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Dergimizin 2024 yılına ait ilk sayısını sizlere sunmanın mutluluğu içindeyiz. Dergimize yoğun ilgi gösteren ve destek sunan araştırmacılarımıza ve değerlendirme sürecinde katkı sağlayan hakemlerimize yayın kurulu olarak teşekkürlerimizi sunarız. Bu sayıda da ilgiyle okuyacağınızı düşündüğümüz, obstetri jinekoloji, onkoloji ve infertilite alanlarına ait 8 araştırma makalesi ve 1 olgu sunumuna yer verdik.

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Erken Evre Non-squamoz Hücreli Serviks Kanserli Hastalarda Lenf Nodu Metastazını Belirleyen Faktörler

Factors Determining Lymph Node Metastasis in Patients with Early Stage Non-Squamous Cell Cervical Carcinoma

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ÖZ

Amaç: Erken evre non-squamoz hücreli serviks kanserli hastaların klinikopatolojik özelliklerinin değerlendirilmesi ve lenf nodu metastazını predikte eden faktörlerin tanımlanması amaçlandı.

Gereçler ve Yöntem: Bu çalışmaya, altı jinekolojik onkoloji merkezinde, 1993-2022 yılları arasında, evre IB1-IIA2 non-squamoz hücreli serviks kanseri nedeniyle radikal histerektomi ve lenfadenektomi uygulanan hastalar retrospektif olarak dahil edildi. Risk faktörlerinin lenf nodu metastazı üzerine etkileri tek değişkenli ve çok değişkenli logistik regresyon analizi kullanılarak değerlendirildi.

Bulgular: Çalışmaya 126 hasta dahil edildi ve median yaş 48'di (aralık, 26-77 yıl). FIGO 2009'e göre hastaların 91'i (%72.2) evre IB1, 24'ü (%19), evre IB2, 9'u (%7.1) evre IIA1 ve ikisi (%1.6) evre IIA2'ydi. Tümör subtipi 93 (%73.8) hastada adenokarsinoma, 28 (%22.2) hastada adenosquamoz karsinomdu. Univaryant analizde; yaş, tümör boyutu, stromal invazyon, parametrial

ABSTRACT

Aim: To evaluate the clinical and pathological characteristics of early stage non-squamous cell cervical carcinoma (non-SCCC) patients and identify factors that predict lymph node metastasis.

Materials and method: Patients who underwent radical hysterectomy plus lymphadenectomy for stage IB1-IIA2 non-SCCC between 1993 and 2022 in six gynecologic oncology centers were included in this retrospective study. The effects of the risk factors on lymph node metastasis were evaluated by using univariate and multivariate logistic regression analysis.

Results: The study involved 126 patients with a median age of 48 years (range, 26-77 years). According to FIGO 2009 staging, 91 patients (72.2%) were at stage IB1, 24 (19%) were at stage IB2, 9 (7.1%) were at stage IIA1, and 2 (1.6%) were at stage IIA2. Tumor subtype were adenocarcinoma in 93 (73.8%) patients and adenosquamous carcinoma in 28 (22.2%) patients. In univariate analysis; age, tumor size, stromal invasion, parametrial invasion, uterine involvement,

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invazyon, uterin invazyon, lenfovasküler alan invazyonu (LVAİ), vajinal invazyon ve cerrahi sınır pozitifliği lenf nodu metastazı ile ilişkiliydi. Multivaryant analizde LVAİ (Hazard Ratio; 19.63, 95% Confidence interval: 3.499-110.166; p=0.001) ve uterin invazyon (Hazard Ratio; 4.36, 95% Confidence interval: 1.178-16.165; p=0.027) lenf nodu metastazı için bağımsız prognostik faktörler olarak tanımlandı.

Sonuç: Erken evre non-squamoz hücreli serviks kanserli hastalarda LVAİ ve uterin invazyon lenf nodu metastazının bağımsız belirleyicilerindendi. Bu faktörler preoperatif dönemde biyopsi örneklerinde ve görüntüleme yöntemlerinde yüksek doğruluk oranıyla tanımlanabilir.

Anahtar Kelimeler: Lenf nodu metastazı, lenfovasküler alan invazyonu, non-squamoz hücreli serviks kanseri, uterin invazyon.

lymphovascular space invasion (LVSI), vaginal involvement, and surgical border involvement were associated with lymph node metastasis. In multivariate analysis, LVSI (Hazard Ratio: 19.63, 95% Confidence Interval: 3.499-110.166; p=0.001) and uterine involvement (Hazard Ratio: 4.36, 95% Confidence Interval: 1.178-16.165; p=0.027) were identified as independent prognostic factors for lymph node metastasis.

