, Maternal cousin breast Ca, Father and 2 maternal uncle prostate Ca, Maternal cousin CNS tm	c.1427C>T (p.Thr476Met)	HET	No
P5	F5	F	55	FATWO	49	Sister breast cancer (AaD: 49y)	c.479T>C (p.Ile160Thr)	HET	No
P6		F	59	Breast Cancer	49	FATWO diagnosis in the sister (AaD: 49y)	c.479T>C (p.Ile160Thr)	HET	No
P7	F6	F	23	Ovarian Cancer	17	No	c.1427C>T (p.Thr476Met)	HET	No
P8	F7	F	29	Colorectal Cancer	26	Maternal grandmother breast cancer	c.100C>T (p.Gln34Ter)	HET	NM_001048174.2 *(MUTYH)*: c.775del (p.Ala259Profs*32) and c.800C>T (p.Pro267Leu) compound heterozygous
P9	F8	F	62	Breast Cancer	52	No	c.592+3A>T	HET	No
P10	F9	F	75	Bilateral Breast Cancer	69	No	c.444+1G>A	HET	No
P11	F10	F	74	Breast Cancer	72	Sister breast, colorectal and thoracic Ca, Son thyroid Ca, Mother leukemia, Maternal uncle stomach Ca	c.1427C>T (p.Thr476Met)	HET	No
P12		M	49	Thyroid Cancer	46	Mother breast Ca Maternal aunt breast, colorectal and thoracic Ca, Maternal grandmother leukemia, Brother of maternal grandmother stomach Ca		HET	No
P13	F11	M	22	Polyposis	17	Maternal uncle colorectal Ca	c.792+1G>T	HOM	No
P14	F12	F	66	Breast Cancer Endometrium Cancer	52 62	Sister breast Ca, Maternal aunt endometrium Ca, Maternal cousin lymphoma	c.190G>A (p.Glu64Lys)	HET	No
P15		F	68	Breast Cancer	42	Sister breast and endometrium Ca, Maternal aunt endometrium Ca, Maternal cousin lymphoma	c.190G>A (p.Glu64Lys)	HET	No
P16	F13	F	50	Breast Cancer	46	Maternal father colorectal Ca	c.1427C>T (p.Thr476Met)	HET	No
P17	F14	F	65	Breast Cancer	59	Three sisters breast Ca	c.427C>T (p.His143Tyr)	HET	No
P18	F15	F	53	Lobular Breast Cancer	46	Maternal grandfather stomach Ca, Maternal grandmother pancreatic Ca	c.433C>T (p.Arg145Trp)	HET	No
P19	F16	F	56	Bilateral Breast Cancer	47	Maternal uncle breast and prostate Ca	c.592+3A>T	HOM	No
P20	F17	F	39	Breast Cancer	36	No	c.1232G>A (p.Trp411Ter)	HET	No
P21	F18	F	51	Breast Cancer Thyroid Cancer	36 37	Brother colon Ca, Maternal uncle with stomach Ca; two of his sons colon Ca, his daughter breast Ca, Maternal aunt with colon Ca; her daughter breast cancer and her son colon Ca	c.1169A>C (p.Tyr390Ser)	HET	No
P22		F	65	Breast Cancer	61	Mother breast Ca, Father skin tm, Brother colon Ca, Paternal grandmother breast Ca, Maternal cousin breast and thyroid Ca, Another maternal cousin colon Ca, Maternal uncle with stomach Ca; two of his sons colon Ca, his daughter breast Ca	c.1169A>C (p.Tyr390Ser)	HET	No
P23		M	69	Colorectal Cancer	62	Mother breast Ca, Father skin tm, Sister breast Ca, Paternal grandmother breast Ca, Maternal cousin breast and thyroid Ca, Another maternal cousin colon Ca, Maternal uncle with stomach Ca; two of his sons colon Ca, his daughter breast Ca	c.1169A>C (p.Tyr390Ser)	HET	No

Continued

Table 1. Clinical and genetic characteristics of the cohort.

P24	F19	F	48	Breast Cancer	43	Two paternal cousins with early-onset breast Ca	c.499G>A (p.Gly167Arg)	HET	No
P25	F20	F	36	Breast Cancer	32	No	c.1169A>C (p.Tyr390Ser)	HET	No
P26	F21	M	51	Pancreatic Cancer	50	Mother gastric Ca, Sister leukemia (AaD: 66), Maternal cousin pancreatic Ca (AaD: 58), Maternal cousin breast Ca (AaD: 50)	c.1427C>T (p.Thr476Met)	HET	No
P27	F22	F	55	Breast Cancer	53	Mother bilateral breast Ca,		HET	No
P28		F	87	Bilateral Breast Cancer	70	Daughter breast Ca	c.1427C>T (p.Thr476Met) mutasyon	HET	No
P29	F23	F	54	Neurofibroma-tosis	40	Father subcutaneous nodules, Sister and maternal aunt axillary freckling, Sister and mother cafe au lait macules	c.1427C>T (p.Thr476Met)	HET	NM_001042492.3 *(NF1)*: c.76G>T (p.Gly26Ter)
P30	F24	F	68	Bilateral Breast Cancer	60	Sister breast Ca, Mother endometrium Ca, Father stomach Ca, Brother and paternal aunt bladder Ca, Maternal aunt and uncle with stomach Ca, Maternal aunts CNS tm	c.1427C>T (p.Thr476Met)	HET	NM_000059.4 *(BRCA2)*: c.3589A>T (p.Lys1197Ter)
P31	F25	F	66	Medullary Thyroid Cancer, Pancreatic NET	67 68	Father prostate Ca, Brother colorectal Ca, Sister cancer of unknown primary, Maternal uncle colorectal Ca, Paternal aunt colorectal Ca	c.1260C>A (p.Cys420Ter)	HET	No
P32	F26	F	37	Breast Cancer	35	Mother Thyroid Papillary Cancer		HET	No
P33	F27	F	62	Breast Cancer	51	Paternal cousin early-onset colorectal Ca	c.100C>T (p.Gln34Ter)	HET	No
P34	F28	F	45	Breast Cancer Thyroid Papillary Cancer	33 33	Nephew leukemia	c.592+3A>T	HET	No
P35	F29	F	46	Breast Cancer	34	No	c.1427C>T (p.Thr476Met)	HET	No
P36	F30	F	76	Breast Cancer Cerebellopontin tumor	54 69	Father prostate Ca, Sister endometrium Ca	c.1232G>A (p.Trp411Ter)	HET	No
P37	F31	F	57	Breast Cancer Thyroid Cancer	42 44	Father and paternal uncle prostate Ca, Paternal aunt and maternal uncle bladder Ca	c.1427C>T (p.Thr476Met)	HET	NM_000314.8 *(PTEN)*: c.407G>A (p.Cys136Tyr)
P38	F32	F	61	Primary serous peritonael carcinoma	57	No	c.592+3A>T	HET	No
P39	F33	F	46	Breast Cancer	42	Paternal uncle thyroid Ca, Paternal cousin leukemia	c.58C>T (p.Gln20Ter)	HET	No
P40	F34	F	52	Breast Cancer	49	Father CNS tm, Maternal aunt stomach Ca (Aad: 45y), Maternal niece stomach Ca (Aad: 35)	c.499G>T (p.Gly167Ter)	HET	No

Bilateral involvement is indicated. When known, the ages of cancer diagnoses in family members are shown in parentheses. ALL: acute lymphoblastic leukemia, AaD: age at diagnosis, Ca: cancer, CNS: central nervous system, F: female, FATWO: Female adnexal tumor of probable Wolffian Origin, HET: heterozygous, HOM: homozygous, M: male, NK: not known, tm: tumor, y: years.

was the most frequently observed diagnosis, affecting 30 patients (75%), 4 of whom had bilateral involvement. This was followed by thyroid cancer in 5 patients (12.5%), which included both medullary and papillary subtypes. Additionally, rare tumors were observed, including Wolffian Tumor (FATWO), a highly uncommon adnexal neoplasm, and Pancreatic Neuroendocrine Tumor. Furthermore, atypical presentations, such as cerebellopontine angle tumors, were identified, which have not been previously reported in association with *CHEK2* variants.

Notably, six patients (15%) presented with multiple primary cancers. These included one individual with medullary thyroid cancer and a pancreatic neuroendocrine tumor, another with a cerebellopontine angle tumor and breast cancer, three patients with breast and papillary thyroid cancers, and one with breast and endometrial cancers. Analysis of pedigrees revealed that 27 of the 34 probands had a significant positive family history of cancer among close relatives.

Genetic findings

Sixteen distinct pathogenic or likely pathogenic variants in *CHEK2* were identified across 34 unrelated probands, demonstrating a diverse spectrum of mutation types (Figure 1). These included missense mutations (n=7), nonsense mutations (n=5), splice-site mutations (n=3), and one frameshift mutation. The most recurrent variant was c.1427C>T (p.Thr476Met), detected in 11 probands.

Domain-specific analysis highlighted that missense mutations were predominantly localized within critical functional domains essential for CHK2's role in the DNA damage response. Of the seven missense mutations, the majority (n=6) were situated within the forkhead-

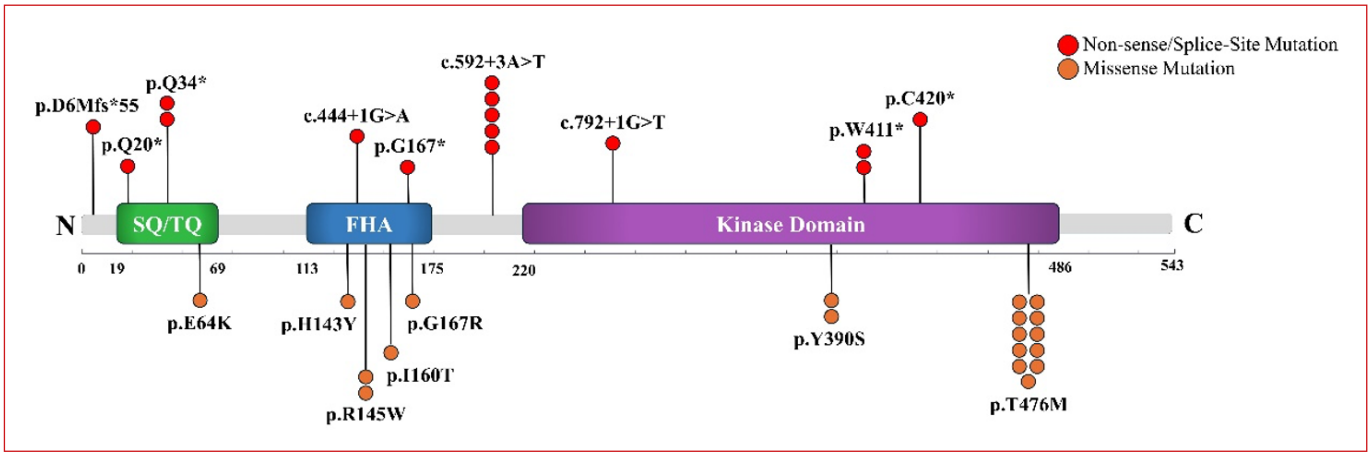

Figure 1. Schematic representation of *CHK2* protein domains and distribution of germline mutations.

The *CHK2* protein consists of three major functional domains: the SQ/TQ domain (amino acids 19–69), which mediates ATM binding; the Forkhead-Associated (FHA) domain (amino acids 113–175), involved in dimerization and activation through phosphorylation; and the Kinase domain (amino acids 220–486), responsible for phosphorylating downstream effector proteins. Each dot represents a family with the indicated mutation (Red: Non-sense/Splice-Site Mutation; Orange: Missense Mutation).

associated (FHA) domain (amino acids 113–175), responsible for dimerization and activation through phosphorylation, and the kinase domain (amino acids 220–486), which mediates phosphorylation of downstream effector proteins. Notably, the recurrent c.1427C>T (p.Thr476Met) variant lies within the kinase domain, suggesting that disrupted phosphorylation may be a key pathogenic mechanism. Additionally, one missense variant, c.190G>A (p.Glu64Lys), was identified within the SQ/TQ domain (amino acids 19–69), which may impair ATM-mediated phosphorylation.

Nonsense and splice-site mutations were distributed throughout the gene, typically resulting in truncated or non-functional proteins. Two patients were homozygous carriers of *CHEK2* mutations (c.792+1G>T and c.592+3A>T), with clinical manifestations including adolescent-onset colon polyposis and bilateral breast cancer, respectively.

Furthermore, 10% of patients (n=4) were found to have Multiple Inherited Neoplasia Alleles Syndrome (MINAS), harboring additional pathogenic variants in other cancer predisposition genes, such as *MUTYH, BRCA2, NF1,* and *PTEN*, adding complexity to their clinical presentations.

DISCUSSION

In this study, we report a cohort of 40 affected individuals from 34 families with *CHEK2* mutations, contributing novel clinical and genetic insights. Our findings further expand the phenotypic spectrum of *CHEK2*-related cancers and, with 75% of patients in our cohort diagnosed with breast cancer, reaffirm its well-established role in breast cancer predisposition. Notably, we found no patients diagnosed with prostate cancer in our cohort, despite its known association with increased risk in individuals with *CHEK2* mutations. This may reflect the tendency for genetic evaluations to overlook prostate cancer, which is frequently observed in men, potentially due to the underestimation of its genetic etiology.