Conclusion: LVSI and uterine involvement were independent predictors of lymph node metastasis in early-stage non-SCCC patients. These factors can be identified with high accuracy in biopsy specimens and imaging methods in the preoperative period.

Keywords: Lymph node metastasis, lymphovascular space invasion, non-squamous cell cervical carcinoma, uterine involvement

INTRODUCTION

Cervical carcinoma (CC) is the fourth most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths in women worldwide. According to the 2020 GLOBOCAN data, there were approximately 600,000 new cases diagnosed annually, resulting in 340,000 deaths (1). Although high-income countries have been able to reduce the incidence and mortality rates of CC through vaccination and screening programs, it remains a significant health problem in low to middle-income countries (2).

In the early stages of cervical carcinoma, excellent survival outcomes are achieved with surgical and/or chemoradiotherapy. However, survival rates in local advanced stages are low. The most important prognostic factors determining survival are the stage of the disease and lymph node involvement (3-5). The FIGO has recently updated the clinical staging guidelines for cervical carcinoma in 2018, highlighting the importance of including the lymph node status in the staging process (6). Accurate identification of lymph node metastasis is essential in managing patients and selecting appropriate treatment modalities.

Squamous cell cervical carcinoma (SCCC) is the most prevalent histological subtype, accounting for approximately 70-80% of all cases (7). Non-squamous cell cervical carcinoma (non-SCCC) represents a group of diseases with different morphologies and prognoses. Its clinicopathological characteristics, oncological outcomes, and behavioral patterns differ from SCCC. In comparison with SCCC, non-SCCC is partially resistant to radiotherapy and more frequently leads to distant metastasis, resulting in a more unfavorable prognosis (8).

Our comprehensive knowledge about cervical carcinoma originates mainly from studies on SCCC patients, but there is limited data available specifically about pure non-SCCC patients. In this study, our primary aim was to evaluate the clinicopathological characteristics of non-SCCC patients. Subsequently, we aimed to identify the factors that predict lymph node metastasis in this patient group.

MATERIALS AND METHOD

This study included patients who underwent abdominal radical hysterectomy and bilateral systematic pelvic±para-aortic lymphadenectomy for 2009 FIGO stage IB1-IIA2 cervical carcinoma between 1993 and 2022 in six gynecologic oncology centers. Clinicopathological data of the patients were retrieved retrospectively from patient files or electronic databases. All patients were staged by bimanual examination under general anesthesia according to FIGO 2009 criteria before surgical treatment. Magnetic resonance imaging and/or computerized tomography were used when necessary. This study was approved by local ethical committee by the file number of E2-23-4901.

Patients with squamous cell cancer, mixed type cancer, non-e-

pithelial cervical cancer, synchronized cancer, micro-invasive cervical cancer, received neoadjuvant chemotherapy, didn't undergo pelvic lymphadenectomy and advanced cervical cancer (2009 FIGO stage IIB-IVB) were excluded. Histopathological evaluation was carried out according to 2020 World Health Organization (WHO) criteria (9). Cervical tumors were classified as; squamous cell carcinomas, adenocarcinomas, other epithelial tumors (carcinosarcoma, adenosquamous, undifferentiated and adenoid basal), mixed epithelial and mesenchymal tumors, and germ cell tumors. Tumor size was considered as the largest diameter of the tumor. Deep stromal invasion was defined as the stromal invasion of a tumor invading the outer half of the cervical stroma. Lymphovascular space invasion (LVSI) was defined as the tumoral cells or cell clusters holding on vessels' walls that were stained with hematoxylin and eosin in the pathologic sections containing both the tumor and the surrounding healthy tissue. Uterine involvement is defined as the spread of the disease above the internal os, involving endometrial and/or myometrial areas. Surgical border involvement is defined as when the tumor is located ≤0.5 cm from the distal end of the specimen. Vaginal involvement is defined as the presence of a tumor in any part of the vagina.