Beyond the well-documented associations, our study highlights the presence of rare tumors in individuals with germline *CHEK2* mutations. We identified a case of Wolffian Tumor (FATWO), an extremely rare neoplasm that has previously been reported in only one patient with a *CHEK2* germline variant (15). Additionally, we describe a patient with cerebellopontine angle tumor, which, to our knowledge, has not been previously linked to *CHEK2* mutations. The presence of such rare tumor types in our cohort suggests that the oncogenic landscape of *CHEK2* may be broader than currently recognized. While larger studies are necessary to determine whether these associations reflect direct contributions of *CHEK2* dysfunction or occur by chance, our findings emphasize the importance of continued investigation into the full phenotypic spectrum of *CHEK2*-related cancers.

Among the 16 distinct mutations identified in our study, 7 were missense mutations (Figure 1). While truncating mutations—including nonsense, splice-site, and frameshift variants such as c.1100del—are well-established as pathogenic, missense mutations present greater challenges in classification. For instance, the p.Ile157Thr and p.Ser428Phe variants have been reported with conflicting interpretations, ranging from established risk alleles to variants of uncertain significance (VUS) or pathogenic mutations. Large-scale studies have further highlighted this uncertainty. These findings suggest that while the p.Ile157Thr and p.Ser428Phe

variants may exert some biological effect, their penetrance is likely too low to warrant clinical actionability (16). Given their limited clinical utility, individuals harboring these variants were excluded from our cohort. The most frequently observed missense mutation in our study was c.1427C>T (p.Thr476Met), located in the kinase domain of *CHEK2*, a region essential for its tumor suppressor function. Functional data strongly suggest that this variant disrupts CHK2's activity (17). However, the functional consequences of most *CHEK2* missense mutations remain poorly understood. Recently, multiplexed assays of variant effect (MAVEs) have emerged as a powerful tool to systematically assess the functional impact of VUS variants across hereditary cancer genes. Saturation genome editing approaches have been successfully applied to genes such as *BRCA2* and *RAD51D* (18, 19), providing large-scale functional insights that directly inform variant classification and patient management. Given the high prevalence of missense mutations in *CHEK2*, similar approaches are essential to refine risk stratification and guide clinical decision-making.

A particularly notable finding in our study is the presence of biallelic *CHEK2* mutations in two patients (Table 1), both of whom exhibited severe clinical phenotypes. One patient (P19), harboring the c.592+3A>T splice-site variant, developed bilateral breast cancer, a hallmark of high-risk hereditary cancer syndromes. Previous studies have suggested that biallelic *CHEK2* mutations, particularly involving truncating variants like c.1100del, may confer significantly higher cancer risks compared to monoallelic carriers (20). In cohorts analyzed for hereditary cancer, biallelic carriers have demonstrated a markedly elevated risk for invasive breast cancer (OR 8.69, 95% CI 3.69–20.47), with earlier onset and a higher frequency of bilateral tumors (21). These findings are consistent with our observation of bilateral breast cancer in a patient carrying the biallelic splice-site *CHEK2* variant. The second patient (P13), carrying the c.792+1G>T splice-site variant in a homozygous state, was the youngest patient in our cohort (17 years old) and was diagnosed with adolescent-onset polyposis. This patient presented with numerous adenomatous polyps and tubular adenomas in the duodenum and colon, many of which showed dysplasia. Recent studies have suggested that biallelic *CHEK2* mutations may represent a novel recessive hereditary cancer syndrome characterized by chromosomal instability and a predisposition to multiple cancers (22, 23). Although we were unable to evaluate chromosomal breakage in our patient, the presence of numerous dysplastic polyps at a remarkably young age, combined with the absence of mutations in known polyposis-associated genes, provides valuable support for this emerging entity.

In 10% of our cohort (n=4), Multiple Inherited Neoplasia Alleles Syndrome (MINAS) was identified, characterized by the co-occurrence of pathogenic variants in multiple hereditary cancer genes (Table 1). This emerging concept, increasingly recognized with the widespread use of multigene panels, presents significant challenges in risk assessment and clinical management of patients (24). Notably, a patient (P37) harboring both *CHEK2* and *PTEN* mutations was diagnosed with breast and thyroid cancer, with breast cancer diagnosed at age 42. While PTEN mutations are well-established in Cowden syndrome and associated with multiple malignancies (25), the potential contribution of *CHEK2* to breast cancer risk or age of onset in this patient remains uncertain. Given the tumor suppressor functions of both genes, their combined effect on tumorigenesis warrants further investigation. Another notable case involved a patient (P30) with both *CHEK2* and BRCA2 mutations, presenting with bilateral breast cancer at diagnosis and a strong family history of cancer on both maternal and paternal sides. Although segregation analysis was not available, the dual presence of *CHEK2* and BRCA2 mutations raises questions about their combined impact on disease penetrance and phenotype. While BRCA2 is strongly associated with high breast cancer risk, the contribution of *CHEK2* to the bilateral presentation and familial clustering in this case remains unclear. Similarly, a patient (P8) with *CHEK2* and biallelic *MUTYH* mutations developed colorectal cancer at age 26, suggesting that *CHEK2* may play a role in accelerating early-onset colorectal cancer in the context of MUTYH-associated polyposis. These cases highlight the complexity of interpreting multiple germline variants and their potential synergistic or additive effects.

Our findings contribute to the growing evidence surrounding biallelic *CHEK2* mutations and MINAS, emphasizing the need for further investigation. Future studies should focus not only on refining the clinical interpretation of *CHEK2* variants, particularly the missense mutations, but also on elucidating its role in a broader range of tumor types.

The predominance of breast cancer in our cohort underscores the clinical importance of *CHEK2* mutations for women's health and reaffirms their well-established role in hereditary breast cancer predisposition. Current NCCN guidelines estimate a lifetime breast cancer risk of 23–27% for women with germline *CHEK2* mutations, with a 10-year cumulative risk of 6–8% for contralateral breast cancer (13). Accordingly, annual mammography from age 40 and consideration of breast MRI beginning at 30–35 years are recommended, while decisions regarding risk-reducing mastectomy should be individualized according to family history. Gynecologic and breast cancers share several risk factors including inherited cancer-associated pathogenic gene variants, family cancer history, early menarche, late menopause, and obesity. The gynecology setting, therefore, may be an ideal environment for

breast cancer risk assessment and subsequent risk management, as many women present first to gynecologists for routine care. In this context, gynecologists play a pivotal role in recognizing hereditary cancer risk, initiating genetic evaluation, and guiding patients to appropriate preventive strategies. The identification of a rare gynecologic tumor (FATWO) in our series further highlights the broader oncologic relevance of *CHEK2* beyond breast cancer. In addition, the frequent familial clustering observed in our cohort emphasizes the importance of cascade testing and genetic counseling for at-risk relatives. Collectively, these findings highlight the need for multidisciplinary collaboration between medical genetics, gynecology, and oncology to optimize risk stratification, surveillance, prevention, and long-term outcomes in women carrying *CHEK2* mutations.

Conflict of interest: The authors declare no competing interests.

Author Contributions: CDD conceptualized and designed the study, performed data analysis, and drafted the manuscript. SA supervised the study and contributed to the manuscript revision. ÖÇA, NB, DDE, and NGL were responsible for genetic analyses, variant interpretation, and manuscript preparation. ÖD, ZA, and SA contributed to the collection and interpretation of clinical data. All authors critically reviewed and approved the final version of the manuscript.

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Luteal phase support in IUI: a game-changer for pregnancy outcomes?

İntrauterin inseminasyonda luteal faz desteği: Gebelik sonuçlarını değiştiren bir faktör mü?

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ABSTRACT

Aim: This study aims to evaluate the impact of luteal phase support (LPS) with progesterone on pregnancy and live birth rates in patients undergoing intrauterine insemination (IUI) treatment.

Materials and Methods: A retrospective analysis was conducted on 88 patients who underwent IUI treatment at a tertiary center between 2019 and 2021. Patients were divided into two groups: Group 1 (n=49) received progesterone for luteal phase support, while Group 2 (n=39) did not receive any luteal support. Clinical, demographic, and biochemical parameters, including age, BMI, infertility duration, and ovarian reserve markers, were compared between the two groups. Treatment outcomes such as pregnancy rates, clinical pregnancy, and live birth rates were analyzed.

Results: No significant differences were observed between Group 1 and Group 2 in terms of demographic characteristics (age, BMI, and infertility duration) or biochemical markers (AMH, FSH, estradiol, and progesterone). The pregnancy rate in Group 1 was 14.2%, compared to 12.8% in Group 2 (p=0.640). Live birth rates were also similar between the groups (12.2% in Group 1 vs. 10.2% in Group 2, p=0.510). Treatment parameters, including endometrial thickness and gonadotropin dosage, showed no significant differences.

Conclusion: Progesterone supplementation for luteal phase support did not significantly improve pregnancy or live birth rates in IUI patients. These findings suggest that luteal phase support may not be necessary in routine IUI cycles, particularly when standard ovulation induction protocols are followed. Further research is needed to clarify its role in specific patient populations.

Keywords: Luteal phase support, progesterone, IUI, pregnancy rates, live birth rates

ÖZ

Amaç: Bu çalışmanın amacı, intrauterin inseminasyon (IUI) tedavisi uygulanan hastalarda progesteron ile yapılan luteal faz desteğinin (LFD) gebelik ve canlı doğum oranları üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntemler: 2019 ile 2021 yılları arasında bir üçüncü basamak merkezde IUI tedavisi gören 88 hastanın retrospektif analizi yapılmıştır. Hastalar iki gruba ayrılmıştır: Grup 1 (n=49) luteal faz desteği olarak progesteron almış, Grup 2 (n=39) ise herhangi bir luteal destek almamıştır. Her iki grubun yaş, vücut kitle indeksi (VKİ), infertilite süresi ve over rezerv belirteçleri gibi klinik, demografik ve biyokimyasal parametreleri karşılaştırılmıştır. Tedavi sonuçları olarak gebelik oranları, klinik gebelik ve canlı doğum oranları analiz edilmiştir.

Bulgular: Grup 1 ve Grup 2 arasında demografik özellikler (yaş, VKİ, infertilite süresi) ve biyokimyasal belirteçler (AMH, FSH, östradiol ve progesteron) açısından anlamlı bir fark saptanmamıştır. Grup 1'deki gebelik oranı %14,2 iken, Grup 2'de bu oran %12,8 olarak bulunmuştur (p=0,640). Canlı doğum oranları da benzer şekilde sırasıyla %12,2 ve %10,2 olup istatistiksel olarak anlamlı değildir (p=0,510). Endometrial kalınlık ve gonadotropin dozu gibi tedavi parametrelerinde de anlamlı bir fark gözlenmemiştir.

Sonuç: Sonuç olarak, luteal faz desteği amacıyla uygulanan progesteron takviyesi, IUI hastalarında gebelik veya canlı doğum oranlarını anlamlı şekilde artırmamıştır. Bu bulgular, özellikle standart ovulasyon indüksiyon protokolleri uygulandığında, rutin IUI siklusunda luteal faz desteğinin gerekli olmayabileceğini düşündürmektedir. Luteal faz desteğinin belirli hasta gruplarındaki rolünü netleştirmek için ileri araştırmalara ihtiyaç vardır.

Anahtar Kelimeler: Luteal faz desteği, progesteron, IUI, gebelik oranı, canlı doğum oranı

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INTRODUCTION

Intrauterine insemination (IUI) remains a fundamental option in the treatment of infertility, particularly in cases of unexplained infertility, mild male factor infertility, ovulatory disorders, and cervical factor infertility (1). As a relatively non-invasive and cost-effective alternative to in vitro fertilization (IVF), IUI is often employed as a first-line approach. However, despite its widespread use, clinical pregnancy and live birth rates associated with IUI remain relatively modest, prompting continued investigation into adjunctive strategies that might improve outcomes (2).

Among these strategies, luteal phase support (LPS)—most commonly in the form of exogenous progesterone administration—has received considerable attention. In IVF cycles, the rationale for LPS is well established, as controlled ovarian stimulation often disrupts endogenous luteal function due to supraphysiologic steroid levels and suppression of luteinizing hormone (LH) secretion (1,3). Although the biological rationale for progesterone supplementation in IUI cycles is plausible—given its essential role in enhancing endometrial receptivity, modulating immune responses, and stabilizing the endometrium—its routine use in IUI remains contentious (4). This is particularly true when gonadotropin-based stimulation is employed, under the assumption that endogenous progesterone production may be sufficient to sustain the luteal phase (5).

The literature on this topic presents conflicting findings. While certain meta-analyses and systematic reviews suggest that progesterone supplementation may confer marginal benefits in selected populations, substantial heterogeneity across stimulation protocols, progesterone formulations, dosing regimens, and patient characteristics hampers definitive conclusions (4,6). For instance, a recent study by Dilday et al. (2023) reported no significant benefit of LPS in letrozole-stimulated IUI cycles (7), whereas Xi et al. (2024) observed an improvement in live birth rates with the use of oral progesterone in a similar clinical setting (8). These discrepancies underscore the importance of identifying specific subgroups—such as women with luteal insufficiency or multifollicular response—who might derive the most benefit from luteal support (9).

The present study aims to evaluate the clinical utility of vaginal progesterone for luteal phase support in IUI cycles stimulated using standard gonadotropin-based protocols. Specifically, it investigates whether luteal support is associated with improved clinical pregnancy and live birth outcomes when compared to IUI cycles conducted without any form of progesterone supplementation. By leveraging real-world data from a tertiary infertility center, this study seeks to clarify the role of LPS in routine IUI practice and inform more individualized treatment approaches.

MATERIALS AND METHODS

This retrospective, single-center cohort study was conducted at the Department of Obstetrics and Gynecology, Ankara City Hospital, and included patients who underwent IUI between 2019 and 2021. Ethical approval was granted by the local ethics committee (Approval No: TABED 2-25-1308). Written informed consent had been obtained from all participants prior to their inclusion in the treatment protocol. Relevant clinical, demographic, and treatment-related data were extracted from hospital records and the institutional electronic health database.

A total of 151 women aged 20 to 40 years with a diagnosis of primary infertility who underwent IUI following controlled ovarian stimulation were initially screened. All patients received stimulation via a conventional "step-up" gonadotropin regimen. IUI indications included unexplained infertility, mild male factor infertility, ovulatory disorders, cervical factor infertility, and stage I–II endometriosis.

To reduce confounding variables and ensure data homogeneity, strict exclusion criteria were applied. Patients were excluded if they had chronic systemic illnesses (e.g., diabetes mellitus, hypertension), a history of major abdominal or pelvic surgery, secondary infertility, or BMI > 40 kg/m². Cases using alternative ovulation induction protocols (e.g., human menopausal gonadotropin [HMG], non–step-up protocols) or with incomplete clinical documentation were also excluded.

After application of these criteria, 88 women were deemed eligible for final analysis. The cohort was stratified into two groups based on luteal phase support status:

- Group 1 (n = 49) received vaginal micronized progesterone for luteal support.
- Group 2 (n = 39) underwent IUI without any luteal phase supplementation.

Treatment Protocol

Ovulation induction was performed via the use of recombinant FSH in all patients. The treatment was individualized on the basis of follicular size and the patient's response. Ovulation was triggered with human chorionic gonadotropin (hCG) when the follicular diameter exceeded 16 mm (folliculometry was performed by an experienced gynecologist and radiologist).

For luteal phase support, vaginal progesterone was initiated immediately after the IUI procedure. Patients in the progesterone group were treated with either of the following:

8% progesterone gel (90 mg/day) was administered vaginally to 32 patients.

Vaginal progesterone (400 mg) was administered twice daily starting from day 2 post-IUI in 17 patients.

Progesterone support was continued until the 10th week of pregnancy. The nonprogesterone group (n=39) did not receive any luteal phase support after IUI. Pregnancy outcomes and live birth rates were compared between the two groups.

Outcome assessment

β-hCG levels were assessed 15 days after the IUI procedure. For patients with positive pregnancy tests, β-hCG and progesterone levels were monitored until the 10th week of pregnancy, with progesterone support continuing during this period. For patients with negative pregnancy tests, treatment was discontinued. Pregnancy rates, clinical pregnancy rates (defined by the detection of intrauterine pregnancy via ultrasonography), and live birth rates were compared between the two groups.

Statistical analysis

All the data were analyzed via SPSS 25.0 (Statistical Package for the Social Sciences, IBM Corporation). Categorical data were analyzed via the chi-square test, whereas continuous data were compared via independent group t tests. A p value of <0.05 was considered to indicate statistical significance. Demographic data (age, basal FSH, body mass index, infertility duration, etc.) were compared between the two groups, and the results are presented in tabular form.

RESULTS

In this retrospective study, 88 patients were divided into two groups: those who received luteal phase support (Group 1, n=49) and those who did not (Group 2, n=39). Demographic, clinical, and biochemical parameters were compared between the groups to assess potential differences in outcomes. The demographic characteristics, including age, BMI, and infertility duration, were not significantly different between the two groups. The mean age in Group 1 was 27.0 ± 6.2 years, whereas that in Group 2 was 28.7±4.3 years (p=0.150), indicating a comparable age distribution. Similarly, BMI values (Group 1: 25.4 ± 3.2 kg/m² vs. Group 2: 25.9±3.5 kg/m², p=0.380) and infertility duration (Group 1: 1.6±1.3 years vs. Group 2: 1.9±1.5 years, p=0.315) were comparable (Table 1).

In terms of biochemical parameters, basal AMH levels were slightly greater in Group 1 (2.8 ± 1.2 ng/mL) than in Group 2 (2.3 ± 1.0 ng/mL), but this difference was not statistically significant (p=0.410). Basal FSH levels, which are often indicative of ovarian reserve, were similar between the groups (p=0.375), as were basal estradiol levels (p=0.290), progesterone levels on day 21 (p=0.260), and the antral follicle count (p=0.755) (Table 1).

Treatment parameters

Similarly, no significant differences were observed in treatment parameters such as endometrial thickness, the number of follicles greater than 16 mm, gonadotropin dose, or gonadotropin duration. The endometrial thickness, which is a critical predictor of implantation success, was similar between Group 1 (8.6 ± 1.2 mm) and Group 2 (8.4 ± 1.1 mm), with a p value of 0.420. The number of follicles larger than 16 mm was slightly greater in Group 1 (1.4 ± 0.1) than in Group 2 (1.2 ± 0.2), although this difference was not statistically significant (p=0.340). Additionally, the total Gn dose used in Group 1 (882.55 ± 82.9 IU) was greater than that used in Group 2 (741.21 ± 88.6 IU), but this difference did not reach statistical significance (p=0.360). Similarly, the duration of gonadotropin stimulation was comparable between the two groups (p=0.440) (Table 2).

Table 1. Comparison of Demographic and Biochemical Parameters between Group 1 and Group 2

Parameter	Group 1 (n=49) Mean ± SD	Group 2 (n=39) Mean ± SD	p value
Age (years)	27.0 ± 6.2	28.7 ± 4.3	0.150
BMI (kg/m²)	25.4 ± 3.2	25.9 ± 3.5	0.380
Infertility Duration (years)	1.6 ± 1.3	1.9 ± 1.5	0.315
Basal AMH (ng/mL)	2.8 ± 1.2	2.3 ± 1.0	0.410
Basal FSH (mIU/mL)	6.1 ± 2.3	6.7 ± 2.1	0.375
Basal Estradiol (E2) (pg/mL)	47.5 ± 16.2	43.0 ± 14.8	0.290
Day 21 Progesterone (ng/mL)	13.0 ± 4.5	11.5 ± 3.8	0.260
Antral Follicle Count (AFC)	10.8 ± 3.4	10.0 ± 3.1	0.755

BMI: Body Mass Index, **AMH**: Anti-Müllerian Hormone, **FSH**: Follicle-Stimulating Hormone, **E2**: Estradiol, **AFC**: Antral Follicle Count, **SD**: Standard Deviation, **ng/mL**: Nanograms per milliliter, **mIU/mL**: Milli-international units per milliliter, **pg/mL**: Picograms per milliliter

Table 2. Comparison of Treatment Parameters between Group 1 and Group 2

Parameter	Group 1 (n=49) Mean ± SD	Group 2 (n=39) Mean ± SD	p value
Endometrial Thickness (mm)	8.6 ± 1.2	8.4 ± 1.1	0.420
Number of Follicles >16 mm	1.4 ± 0.1	1.2 ± 0.2	0.340
Gonadotropin Dose (IU)	882.55 ± 82.9	741.21 ± 88.6	0.360
Gonadotropin Duration (days)	11.2 ± 2.2	10.9 ± 2.3	0.440

SD: Standard Deviation, **mm**: Millimeters, **IU**: International Units, **>**: Greater Than

Table 3. Comparison of Pregnancy and Live Birth Rates between Groups 1 and 2

Outcome	Group 1 (n=49)	Group 2 (n=39)	p value
Pregnancy Rate (%)	7 (14.2%)	5 (12.8%)	0.640
Live Birth Rate (%)	6 (12.2%)	4 (10.2%)	0.510

Pregnancy and Live Birth Rates

The pregnancy and live birth rates were also similar between the two groups, with no statistically significant differences observed. Group 1 had a pregnancy rate of 14.2%, whereas Group 2 had a rate of 12.8% (p=0.640). Similarly, the live birth rates were 12.2% in Group 1 and 10.2% in Group 2 (p=0.510) (Table 3).

DISCUSSION

LPS has long been considered essential in IVF protocols, largely due to the disruption of endogenous hormonal balance following controlled ovarian stimulation. In contrast, its role in IUI cycles remains less clear. In our study, the use of vaginal progesterone for LPS in gonadotropin-stimulated IUI cycles did not lead to significant improvements in clinical pregnancy or live birth rates. This finding aligns with a growing body of evidence suggesting that routine LPS in non-IVF settings may offer limited clinical benefit.

Hill et al. (2017), in a well-conducted meta-analysis, similarly found that progesterone supplementation after ovulation induction in IUI cycles had no meaningful effect on pregnancy rates, though they acknowledged potential benefits in select subgroups (6). Supporting this, Salang et al. (2022) reported only marginal gains in pregnancy outcomes with LPS in both IUI and natural conception settings, with no reduction in miscarriage rates (2). These findings echo our results, which were drawn from a clinically and demographically balanced cohort—reducing the likelihood that observed outcomes were confounded by baseline differences such as age, BMI, ovarian reserve, or endometrial thickness.

One reason for the inconsistent literature may lie in the variability of LPS protocols across studies—differences in progesterone type, route of administration, dosage, and patient selection can all influence outcomes. While Ciampaglia and Cognigni (2015) argued that vaginal progesterone offers better physiological absorption (3), our findings—and those of Tokgöz et al. (2020), who saw no improvement in patients with multifollicular development—suggest that such advantages may not translate into clinical benefit (9). Conversely, Xi et al. (2024) reported improved live birth rates with oral progesterone in letrozole-stimulated cycles (8), a result not replicated in similar trials such as that of Dilday et al. (2023) (7). These discrepancies underscore the complexity of LPS and the need for a more personalized approach.

The issue of optimal progesterone dosing also remains unresolved. Biberoglu et al. (2016) compared low- and high-dose vaginal progesterone (300 mg vs. 600 mg) and found no significant difference in outcomes, highlighting concerns around overtreatment and cost-effectiveness (5). Broader reviews, such as that by Miralpeix et al. (2014), suggest that the utility of LPS may be restricted to specific subpopulations, particularly those with hormonal or endometrial vulnerabilities (4).

Recent studies published in the past two years have provided new insights into the role of LPS in IUI cycles. Simopoulou et al. (2025) emphasized the growing importance of metabolomic analysis in assisted reproductive technologies, highlighting that LPS should be considered within the framework of personalized treatment protocols (10). In a study involving women with endometriosis, Gainder et al. (2024) demonstrated that luteal support with dydrogesterone following laparoscopy improved pregnancy rates

in subsequent IUI treatments (11). Furthermore, Agarwal et al. (2025) reported that the addition of piroxicam to conventional progesterone support significantly enhanced IUI success rates (12). In light of these findings, although our study found no significant benefit of routine LPS across all patients, it suggests that certain subgroups may derive clinical advantages from targeted luteal support strategies.

In recent years, several randomized controlled trials have continued to evaluate the efficacy of luteal phase support in IUI cycles. A prospective RCT conducted by Keskin and Aytac (2020) reported no statistically significant difference in pregnancy rates between patients who received vaginal progesterone and those who did not, following gonadotropin-stimulated IUI (13). Similarly, a study by Ebrahimi et al. (2010) involving couples with unexplained infertility found that luteal phase support did not significantly improve pregnancy outcomes (14). In contrast, Rashidi et al. (2014), in a double-blind, placebo-controlled trial, observed that luteal support with progesterone was associated with higher pregnancy rates specifically in women over 30 years of age (15). These findings highlight the importance of patient selection and support a more individualized approach to luteal phase support, rather than its routine application in all IUI cycles.

A major strength of our study is its internal consistency: all participants underwent ovulation induction using the same step-up gonadotropin protocol, within a single tertiary care center. This uniformity strengthens the validity of our comparisons and enhances the interpretability of our results. Moreover, the clinical and demographic similarities between the LPS and non-LPS groups reduce the risk of confounding and reinforce the reliability of our findings.

That said, several limitations should be acknowledged. As a retrospective study, our analysis is subject to inherent selection and information biases. The relatively modest sample size may also have limited our ability to detect subtle but clinically relevant differences. Additionally, we did not stratify patients based on luteal phase sufficiency, which may have obscured potential subgroup benefits. The lack of serum progesterone monitoring is another important limitation, as interindividual variation in absorption and metabolism may have affected treatment efficacy.