All operations were performed by gynecologic oncologists. Bilateral pelvic lymphadenectomy was performed to complete skeletonization, with all lymphatic tissue of the common, external and internal iliac vessels and the obturator fossa removed after visualization of the obturator nerve. The superior surgical dissection margin for the pelvic nodes was the aortic bifurcation, and the anterior distal surgical dissection margin was the circumflex iliac vein. The presacral lymphatic tissue was harvested separately. Each of common iliac, external iliac, internal iliac, obturator and presacral regions was included in the pelvic region. Para-aortic lymphadenectomy was added to the surgical procedure depending on the presence of suspicious lymph nodes in the paraaortic region and at the discretion of the senior surgeon, often performed up to the level of the inferior mesenteric artery. Bilateral salpingo-oophorectomy (BSO) was performed according to the patient's age and attending surgeon's discretion.

Statistics

Categorical variables are expressed as number and percentage and were analyzed using Pearson's Chi-square ($\chi 2$) test or Fisher's exact test for univariate analysis, as appropriate determine whether they had statistically significant effects on lymph node metastasis. Multivariate analysis was performed using a Cox proportional hazards model. Variables identified as risk factors in univariate analysis (p value <0.05) were used to create an exact logistic regression model. Hazard ratios with 95% confidence intervals were calculated. p value <0.05 was considered statistically significant for the results. Data analyses were performed by using Statistical Package for Social Sciences (IBM SPSS Inc, Chicago, IL, USA) version 20.0.

RESULTS

A total of 126 patients were enrolled in the study, with a median age of 48 years (range, 26-77 years). According to the FIGO 2009 classification, 91(72.2%) patients were staged as IB1, 24 (19%) as IB2, 9 (7.1%) as IIA1, and 2 (1.6%) as IIA2. Tumor subtypes were identified as adenocarcinoma in 93 (73.8%) patients and adenosquamous carcinoma in 28 (22.2%) patients. The median tumor size was 30 mm (range, 8-72 mm). Forty-five (35.7%) patients presented tumors ≤20 mm and 26 (20.6%) patients had tumors >40 mm.

The parametrial invasion was detected in 23 (18.3%) patients, surgical border involvement in 14 (11.1%) patients, vaginal involvement in 20 (15.9%) patients, lymphovascular space invasion (LVSI) in 57 (45.2%) patients, deep stromal invasion in 83 (65.9%) patients, and uterine involvement in 27 (21.4%) patients. Bilateral salpingo-oophorectomy was performed on 113 patients and 6 (5.2%) patients had .ovarian metastasis.

While pelvic lymphadenectomy was conducted in all patients, para-aortic lymphadenectomy was additionally performed in 121 (96%) patients. The median number of lymph nodes removed was 37 and ranged from 11 to 113. Lymph node metastasis was observed in 32 (25.4%)patients. Twenty-two (17.5%) patients showed metastasis solely in the pelvic region and 10 (7.9%) patients had metastasis in both the pelvic and para-aortic regions. Detailed information regarding clinical, surgical, and pathological factors is presented in Table 1.

Table 1. Clinical and surgico-pathological features

Characteristics		**Mean±SD**	**Median (range)**
Age at initial diagnosis		51.4±11.34	48 (26-77)
Tumor size (mm)		29.9±14.69	30 (8-72)
Number of removed lymph nodes		49.5±24.06	37 (11-113)
Number of metastatic lymph node		5.7±7.32	1 (1-37)
		n	**%**
FIGO 2009 stage	IB1	91	72.2
	IB2	24	19
	IIA1	9	7.1
	IIA2	2	1.6
Tumor type	Adenocarcinoma	93	73.8
	Others [1]	33	26.2
Tumor size	≤20 mm	45	35.7
	>20 mm - ≤40 mm	55	43.7
	>40 mm	26	20.6
Parametrial invasion	Negative	103	81.7
	Positive	23	18.3
Surgical border involvement	Negative	112	88.9
	Positive	14	11.1
Vaginal involvement	Negative	106	84.1
	Positive	20	15.9
Lymphovascular space invasion	Negative	59	46.8
	Positive	57	45.2
	Not reported	10	7.9
Stromal invasion	≤ %50	42	33.3
	> %50	83	65.9
	Not reported	1	0.8
Bilateral salpingo-oophorectomy	Not performed [2]	13	10.6
	Performed	113	89.7
Ovarian metastasis [3]	Negative	110	94.8
	Positive	6	5.2
Uterine involvement	Negative	94	74.6
	Positive	27	21.4
	Not reported	5	4
Lymph node metastasis	Negative	94	74.6
	Positive	32	25.4
Site of metastatic lymph node	Only pelvic	22	17.5
	Only paraaortic	-	-
	Pelvic and paraaortic	10	7.9

In univariate analysis, various factors were defined as statistically predictive of lymph node metastasis, including age, tumor size, stromal invasion, parametrial invasion, uterine involvement, LVSI, vaginal involvement, and surgical border involvement (Table 2).