Moving forward, prospective, randomized, multicenter trials are needed to more definitively clarify the role of LPS in IUI. Such studies should include predefined subgroup analyses—for example, among women with luteal insufficiency, low ovarian reserve, or advanced age—to identify those most likely to benefit. Comparative investigations of progesterone formulations (vaginal, oral, intramuscular), doses, and administration timing, ideally coupled with pharmacokinetic profiling and biomarker analysis, may help establish evidence-based, individualized protocols.

CONCLUSION

The results of the present study indicate that administering vaginal progesterone for luteal phase support does not yield a statistically significant enhancement in pregnancy or live birth rates among women undergoing intrauterine insemination with conventional ovulation induction protocols. These findings are consistent with previous research suggesting that routine luteal phase support in IUI cycles may not be universally required. Instead, adopting a more tailored approach that considers individual patient characteristics and clinical risk factors may offer greater benefit. To substantiate these observations and inform clinical decision-making, further large-scale, prospective, and randomized controlled trials are essential.

Ethical Approval: Ethics committee approval was obtained from the ethics committee unit of the Ankara Bilkent City Hospital (TABED 2-25-1308). The study commenced after obtaining the relevant ethical committee approval, and consent was obtained from the relevant clinics.

Consent to participate: Following ethics committee approval, written informed consent forms were obtained from all participants for their participation in the study.

Consent for publication: There are no circumstances in the study that violate anonymity, and identifying information has been kept confidential. There are no issues regarding its publication.

Availability of data and materials: Patient data is stored indefinitely in the hospital's HICAMP® automation system. It can be shared upon request, provided that patient identity remains confidential.

Competing interests: There are no conflicts of interest among the authors.

Authors' contributions: M.İ.H., M.İ.K collected the patient data. B.T. was responsible for the study design and research protocol. U.Z. and B.T. wrote the manuscript, while Ö.M.T. reviewed the study.

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OLGU SUNUMU / CASE REPORT

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Case report of spontaneous heterotopic pregnancy and review of literature

Spontan heterotopik gebelik olgu sunumu ve literatürün gözden geçirilmesi

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ABSTRACT

Heterotopic pregnancy is the simultaneous occurrence of an intrauterine pregnancy (IUP) and an extrauterine pregnancy. It is an extremely rare condition, with an estimated incidence of 1 in 30,000 pregnancies. Despite its rarity, the presence of a confirmed IUP does not exclude the possibility of a concurrent extrauterine pregnancy. The clinical presentation typically includes abdominal pain, vaginal bleeding, and an adnexal mass alongside an intrauterine pregnancy. A ruptured ectopic pregnancy is a critical condition requiring urgent diagnosis and intervention due to the risk of intra-abdominal bleeding and hemorrhagic shock. In such cases, the ectopic gestational sac should be surgically removed, either via laparotomy or laparoscopy.

Keywords: Heterotopic pregnancy, hemorrhagic shock, ruptured ectopic pregnancy, transvaginal ultrasound

ÖZ

Heterotopik gebelik, intrauterin gebelik (IUG) ile ekstrauterin gebeliğin eşzamanlı olarak meydana gelmesidir. Oldukça nadir görülen bir durumdur ve tahmini insidansı 30.000 gebelikte 1'dir. Nadir görülmesine rağmen, doğrulanmış bir intrauterin gebeliğin varlığı, eşzamanlı bir ekstrauterin gebelik olasılığını dışlamaz. Klinik tablo genellikle intrauterin gebeliğe eşlik eden karın ağrısı, vajinal kanama ve adneksiyal kitleyi içerir. Rüptüre ektopik gebelik, intraabdominal kanama ve hemorajik şok riski nedeniyle acil tanı ve müdahale gerektiren kritik bir durumdur. Bu gibi vakalarda, ektopik gestasyonel kese cerrahi olarak çıkarılmalıdır; bu işlem laparotomi veya laparoskopi yoluyla gerçekleştirilebilir.

Anahtar Kelimeler: Heterotopik gebelik, hemorajik şok, rüptüre ektopik gebelik, transvajinal ultrason

INTRODUCTION

A heterotopic pregnancy refers to the simultaneous occurrence of an intrauterine pregnancy (IUP) and an extrauterine pregnancy. The incidence of spontaneous heterotopic pregnancy is approximately 1 in 30,000 pregnancies (1). Ectopic pregnancies can occur in the fallopian tubes, ovaries, cervix, cornua, or abdominal cavity, with tubal pregnancies being the most common, accounting for 95–97% of cases (1).

The risk factors for heterotopic pregnancy are similar to those of ectopic pregnancy and include a history of previous ectopic pregnancy, pelvic inflammatory disease, tubal surgery, infertility, assisted reproductive techniques, endometriosis, smoking, and advanced maternal age (over 35 years) (2, 3, 4). Diagnosis is based on clinical symptoms such as abdominal pain, a positive beta-hCG test with a significant rise above the expected threshold, and the identification of both an ectopic and intrauterine pregnancy on ultrasound (5).

In this study, we present the management of a case of heterotopic pregnancy occurring during a natural menstrual cycle, complicated by a ruptured ectopic pregnancy.

CASE

A healthy 31-year-old patient (gravida 4, para 2, abortion 1, living 2) by natural conception presented to the emergency department with acute lower abdominal pain and vaginal spotting. Based on her last menstrual period, her pregnancy was estimated to be at 7 weeks and 3 days. This was a spontaneous conception with no history of fertility treatment, and she had not used any contraception.

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Her medical history did not suggest a history of pelvic inflammatory disease. However, she had one cesarean section and one curettage. On abdominal examination, findings were consistent with an acute abdomen, including severe tenderness, guarding, and rigidity. Speculum examination revealed brown spotting on the cervix.

Transvaginal ultrasonography revealed a 23 mm intrauterine gestational sac containing a yolk sac but no embryo (Figure 1). Additionally, a second gestational sac with a positive fetal heartbeat was detected in the right fallopian tube (Figure 2). Free fluid of 24 mm was also observed in the Douglas pouch.

Laboratory results on admission showed a white blood cell count of 13,103 elements/mm^3, a serum hemoglobin concentration of 10.3 g/dl, and a normal platelet count of 236,000 /mm^3. Blood pressure was 100/40 mmHg and pulse rate was 94 bpm. The patient was diagnosed with heterotopic pregnancy.

Laparoscopic surgery was scheduled due to the detection of a fetal heartbeat in the ectopic pregnancy and the patient's presyncopal symptoms. During the procedure, intra-abdominal examination revealed extensive coagulum in the pelvis and a 3–4 cm right tubal ectopic pregnancy. A total salpingectomy was performed with removal of the hemoperitoneum and peritoneal lavage. The intrauterine pregnancy was preserved.

Postoperatively, the patient's general condition was good, and cardiovascular findings remained stable. Histology of the salpingectomy specimen confirmed chorionic villi suggestive of an ectopic pregnancy.

To mitigate the risk of miscarriage potentially associated with abdominal surgery, prophylactic intravaginal progesterone was administered to preserve the intrauterine pregnancy. At the 8th postoperative hour, the patient's hemoglobin (Hb) level was measured at 7.0 g/dL and hematocrit (Hct) at 19.6%. Thereafter, two units of erythrocyte transfusion were administered, resulting in an increase in Hb to 9.1 g/dL.

Postoperative transvaginal ultrasonography indicated the absence of any issues with the intrauterine gestational sac. The patient, in good general condition and hemodynamically stable, was discharged. During a follow-up, one week later, transvaginal ultrasonography revealed an intrauterine gestational sac (GS) measuring with 2.95 cm, consistent with 8 weeks of gestation, along with a yolk sac. However, no embryo was visualized. Following the diagnosis of anembryonic pregnancy, a medical abortion was recommended. The patient subsequently received treatment at another hospital.

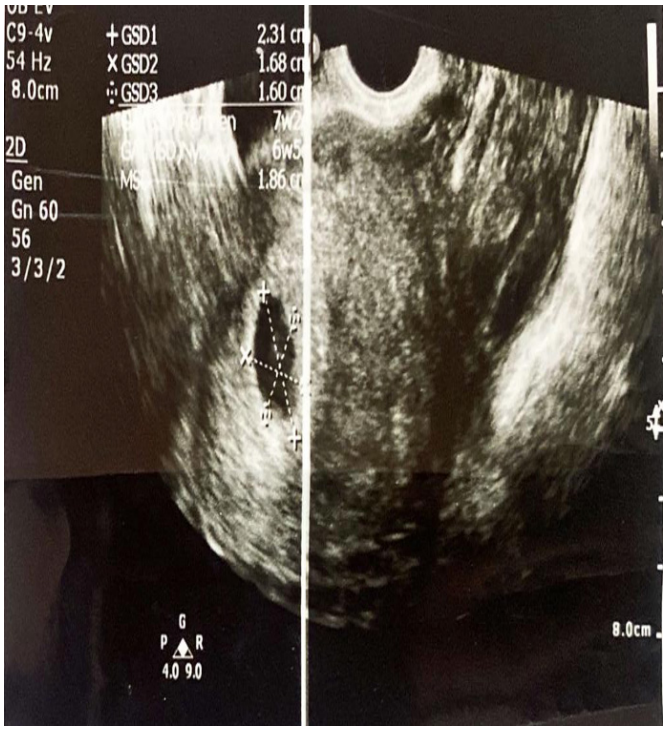

Figure 1. Intrauterine gestational sac

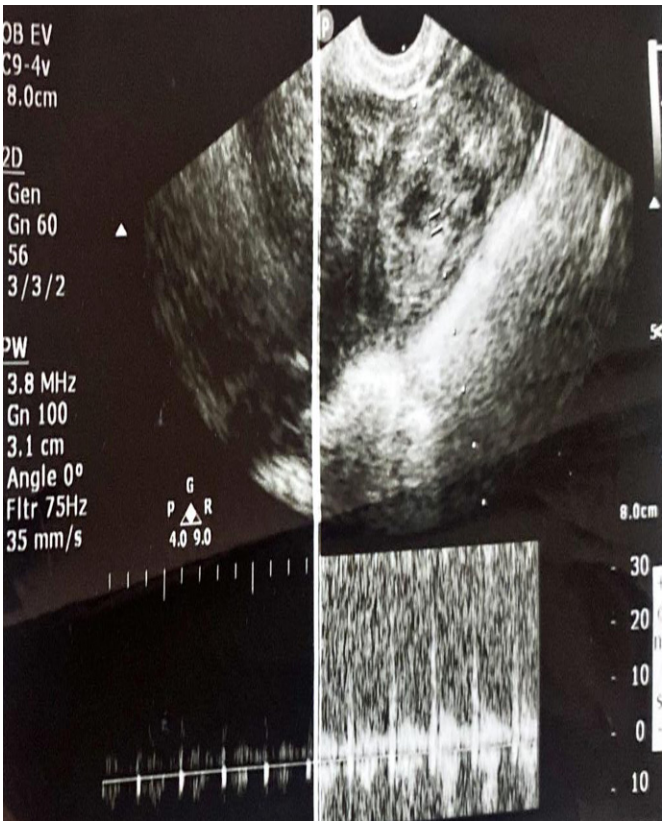

Figure-2. Fetal heartbeat-positive pregnancy material in the right adnexa

Table 1. Ruptured spontaneous heterotopic pregnancy cases in literature

	Authors	Year	Age	Gravida	Gestational Age at Diagnosis	Location of Ectopic Pregnancy	Type of Intervention	IUP Outcome
1	Varras et al. (10)	2003	28	G1	11 week	Tubal	Laparotomy	Vaginal Delivery
2	Simsek et al. (20)	2008	37	G2P0	9 week	Tubal	Laparotomy	Vaginal Delivery
3	Govindarajan et al. (32)	2008	22	G1	10 week	Tubal	Laparoscopy	Vaginal Delivery
4	Tandon et al. (6)	2009	24	G1	8 week	Tubal	Laparotomy	Vaginal Delivery
5	Phupong et al. (17)	2010	?	?	7 week	Tubal	Laparoscopy	Cesarean Delivery
6	Yeral et al. (21)	2011	21	G1	8 week	Tubal	Laparoscopy	Cesarean Delivery
7	Basile et al. (27)	2012	28	G1	7 week	Ovarian	Laparotomy	Cesarean Delivery
8	Apocha et al. (31)	2012	33	G3P1	10 week	Tubal	Laparoscopy	Vaginal Delivery
9	Uysal et al. (18)	2013	?	?	6 week	Cervical	Aspiration	Vaginal Delivery
10	Ikechukwu (19)	2013	35	G5P4	10 week	Tubal	Laparotomy	Vaginal Delivery
11	Arsala et al. (13)	2014	27	G5P2	6 week	Tubal	Laparoscopy	D/C
12	Siraj et al. (33)	2014	28	G1	8 week	Tubal	Laparoscopy	Unknown
13	Russman et al. (29)	2015	22	G2P1	9 week	Tubal	Laparoscopy	Vaginal Delivery
14	Kürekeken et al. (26)	2016	24	G1	7 week	Tubal	Laparoscopy	D/C
15	Chadee et al. (15)	2016	34	G3P1	9 week	Tubal	Laparotomy	D/C on Demand
16	Chadee et al. (15)	2016	32	G1	7 week	Cornual	Laparotomy	D/C
17	Fatema et al. (16)	2016	38	G7P3	9 week	Tubal	Laparotomy	D/C
18	Okunowo et al. (22)	2016	32	G2P0	20 week	Tubal	Laparotomy	Cesarean Delivery
19	Mihmanlı et al. (28)	2016	34	?	10 week	Tubal	Laparotomy	Unknown
20	Stanley et al. (30)	2018	36	G7P4	4 week	Ovarian	Laparoscopy	D/C
21	Xie et al. (23)	2018	30	G2P0	12 week	Tubal	Laparoscopy	Vaginal Delivery
22	Ramalho et al. (1)	2019	32	G4P3	8 week	Ovarian	Laparotomy	Vaginal Delivery
23	Guimaraes et al. (24)	2019	21	G1	8 week	Tubal	Laparotomy	Cesarean Delivery
24	Migle et al. (4)	2020	28	G1	7 week	Tubal	Laparoscopy	Vaginal Delivery
25	Aziz et al. (25)	2020	28	G1	7 week	Tubal	Laparoscopy	D/C
26	Rubattu et al. (34)	2020	37	G1	6 week	Tubal	Laparoscopy	Vaginal Delivery
27	Nyugen et al. (11)	2022	27	G4P1	5 week	Tubal	Laparoscopy	D/C
28	Our case	2024	31	G4P2	7 week	Tubal	Laparoscopy	D/C

IUP: Intrauterine pregnancy. D&C: Dilation and curettage

DISCUSSION

Heterotopic pregnancy is a rare but potentially life-threatening clinical condition. The risk is particularly increased in patients undergoing in vitro fertilization, those with a history of abdominal surgery, pelvic inflammatory disease, or previous ectopic pregnancy (6, 7).

Tal et al. reported that 70% of heterotopic pregnancies are diagnosed between 5 and 8 weeks, 20% between 9 and 10 weeks, and only 10% after 11 weeks (8). Our case was admitted to the hospital with a ruptured ectopic pregnancy at a gestational age that is consistent with previously reported spontaneous heterotopic cases. In the majority of cases, diagnosis of heterotopic pregnancy is made late, when rupture occurs, and patients present with hemoperitoneum.

Heterotopic pregnancy is difficult to diagnose early because of its nonspecific clinical symptoms. Usually, signs of the extrauterine pregnancy predominate. Abdominal pain, adnexal mass, peritoneal irritation, and an enlarged uterus are identified in the literature as the four common signs and symptoms (9). The diagnosis was made using clinical signs and ultrasonography. Ultrasound simultaneously provided visualization of the ectopic gestational sac and the intrauterine gestational sac. However, unlike our case, where diagnosis was straightforward via ultrasound, distinguishing an anembryonic gestational sac from a corpus luteum cyst may be difficult. Morphological ultrasound features can aid in the diagnosis. The 2–6 mm thick ring representing trophoblastic invasion surrounding the fluid content of the gestational sac is generally more echogenic than the ovarian tissue surrounding the corpus luteum (10). Additionally, Doppler ultrasound may demonstrate a "ring of fire" appearance around the gestational sac, caused by high diastolic flow (11).

In the management of heterotopic pregnancy, medical or surgical treatments can be used. The standard treatment for ectopic

pregnancy is surgery by laparoscopy or laparotomy depending upon the condition of the patient. The primary goal of the surgery should be the preservation of the intrauterine pregnancy with minimal manipulation of the uterus. Medical treatment for ectopic pregnancy with an intact tube is a local injection of potassium chloride and hyperosmolar glucose (12–13). When intrauterine pregnancy is to be preserved, systemic or local methotrexate cannot be used because of its effects on intrauterine pregnancy (14). Since we wanted to preserve the intrauterine pregnancy and the patient was hemodynamically unstable, we preferred to remove the ectopic pregnancy material laparoscopically.

Postoperative complications such as anemia, spontaneous pregnancy loss, or cessation of fetal heart activity may occur in patients undergoing surgical treatment (2). The literature indicates that approximately 66% of pregnancies continue in such cases (4). The outcome of the intrauterine pregnancy depends on many factors, such as the maternal status at the moment of admission and the location of the extrauterine pregnancy. Hypovolemic shock of the mother can lead to a poor prognosis of the intrauterine pregnancy. Oancea et al. found that intrauterine pregnancy outcomes were better when extrauterine pregnancies were situated in the fallopian tubes, compared to those with interstitial ectopic sacs (14). In this case, prophylactic progesterone was administered during the postoperative period to prevent miscarriage. While studies supporting the use of progesterone to increase live birth rates in these situations are lacking, prescribing progesterone for first-trimester bleeding is a common clinical practice (4). Transvaginal ultrasound follow-up revealed that the intrauterine pregnancy was anembryonic. As a result, an abortion was performed to remove the non-viable pregnancy tissue.

The main aspect of our case is a heterotopic pregnancy in a natural menstrual cycle, along with the ruptured ectopic pregnancy. To investigate heterotopic pregnancies occurring in natural menstrual cycles, we conducted a literature search using the PubMed/Medline, Google Scholar, and ScienceDirect databases. The keywords used were “heterotopic pregnancy” and “spontaneous heterotopic pregnancy” focusing on cases reported since 2003 (Table 1).

The reviewed cases included data on maternal age, gestational age at diagnosis, parity, the location of the ectopic pregnancy, the intervention performed, and the outcome of the intrauterine pregnancy. Maternal age ranged from 21 to 38 years, with a mean of 30 years across a total of 28 patients. Among these women, 40% were multiparous, while 60% were primiparous.

Diagnosis was primarily made during the first trimester of pregnancy. The most frequent weeks of diagnosis were between 7 and 8 weeks (42.8%). Extrauterine pregnancies were mostly located in the fallopian tubes. The preferred treatment approach was surgical. laparoscopy or laparotomy is preferred depending on the surgeon’s experience and the patient’s condition. No significant difference was observed in the outcome of intrauterine pregnancy between the two surgical methods. Salpingectomy was the most commonly performed procedure for the removal of the ectopic pregnancy.

Cervical ectopic pregnancy material was observed in one case and was removed by aspiration (9). In other case, ovarian ectopic pregnancy was observed and ovarian wedge resection was performed (27). Prophylactic progesterone was used in some of the cases in literature. Migle et al. used progesterone until the 12th week of gestation and labour occurred at term (24). However no studies have yet shown the results of progesterone supplementation in heterotopic pregnancies. In two cases, triplet pregnancy was observed by natural cycle. After removal of ectopic pregnancy material, they delivered twins at term. In 28 cases of spontaneous heterotopic pregnancies reviewed in the literature, 65.4% of intrauterine pregnancies resulted in live birth. No maternal deaths were reported.

CONCLUSION

Although spontaneous heterotopic pregnancy is extremely rare, it remains a possibility. Observing an intrauterine pregnancy during an ultrasound examination can lead to the assumption of a normal pregnancy. However, as demonstrated by this case, the evaluation of the adnexa should not be overlooked. Early diagnosis of heterotopic pregnancy can thus be achieved, life-threatening conditions such as intra-abdominal hemorrhage can be identified, and the most appropriate management options can be provided to sustain the intrauterine pregnancy.

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OLGU SUNUMU / CASE REPORT

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Cleft palate association described for the first time in a rare molybdenum cofactor deficiency Type B newborn case

Yarık damakla birliktelik gösteren molibden kofaktör eksikliği Tip B tanısı alan yenidoğan vakası

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ABSTRACT

Molybdenum Cofactor Deficiency (MoCD) is an extremely rare and severe autosomal recessive metabolic disorder with serious clinical manifestations. Symptoms, such as lethargy, hypotonia, and seizures, are commonly observed in affected individuals and may appear immediately or within days of birth. It is crucial to differentiate MoCD from hypoxic-ischemic encephalopathy (HIE), which can present with similar neurological symptoms and require urgent medical intervention. In this case report, we describe a newborn who presented with HIE-like symptoms but was eventually diagnosed with MoCD by laboratory testing and brain magnetic resonance imaging (MRI). Further genetic analysis confirmed the diagnosis with the identification of a MOCS2 Type B (c.226G>A, (p.G76R) (p.Gly76Arg) mutation, which has only been observed in a small number of cases. Additionally, this case is unique in that the patient also had a cleft palate, a rare occurrence of MoCD. We aimed to emphasize the importance of accurate diagnosis in newborns presenting with neonatal encephalopathy, as inappropriate treatment with therapeutic hypothermia may have serious consequences.

Keywords: Molybdenum cofactor deficiency, cleft palate, newborn

ÖZ

Molibdenum Kofaktör Eksikliği (MoCD), nadir ve ciddi klinik bulgularla seyreden, otozomal resesif kalıtılan doğumsal bir metabolik hastalıktır. Klinik olarak letarji, hipotoni ve nöbetler gibi nörolojik bulgular gözlenir. Klinik bulgular doğumdan hemen sonra veya günler içinde ortaya çıkabilir. Nörolojik bulguların doğumdan hemen sonra görülebildiği ve acil tedavi gerektiren hipoksik-iskemik ensefalopatiden (HİE) hızla ayırt edilmesi gereklidir. Bu çalışmada, doğumdan hemen sonra HİE benzeri klinik bulgular gösteren ve laboratuvar ile beyin manyetik rezonans görüntüleme (MRI) yardımıyla hızla MoCD tanısı konulan hastamızı sunuyoruz. Takip sürecinde, hastamızda tanı, genetik olarak az sayıda vakada tanımlanan Molybdenum kofaktör sentezi 2 (MOCS2) Tip B (c.226G>A, (p.G76R) (p.Gly76Arg) mutasyonu) ile doğrulandı. Ek olarak, vakamız, MoCD'ye yarık damak eşlik eden ilk vaka olmasıyla dikkat çekmektedir. Bu vakayı sunmaktaki amacımız, doğumdan hemen sonra neonatal ensefalopatiye neden olan durumların ayırt edilmesinin önemini vurgulamak ve hipoksik-iskemik ensefalopati tanısının hatalı konulması nedeniyle uygunsuz şekilde terapötik hipotermi tedavisi verilmemesi gerektiğini belirtmektir.

Anahtar Kelimeler: Molibden kofaktör eksikliği, yarık damak, yenidoğan

INTRODUCTION

Although the incidence of Molybdenum Cofactor Deficiency (MoCD) is 1 in 100,000–500,000 live births, approximately 200 cases have been reported to date. MoCD occurs as a result of a congenital genetic metabolic error caused by deficiency of sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase, which are enzymes dependent on molybdenum cofactor. Mutations in the autosomal recessive MoCD, Molybdenum Cofactor Synthesis 1 (MOCS1, Type A), molybdenum cofactor synthesis 2 (MOCS2, Type B), gephyrin (GPHN, Type C), and molybdenum cofactor synthesis 3 (MOCS3) genes have been previously described. Approximately 75% of the cases are MOCS1, and the rest are genetic mutations (1,2).

Sulfite, xanthine, and hypoxanthine accumulate in the body of MoCDs. This causes neuronal damage, particularly in the brain. Therefore, it may clinically present with neonatal encephalopathy such as hypo- or hypertonia, malnutrition, lethargy, seizures, and neurological deficits after birth. It may be accompanied by microcephaly or macrocephaly, lens dislocation, spherophakia, and nystagmus. Neurodegeneration with severe consequences can develop rapidly within a few days or months of clinical follow-up, ultimately leading to fatal outcomes (2,3). Brain magnetic resonance images (MRI) of patients show typical diffuse cerebral edema, cortical necrosis and atrophy, gliosis, cessation of myelination development, inactive areas affecting the white matter, basal ganglia, and cortex, and multicystic encephalomalacia (2-4).

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Our patient was born with neonatal encephalopathy including decreased neonatal reflexes, hypotonia, and lethargy. In our patient, who did not have an antenatal diagnosis, hypoxic-ischemic encephalopathy (HIE) was considered as the most likely preliminary diagnosis. Postnatal dysmorphic findings supported the diagnosis of MoCD after a low serum uric acid level in the first laboratory test. Our patient was diagnosed with MoCD on the basis of other laboratory and cranial MRI findings. Subsequently, the genetic diagnosis of MoCD Type B was confirmed. Thus, appropriate treatment for MoCD was initiated early without applying therapeutic hypothermia, which is not appropriate for MoCD.

We emphasize the urgent need to distinguish between the neonatal case we present here and patients with similar neonatal encephalopathy, such as HIE and MoCD. We also aimed to present the first case from our country with the c.226G>A mutation in exon 4 and the association between MoCD and cleft palate.

CASE

Our patient was born vaginally at 37 weeks as a 3170 g (50-75 percentile) male baby, the third of her 27-year-old mother's 5th pregnancy. The 1st minute Apgar score was 4 and the 5th minute Apgar score was 7. His birth head circumference was 35 cm (75-90 percentile) and height was 50 cm (50-75 percentile). Positive-pressure ventilation was applied once for 30 seconds to the patient with apnea in the delivery room. In our patient's family history, it was learned that the mother and father were 1st degree cousins, and that the mother had no pregnancy follow-up. The family asserted that no genetic, neurological, or metabolic disorders were present within the family.

In the physical examination of the patient, inadequate respiration, decrease in muscle tone and neonatal reflexes (sucking, searching, catching and Moro), plump cheeks, broad nasal bridge, long philtrum, dysmorphic facial appearance, and cleft palate were detected as pathological examination findings. The other systemic examination findings were normal. The patient was started on respiratory support with nasal continuous positive airway pressure (nCPAP) and free-flow oxygen due to respiratory distress. Our patient was admitted to the neonatal intensive care unit with a preliminary diagnosis of syndromic infant, neonatal encephalopathy, and HIE.

Because he was hypotonic at birth and his Apgar score was low, HIE, which is the most common cause of neonatal encephalopathy, was considered as a preliminary diagnosis. However, in the patient's umbilical cord blood gas, pH: 7.30, partial carbon dioxide pressure (pCO2): 51 mmHg, bicarbonate (HCO3): 21 mmol/L, bass deficit (Bd): -4.4 mmol/L and lactate: 3.9 mmol/L. Based on the

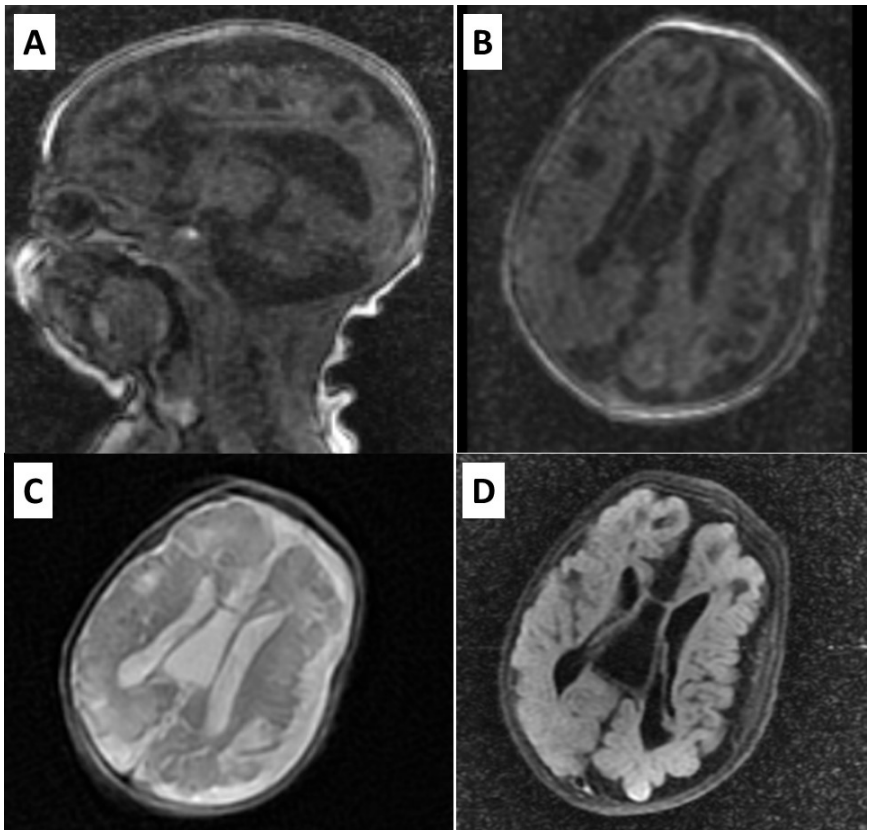

Figure 1. A and B: millimetric cystic encephalomalacia and cortical atrophy on non-contrast magnetic resonance, C and D: widespread cortical diffusion restriction on diffusion magnetic resonance

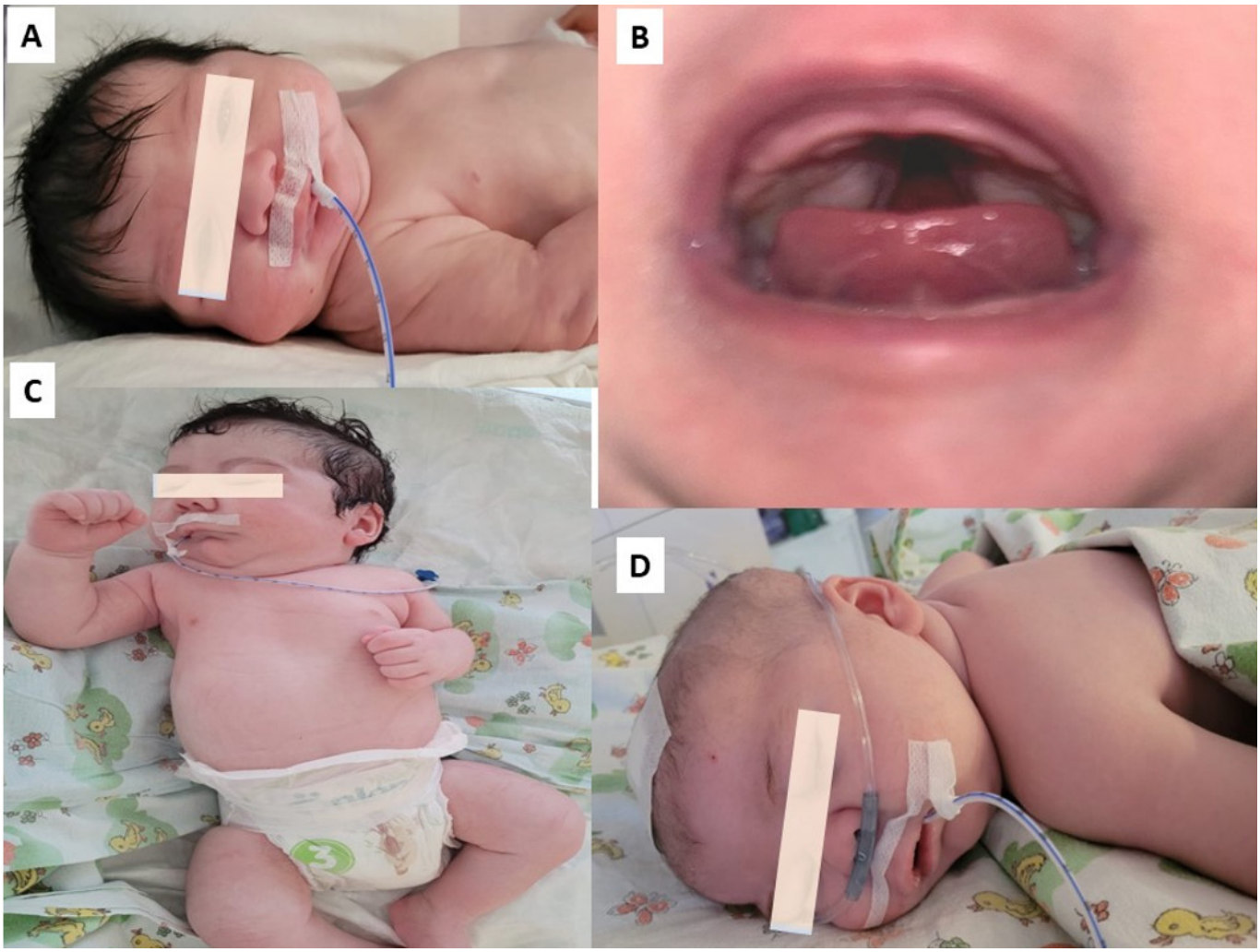

Figure 2. A: postnatal photo of the patient, B: cleft palate photo, C: photo at the 6th postnatal month, D: photo at the 10th postnatal month

blood gas results, a diagnosis of HIE was considered suspicious. Considering other laboratory findings, the complete blood count, blood sugar, and kidney and liver function tests were within the normal limits for a newborn baby. In addition, MoCD was suspected because the uric acid value was determined to be 0.1 mg/dL (2.2-11), thus was well below the normal reference values, as well as its dysmorphic appearance and accompanying neurological findings. The homocysteine level was 0.4 µmol/L (5-15) and was found to be low. A positive sulfite test, high urine S-sulfocysteine and xanthine levels, low cystine levels in the blood and urine, and low urine uric acid and taurine levels confirmed a diagnosis of MoCD.

Brain MRI of patient was revealed corpus callosum agenesis, dilated lateral ventricles, increased frontotemporoparietal subarachnoid cerebrospinal (CSF) distances, widespread cortical diffusion restriction, diffuse millimetric cystic encephalomalacia at the interventricular level and in both cerebral hemispheres, cortical atrophy, and hyperintense signal changes. Hemorrhagic deposits and laminar necrosis were also observed. Levels in the basal ganglia, internal capsule, thalamus, cerebellum, mesencephalon, and pons were normal, and these findings were compatible with MoCD (Figure 1). On electroencephalography (EEG), the background activity was evaluated as a focal paroxysmal disorder with 4-5 Hz theta waves, 3-4 Hz delta waves, and sharp wave discharges. The patient's preliminary diagnosis of MoCD was confirmed using cranial MRI and EEG.

Our patient's Apgar scores and laboratory findings were not compatible with HIE (5). Within the first 6 h after birth, the diagnosis of HIE was excluded using clinical, laboratory, and imaging methods, and our patient was diagnosed with MoCD. Since the patient's results were compatible with MoCD, therapeutic hypothermia treatment was not initiated. The genetic test performed for the diagnosis of MoCD detected a homozygous single nucleotide change NM_004531.5: c.226G>A, (p.G76R) (p.Gly76Arg) in exon4 of the MOCS2 gene. The diagnosis of MoCD Type B was confirmed and pyridoxine therapy was initiated.

Our patient, who was examined for other systemic findings of MoCD, showed normal echocardiographic, abdominal ultrasonography, and eye examination findings. During clinical follow-up, antiepileptic treatment was initiated for resistant myoclonic seizures on the first postnatal day. During follow-up, the patient required triple antiepileptic treatment for refractory seizures. The patient's respiratory support was provided in the form of free-flow oxygen and nCPAP according to her needs until the 11th postnatal month. The patient was fed via an orogastric tube due to sucking dysfunction. During postnatal follow-up, while weight and height development were appropriate for age, head circumference remained constant at 35 cm and no growth was achieved. During the follow-up period, serious neurodevelopmental delay was detected according to age. As our patient had no seizures during follow-up, seizure control was achieved with a single antiepileptic treatment. Images of our patient at birth, at 6th month, and 10th month were shown in Figure 2. Our patient died in the 11th postnatal month because of clinical deterioration characterized by severe bradycardia and desaturation unresponsive to treatment while he was receiving respiratory support treatment with a mechanical ventilator due to lower respiratory tract infection.

DISCUSSION

There are four main molybdoenzymes: sulfite oxidase, xanthine oxidase, aldehyde oxidase, and a mitochondrial amidoxime-reducing component. As a result of deficiency in these enzymes, MoCD develops, and sulfite accumulation occurs in the body (2,3,6). Sulfites cause cellular damage by reacting with lipids and proteins to form radicals that damage nucleic acids and attack disulfide bonds. Sulfites disrupt the tricarboxylic acid cycle in the mitochondria, causing adenosine triphosphate (ATP) loss and magnesium release. It causes excitotoxic neuronal damage by increasing intracellular calcium and magnesium levels due to the excessive production of sulfur-containing amino acids (e.g., S-sulfocysteine) and excessive activation of the N-methyl-D-aspartate (NMDA) receptor. As a result of neuronal damage, seizures and neurodevelopmental delay occur clinically (2,6,7).

The vast majority of patients with MoCD (75%) harbor MOCS1 mutations, while the remaining portion (25%) harbor mutations in MOCS2, GEPH, or MOCS3, with the latter being the least likely (3,7). Mutations in MoCD2 are autosomal recessive, and extremely rare. Patients with MOCS2 mutations may exhibit two different forms: the early type, which presents with symptoms in the neonatal period, and the late type, which has a later onset. The number of early-onset cases reported is very low (2,6,8). In the early onset form of MoCD, there are severe encephalopathy symptoms, such as refractory seizures, hyper/hypotonia, apnea, and feeding difficulties, that begin in the first days of life. The patients had narrow bifrontal diameters, micro/macro cephalad, long faces, elongated palpebral fissures, lens dislocation, widely spaced eyes, small nose, asymmetric skull, prominent forehead, deep-set eyes, broad nasal bridge, long philtrum, and thick plump cheeks. Facial dysmorphism, such as lip dysmorphism, can be detected (1,6). It can be confused with HIE, especially postnatal neonatal encephalopathy, as observed in our patient. Having dysmorphic findings is a warning for clinician (6,8). Some dysmorphic findings previously described for MoCD were observed in our patient. However, cleft palate association in our patient has not been previously described in MoCD. Patients with late-onset MoCD generally exhibit mild symptoms (6). Antenatal diagnoses are not commonly performed and the follow-up process is often devastating, ultimately leading to patient death. However, enzyme activity in chorionic villus samples and sulfocysteine levels in amniotic fluid are sometimes used to diagnose conditions during pregnancy. DNA analysis is also used to confirm the diagnosis (1,6,8).

To ensure an accurate diagnosis of MoCD, it is crucial for the clinic to collaborate with the laboratory. The first diagnostic test is typically a biochemical test to detect low uric acid levels. Additionally, low serum homocysteine levels, a positive sulfite test, elevated S-sulfocysteine and xanthine levels in the urine, and low cystine levels in both the blood and urine can support the diagnosis of MoCD. Furthermore, low uric acid and taurine levels in the urine may also indicate the presence of the disorder. Serum uric acid levels should be evaluated for the differential diagnosis of HIE and MoCD in patients with neonatal encephalopathy, as in our patient. In the presence of low uric acid, the diagnosis of MoCD should be suspected (1,4,8).

Cranial MRI is the preferred imaging method for the diagnosis of MoCD and typically shows MRI findings. Early brain MRI revealed cerebral hemispheres, basal ganglia, thalamus, globus pallidus, cerebral peduncles in the midbrain, corpus callosum thinness or absence, cortical atrophy, thalamic and subthalamic diffuse brain edema, diffuse diffusion restriction, hyperintense signal changes, cystic encephalomalacia, and atrophy in the cortex and white matter. These images, similar to HIE, include curvilinear areas with reduced signal intensity at the gray/white matter junction, hemorrhagic deposits and laminar necrosis, which are more specific findings for MoCD (2,6,7,9). In HIE, diffusion restriction occurs in the deep cortical regions, whereas in MoCD, it is more common in the cerebral cortex and is a supportive finding for the diagnosis of MoCD. While MRI images can be detected even in the early stages in MoCD, MRI findings in HIE can be seen in the later days (2,4,10). In our patient, the diagnosis of HIE was excluded and the diagnosis of MoCD was supported by the corpus callosum,

cortical atrophy, cystic encephalomalacia, and diffuse diffusion restriction in the cortex on cranial MRI. In addition to the typical MRI findings, the diagnosis of MoCD was confirmed in our patient using clinical and biochemical tests and genetic analysis. As in our case, the distinction between HIE and other congenital metabolic diseases should be made immediately after birth to differentiate neonatal encephalopathy. Especially in cases of accompanying dysmorphic findings in patients with neonatal encephalopathy, MoCD is considered and uric acid levels provide diagnostic guidance. Although patients with MoCD seem rare, as in our case, HIE overlap may occur. Therefore, rapid differentiation of neonatal encephalopathy can prevent incorrect diagnosis of HIE (6,7). The treatment and prognosis of HIE and MoCD are completely different from each other. In addition, a diagnostic distinction between HIE and MoCD should be made, and therapeutic hypothermia treatment for HIE should be initiated within the first six hours after birth.

In recent years, minimal improvements in clinical and laboratory findings have been observed with dietary sulfur-containing amino acid restriction, cyclic pyranopiterine monophosphate (cPMP), an NMDA receptor antagonist MK801, treatment in only a small number of patients with MOCS1 mutations, and molybdate treatment in patients with GPHN mutations (2,4). However, its positive effects on cranial injuries have not been determined (2,9). Therefore, there is currently no definitive treatment for patients (4,9). In patients with MOCS2 mutations, pyridoxine treatment may help to reduce some symptoms (2,9). It may have been possible with pyridoxine treatment to reduce antiepileptic treatment for seizure control in our patient and to avoid the need for mechanical ventilation and respiratory support in most of his life. Neurodevelopmental retardation in our patient demonstrates that the effect of pyridoxine on the central nervous system and neurological findings is limited (2,9). The primary objective of MoCD is to manage complications effectively through early comprehensive supportive care. The severity of cerebral lesions established prior to initiating treatment significantly influenced patient outcomes. Although therapy improves life expectancy, sadly, many patients still pass away in their infancy (2,6,7).

Approximately 30 patients with MOCS mutations and MoCD type B have been previously described (8). To date, mutations in exon 4 (c.226G>A) have been identified in 4 patients of Asian origin. However, no MoCD patient with a mutation in Type B exon 4 (c.226G>A) has been previously described in our country. This is the 5th case in the world and the first case from our country with a mutation in exon 4 (c.226G>A). In addition, cleft palate in our patient has not been previously reported among the dysmorphic findings of MoCD. The association between cleft palate and MoCD may be a new component of the MoCD clinical complex.

CONCLUSION

Newborns with neonatal encephalopathy may exhibit symptoms, such as neonatal seizures and feeding difficulties, which may serve as the first signs of MoCD. Serum uric acid levels should be measured to differentiate MoCD and HIE in newborns. Moreover, dysmorphic findings, laboratory tests supporting the diagnosis of MoCD, and typical cranial MRI findings should be considered within six postnatal hours to avoid inappropriate treatment. Therefore, it is crucial to genetically support MoCD diagnosis. In our patient, we identified a rarely identified MOCS2 type B homozygous mutation and presented an association between MoCD and cleft palate for the first time. Although there is no effective treatment for MOCS2 patients, early diagnosis and genetic analysis can facilitate adequate genetic counseling.

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Periodontal manifestations of diseases / conditions related with female sex steroid hormones

Kadın cinsiyet hormonları ile ilişkili hastalıkların / durumların periodontal bulguları

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ABSTRACT

The primary etiological factor for periodontal diseases is microbial dental plaque deposited on tooth surfaces. However, fluctuations in sex steroid hormone levels increase the susceptibility and/or severity of clinical manifestations of periodontal diseases. The aim of this narrative review is to provide current evidence on the clinical findings in women's periodontal tissues regarding changes in female sex steroid hormones. Electronic databases were searched for studies evaluating clinical findings in women with conditions/diseases that cause changes in female sex hormones. Clinical studies published before February 2024 were included in the review. Women show fluctuations in sex steroid hormone levels at various stages of their lives, and these, together with some disease-related changes, lead to characteristic or regular clinical periodontal findings. Close collaboration between dentists and gynecologists can help to ensure early diagnosis and treatment of such conditions.

Keywords: Menopause; menstrual cycle; periodontal disease; pregnancy; polycystic ovary syndrome; puberty

ÖZ

Periodontal hastalıklar için birincil etiyolojik faktör diş yüzeylerinde biriken mikrobiyal dental plaktır. Bununla birlikte, cinsiyet hormon seviyelerindeki dalgalanmalar periodontal hastalıkların klinik belirtilerinin duyarlılığını ve/veya şiddetini artırmaktadır. Bu derlemenin amacı, kadın cinsiyet hormonlarındaki değişikliklerle ilişkili olarak kadınların periodontal dokularındaki klinik bulgular hakkında güncel kanıtlar sunmaktır. Elektronik veri tabanlarında, kadın cinsiyet hormonlarında değişikliklere neden olan durumları/hastalıkları olan kadınlarda klinik bulguları değerlendiren çalışmalar araştırılmıştır. Şubat 2024' den önce yayınlanan klinik çalışmalar derlemeye dahil edilmiştir. Kadınlar yaşamlarının çeşitli evrelerinde seks steroid hormon seviyelerinde dalgalanmalar gösterir ve bunlar hastalıkla ilişkili bazı değişikliklerle birlikte karakteristik veya düzenli klinik periodontal bulgulara yol açar. Diş hekimleri ve jinekologlar arasındaki yakın iş birliği, bu tür durumların erken teşhis ve tedavisinin sağlanmasına yardımcı olabilir.

Anahtar Kelimeler: Menopoz; menstrüel siklus; periodontal hastalıklar; hamilelik; polikistik over sendromu; puberte

INTRODUCTION

Periodontal disease is a chronic inflammatory disease, and its established form is characterized by loss of periodontal attachment and destruction of the surrounding alveolar bone (1). It is considered one of the two major threats to oral health and is the primary cause of tooth loss. Approximately 800 species of bacteria have been identified in the oral cavity and the interaction between bacterial infection and host response is complex (2). Periodontal disease has a high global prevalence. It is estimated that severe periodontitis affects 11% of the World population. Disease progression and severity depend on the balance between subgingival plaque bacteria and the individual host immune response, which is modulated by genetic, epigenetic context and environmental factors such as smoking (3). There are studies in the literature stating that periodontal diseases are more common in men (4,5). The possible explanations are men's neglect of oral care, higher B lymphocyte activation and the level of antibodies produced in women.[4] However, a recent study of a large group of Italian people showed that periodontitis affects women more than men, with a ratio of 3 to 2. This ratio was also similar among the younger patients (those under 35 years old) (6). The physiological changes in female sex hormones, the distribution of estrogen and progesterone receptors, and the metabolism of these hormones became a field of

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investigation to uncover the pathogenetic mechanisms underlying periodontal disease in women. Associations between periodontal disease and puberty, menstruation, pregnancy, oral contraceptive use, and menopause have been reported in several studies (7). The aim of this narrative review is to present data on the relationship between sex hormones, systemic diseases in women, and periodontal disease.

A literature search was conducted using PubMed, Web of Science and Scopus search engines. Electronic databases were searched for studies evaluating clinical findings in women with conditions/diseases that cause changes in female sex hormones. Only studies in the Turkish and English language were considered. Clinical studies published before February 2024 were included in the review.

Puberty

Sex hormones have an effect on the gingival tissue, alveolar bone and formation of subgingival microflora. Hormone levels as well as the frequency of gingival pathologies increase at the age of sexual maturation. Puberty is a temporary physiological state, considered a complex process of sexual maturation, directly linked to increased levels of the sex steroid hormones – oestradiol, progesterone, and testosterone (8,9). The gingival inflammatory response to dental plaque can be affected by both normal and abnormal hormone fluctuations, including alterations in gonadotrophic hormone levels at the onset of puberty. Similarly, alterations in insulin levels in diabetic patients can influence gingival health. In both instances, there is an elevated inflammatory response to dental plaque. However, the gingival condition generally improves with the comprehensive removal of bacterial deposits and enhanced daily oral hygiene practices. The effects of these hormones on gingival inflammation have not been fully studied yet. While it is undisputed that the biofilm plays a key role in the occurrence of a gingival inflammatory response, it is not yet clear whether the sex hormones participate in the aggravation of this response (9).

Menstrual Cycle

Menstruation is regulated by hormones synthesized in the hypothalamus, pituitary gland, and ovaries. The lining of the uterus sheds in an orderly fashion during the menstrual cycle. The menstrual cycle comprises the follicular phase, lasting 14 days, and the luteal phase, which ranges from 10 to 16 days. Cycle length is defined as the number of days between the first day of bleeding and the start of the next period. The typical menstrual cycle lasts 28 days and the average duration of menstruation is 4 to 6 days (10). Alterations in sex steroid hormones, evident during the menstrual cycle in women, may influence periodontal health (11). Khosravisamani et al (12). suggested that changes occurring during the menstrual cycle influence the periodontium and induce inflammatory conditions. The corpus luteum is a hormone-secreting yellow body found in the ovaries of women and secretes higher TNF- α during the late luteal phase compared to the early luteal phase. One study shows that there are marked fluctuations in tumor necrosis factor-alpha (TNF- α) levels in the blood during the menstrual cycle, which is also observed during periodontal disease (13). In one study, 27 female participants received oral hygiene instruction at baseline, and for two months their plaque index scores were taken once a week, along with the gingival index, bleeding on probing (BOP) and probing depths to determine the periodontal status of the participants. The menstrual cycle's duration and regularity were also recorded. Gingival crevicular fluid (GCF) samples were collected to measure the levels of interleukin (IL)-1beta and TNF-α on the first menstruation day (MD), estimated ovulation day (OD), and estimated predominant progesterone secretion day (PgD). It has been shown that gingival inflammation during the menstrual cycle is influenced by changes in sex steroid hormones (14). In the study of Becerik et al. (11), twenty-five patients with gingivitis and twenty-five periodontally healthy individuals with regular menstrual cycles were examined during menstruation (ME) (first to second days), ovulation (OV) (12 to 14 days), and the premenstrual phase (PM) (22 to 24 days). GCF and saliva samples were obtained, and periodontal indicators such as plaque index and bleeding on probing were documented during each menstrual phase. Exact menstrual cycle days were determined by analyzing salivary estrogen and progesterone levels. GCF levels of IL-6, prostaglandin E_2 (PGE_2), tissue plasminogen activator (t-PA), and plasminogen activator inhibitor (PAI)-2 were measured by enzyme-linked immunosorbent assay (ELISA). It was suggested that fluctuations in sex steroid hormones throughout the menstrual cycle may have a slight effect on the inflammatory condition of the gingiva, and that GCF cytokine levels remained unaffected (11). In another study, it was indicated that ovarian hormones have a negligible effect on clinically healthy periodontium. However, these hormones may exaggerate pre-existing inflammation in gingival tissues, but the clinical significance of these changes remains uncertain (7).

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS), the most prevalent endocrinopathy in women, predominantly affects the reproductive system but also has significant negative effects on cardiovascular, psychological, and metabolic functions. PCOS is a multifaceted, heterogeneous endocrine condition, distinguished by menstrual irregularities (oligomenorrhea or amenorrhea), chronic anovulation or oligo-ovulation, clinical or biochemical indicators of hyperandrogenism (hirsutism, acne, or androgenic alopecia), and ultrasound findings. It typically impacts women during their reproductive years (15). Akcali et al. (16) conducted the first study to examine the correlation

between oral microbiota in saliva and serum antibody responses, as well as gingival inflammation in PCOS. They observed discrepancies in microbiological parameters between PCOS patients and control group with periodontal disease. Patients with PCOS and gingivitis exhibited elevated levels of *P. gingivalis* and *F. nucleatum* in saliva samples, along with antibodies for *P. intermedia, P. gingivalis,* and *S. oralis* in the serum. According to a recent review, the composition of the oral microbiota may be quantitatively impacted by PCOS, which could explain the increased systemic response to specific members of this microbial community.[16] The periodontal disease caused by dental plaque might be exacerbated worse by PCOS through a number of pathophysiological pathways, including low-grade systemic inflammation, oxidative stress, insulin resistance, advanced glycation end products (AGEs), and systemic hormone levels (17). Evidence indicates that periodontal disease induces persistent subclinical inflammation, resulting in insulin resistance and subsequently facilitating the onset of type 2 diabetes, a significant characteristic of PCOS. Therefore, we could assume that a bidirectional association exists between PCOS and periodontal disease (17). Another recently published review also indicated a correlation between periodontal disease and PCOS, as periodontal parameters were considerably altered in PCOS patients compared to healthy young women, particularly in the presence of gingivitis and periodontitis. This response may be first influenced by a local and systemic proinflammatory environment that promotes a pro-oxidant condition, resulting in oxidative stress and ultimately causing irreversible damage to periodontal tissue. Nonetheless, the interaction between PCOS and periodontal diseases in exacerbating the burden on cellular pathways remains ambiguous (18).

Pregnancy

Pregnancy is associated with a high prevalence of periodontal disease, particularly gingivitis. This is mainly due to significant changes in the levels of female sex hormones during pregnancy. At the end of the third trimester, plasma concentrations of progesterone and estrogen are 10 and 30 times higher, respectively, than during the menstrual cycle. Increases of these sex hormones during pregnancy have been associated with an increase in the prevalence, and severity of gingivitis (19). Moreover, receptors for these hormones have been identified in various subsets of periodontal cells, making periodontal tissue a potential target. In addition, periodontal disease may trigger local and systemic inflammation and increase levels of reactive oxygen species (ROS). This systemic disorder can jeopardize pregnancy outcomes for expectant mothers. In a case-control study, 187 women (pregnant and non-pregnant) were included, and oxidative stress markers were analyzed in saliva samples of the participants. The results of the study showed that there are changes in the oxidant/antioxidant balance in saliva during pregnancy and after delivery, which may be influenced by the periodontal condition. It has been suggested that early detection of ROS markers in saliva may have clinical value in the periodontal management of pregnant women (20).

Pregnancy Gingivitis

"Pregnancy gingivitis" is a common finding among pregnant women. Although the amount of plaque is low in this disease, clinical signs of gingivitis are prominent. Its pathogenesis is very similar to that of plaque-induced gingivitis. Clinical attachment loss is very uncommon, even with this exacerbated inflammatory response and associated increase in gingival sulcus depth, GCF flow, and bleeding on probing (19).

Epulis Gravidarum

Epulis gravidarum is a benign vascular mucosal lesion observed in pregnant women. It may manifest as a localized inflammatory lesion (i.e., pregnancy granuloma) in 0.2-9.6% of pregnant women. Commonly referred to as lobular capillary hemangioma, it is a benign vascular neoplasm of the skin and mucous membranes observed in children, young adults, and pregnant women. The lesion presents as an exophytic, fragile, red to yellow nodule that may increase in size, hemorrhage, or undergo ulceration. It is usually solitary but can also be seen as multiple satellite lesions. It has been reported that tumor size can vary from a few millimeters to a few centimeters (21). The lesion histologically comprises loose granulation tissue characterized by the proliferation of capillaries and endothelial cells organized in lobules. These lesions are caused by hormonal changes during pregnancy. Even though decreased hormone levels after pregnancy may allow these lesions to resolve, excision is often necessary after delivery (22).

Gestational Diabetes

Gestational diabetes mellitus (GDM) is one of the most common metabolic disorders during pregnancy, and its current increase in prevalence has been linked to the rising incidence of maternal obesity over recent decades. The etiology of GDM is complex, involving both genetic and environmental factors, as suggested by epidemiological studies (23). Multiple studies have demonstrated an association between periodontitis and GDM (24-26), with current evidence suggesting that pregnant women with severe periodontitis have a higher risk of developing GDM (27). A study based on the National Health and Nutrition Examination Survey (NHANES III) showed the prevalence of periodontitis to be 44.8% in women with GDM and 13.2% in normoglycemic pregnant women (OR = 9.11, $p<0.05$) (28). Additionally, women with a previous history of GDM (with or without existing diabetes mellitus at the time of examination) were more likely to have periodontitis than women without a history of GDM (29). In a cross-sectional study, clinical periodontal parameters, along with the levels of tumor necrosis factor-alpha (TNF-α), interleukin-10 (IL-10), and interleukin-33 (IL-

33) in the gingival crevicular fluid (GCF) and serum, were compared between women with GDM and those without the condition. The results showed that the GDM group had higher plaque index and bleeding on probing (BOP) scores, as well as higher levels of GCF IL-10, which are thought to result from increased inflammation (30). However, to date, there are no prospective longitudinal studies evaluating the possible bidirectional relationship between periodontitis and GDM. It has been suggested that sustained hyperglycemia, a standard feature of diabetes, may have an impact on the severity of periodontitis during pregnancy (31).

Pre-term Birth and Low-Birthweight

Low birth weight is defined as birth weight less than 2500 grams. Today, it continues to be an important public health problem in both developed and developing countries. This situation is usually a direct consequence of preterm birth and is referred to as preterm birth of low-birth-weight infants (PLBW). Although efforts have been made to reduce the impact of risk factors through preventive methods, the incidence of PLBW births has not decreased significantly over the past decade, and the risk factors for PLBW are not fully understood. Identified risk factors for PLBW include old (> 34 years) and young (<17 years) maternal age, African American origin, low socioeconomic status, inadequate prenatal care, drug, alcohol and tobacco abuse, hypertension, genitourinary infections, diabetes and multiple pregnancies. Smoking during pregnancy is associated with 20-30% of low birth-weight births and 10% of fetal and infant deaths (32).

Infection is now recognized as one of the main causes of PLBW births and is responsible for 30% to 50% of all cases. Bacteremia is defined as the passage, intermittent or continuous presence of bacteria into the bloodstream. In periodontitis, the pathogenic subgingival microbiota is in close contact with the ulcerated epithelium of periodontal pockets, resulting in the passage of pathogenic bacteria into the bloodstream. Chronic low-level bacteremia has been proposed as a direct mechanism to explain the link between adverse pregnancy outcomes and periodontitis. The theory that infections at distant sites may cause PLBW has been supported by several studies using the pregnant golden hamster model (33-35). Pregnancy outcomes were evaluated in these animals after inducing experimental periodontitis, (34) creating a localized subcutaneous infection with *P. gingivalis* that did not spread,[33] or administering intravenous injections of lipopolysaccharide from *P. gingivalis* (35). Fetal weights were notably reduced in the experimental groups, and the extent of the adverse effects on the fetus correlated directly with the levels of PGE_2 and TNF-α.

Bacterial culture results are negative in many cases of PLBW with histological evidence of chorioamnionitis, indicating that local infection is not a requirement for triggering inflammatory mediators of preterm labour. LPS stimulates prostaglandin production by the placenta and chorioamnion, and high LPS concentrations in amniotic fluid have been measured in PLBW cases. Gram-negative anaerobic bacteria responsible for progressive periodontitis provide a chronic reservoir of LPS that may contribute to PLBW (36).

The pro-inflammatory cytokines, IL-1, IL-6 and TNF-α, stimulate PGE2 synthesis by the human placenta and chorioamnion, and amniotic fluid levels of these cytokines are often elevated in women in preterm labor. These cytokines can cross human fetal membranes and it is conceivable that high concentrations of these cytokines, produced at sites of chronic periodontitis and measured at higher levels in the plasma of patients with periodontitis, may affect the fetoplacental unit and cause PLBW (37). In summary, it can be said that chronic periodontal infection, serving as a reservoir for bacterial products (such as LPS) and/or various inflammatory mediators, may play an important role in the development of PLBW.

Menopause

Menopause is associated with significant systemic and oral manifestations. During menopause, the gingival epithelium becomes thinner and more prone to atrophic and inflammatory changes. Furthermore, various oral conditions develop with the reduction in the salivary flow rate and changes in its composition. The sudden and sharp decrease in estrogen production that occurs at menopause is considered as the main cause of primary osteoporosis, which also affects the jawbones. It has been suggested that this reduction in bone mineral density may contribute to the progression of periodontal disease. Besides its effects on alveolar bone, estrogen also interfere with other periodontal tissues (gingiva and periodontal ligament) and influence the host's immune-inflammatory responses (38). Several studies have associated menopause with various periodontal conditions, although different methods for identifying and evaluating osteoporosis, alveolar bone loss, and periodontitis make it difficult to compare results (39).

Osteoporosis

The majority of published studies have emphasized the relationship between osteoporosis and periodontal disease, suggesting that treatment of one disease will be beneficial in the treatment of the other (40). To better understand the relationship between these two diseases, it is necessary to look at the potential mechanisms. While osteoporosis is a systemic disease that occurs primarily in the cancellous bone, periodontal disease is a localized infection of the periodontium that initially affects the cortical bone and causes a dimensional change in the alveolar bone. Areas of decreased bone density in the jaw bones due to osteoporosis may create a potential for rapid progression of gingival disease. Furthermore, it has been

suggested that the incidence of microfractures increases in the presence of osteoporosis in situations of increased occlusal forces and bone fatigue (41).

Numerous studies have investigated the possible relationship between periodontal disease and osteoporosis. In a study conducted by Tezal et al. (42), in a population of 70 postmenopausal women aged 51-78 years, bone mineral density, clinical attachment level and interproximal alveolar bone loss were measured using dual energy X-ray absorptiometry. The results of the study showed that mean alveolar bone loss and clinical attachment levels were significantly associated with systemic bone mineral density (42). In another study, clinical periodontal measurements were recorded in 100 postmenopausal women (50 osteoporotic, 50 healthy) aged 50-65 years. The results of the study showed that probing depth, clinical attachment level, interproximal alveolar bone loss and the number of teeth lost were significantly higher in the women with osteoporosis compared to those without osteoporosis (43). A systematic review and meta-analysis examining the association between osteoporosis and periodontal disease suggests that postmenopausal women with osteoporosis or osteopenia may have higher clinical attachment loss compared to women with normal bone mineral density (44).

Several hormones play an important role in the regulation of bone homeostasis, including estrogen, testosterone, cortisol, parathyroid and thyroid hormones. Imbalance of these hormones affects calcium/phosphate metabolism, bone homeostasis and inflammatory mechanisms. Decreased estrogen levels in postmenopausal women are an important risk factor for osteoporosis. This deficiency has been found to decrease calcium absorption and increase calcium excretion, and it has been reported that decreased estrogen levels induce osteocyte apoptosis, which disrupts bone homeostasis. It can be speculated that estrogen has both pro-inflammatory and anti-inflammatory functions in inflammation, with low estrogen levels stimulating IL-1 mRNA expression and high estrogen levels reducing oxidative stress. In experimental animal studies, estrogen deficiency has been observed to increase the severity of periodontitis (45). In humans, hormone replacement therapy has been found to improve mandibular bone density and reduce gingival bleeding, and the number of teeth lost to periodontitis (46). These results suggest a potential role for estrogen deficiency in periodontal disease.

Another important hormone for bone homeostasis is the parathyroid hormone, which increases bone resorption to provide adequate calcium in the blood. Intermittent administration of parathyroid hormone has been shown to increase periodontal healing and support bone regeneration at extraction sites (47). These findings suggest that there may be a mechanism linking the interaction of hormones associated with bone remodeling and inflammation, where high levels of systemic pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α have been found in patients with osteoporosis. All these identified cytokines are thought to induce bone resorption. These inflammatory cytokines and other circulating factors not only affect systemic bone remodeling, but also act locally to influence the tissue response to periodontal disease (TNF-α also induces collagenase activity) (48). Similarly, in local infection of the periodontium, these inflammatory cytokines are released into the circulation and have a significant impact on periodontal disease. It is likely that one of the mechanisms underlying both diseases is related to these inflammatory pathways.

CONCLUSION

It is known that women experience various hormonal changes throughout their lives, starting from puberty. The link between hormonal changes, inflammatory pathways and periodontal tissues and diseases should not be neglected. It is important that both physicians and dentists are aware of the possible effects of hormonal changes on the pathogenesis of periodontal disease in women and refer the patient to an appropriate evaluation, prevention and treatment program.

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