Table 2. Factors predicting the lymph node metastasis

Factors		**Univariate Analysis**	**Multivariate Analysis**			
	Positive Lymph Node		**Risk of Lymph Node Metastasis**			
	Percentage	***p* Value**	**Hazard Ratio**	**95% Confidence Interval**	***p* Value**	
Age [1]	<48 years	14.3	***0.014***	1 (Reference)	0.732-9.721	*0.137*
	≥48 years	33.3		2.667		
Histopathology	Adenocarcinoma	26.9	*0.520*			
	Others	21.2				
FIGO 2009 stage	Stage I	23.5	*0.110*			
	Stage II	45.5				
Tumor size	≤20 mm	22.2	***0.022***			
	>20 mm - ≤40 mm	18.2				
	>40 mm	46.2				
Tumor size [1]	≤30 mm	21.8	*0.236*			
	>30 mm	31.2				
Tumor size	≤40 mm	20.6	***0.006***	1 (Reference)	0.601-10.942	*0.204*
	>40 mm	46.2		2.564		

Stromal invasion	≤%50	9.5	***0.003***	1 (Reference)	0.348-8.033	*0.520*
	>%50	33.7		1.673		
Parametrial invasion	Negative	18.4	***<0.001***	1 (Reference)	0.262-5.099	*0.848*
	Positive	56.5		1.156		
Uterine involvement	Negative	13.8	***<0.001***	1 (Reference)	1.178-16.165	***0.027***
	Positive	55.6		4.364		
Lymphovascular space invasion	Negative	3.4	***<0.001***	1 (Reference)	3.499-110.166	***0.001***
	Positive	45.6		19.633		
Vaginal involvement	Negative	20.8	***0.006***	1 (Reference)	0.610-14.088	*0.180*
	Positive	50		2.931		
Surgical border involvement	Negative	20.5	***<0.001***			
	Positive	64.3				

Three different categorizations were used for tumor size: (i) the cohort's median value (>30 mm), (ii) values stratified according to FIGO 2018 (≤20 mm, >20 mm - ≤40 mm, and >40 mm), and (iii) values stratified according to FIGO 2009 (>40 mm).

Correlations were examined among the factors found significant in univariate analysis. A high correlation was observed between surgical border involvement and vaginal involvement. Therefore, surgical border involvement was not included in the multivariate analysis model. Age (<48 years vs. ≥48 years), tumor size (>40 mm vs. ≤40 mm), parametrial invasion (positive vs. negative), uterine involvement (positive vs. negative), LVSI (positive vs. negative), vaginal involvement (positive vs. negative), and stromal invasion (>%50 vs. ≤%50) were used to create a model for multivariate analysis. According to this model, only LVSI (Hazard Ratio: 19.63, 95% Confidence Interval: 3.499-110.166; p=0.001) and uterine involvement (Hazard Ratio: 4.36, 95% Confidence Interval: 1.178-16.165; p=0.027) were identified as independent prognostic factors for lymph node metastasis in non-SCCC (Table 2).

DISCUSSION

One of the most important routes of spread in CC is lymph node metastasis. Lymph node metastasis plays a crucial role in determining the stage and management of the disease, as a significant prognostic factor. The 5-year overall survival (OS) rate is around 90% when there is no lymph node metastasis and it drops to 30-60% in the presence of lymph node involvement (10,11). Due to the prognostic importance of lymph node metastases, accurate identification of metastases before treatment allows the identification of CC patients who will not undergo surgery or who may benefit from adjuvant treatment (expanded field radiotherapy). In our study, we retrospectively examined the clinical and pathological characteristics of surgically treated stage IB-IIA non- SCCC patients and assessed factors predicting lymph node metastasis. The lymph node metastasis rate in our study was 25.4%. LVSI and uterine involvement were identified as independent factors predicting lymph node metastasis.

In early-stage CC, the standard surgical treatment is radical hysterectomy plus lymph node dissection. The goal of this surgical approach is to remove both macroscopic and potential microscopic metastases, identifying the patients that have metastasis and might benefit from postoperative adjuvant therapy. Studies report that lymph node metastasis rates in surgically treated stage IB-IIA CC patients range from 12% to 51% (2,3,11,12). However, the majority of removed lymph nodes are non-metastatic and due to the questionable contribution of lymphadenectomy in early stages to overall survival, unnecessary lymph node dissection can lead to complications like infections, nerve damage, lymphatic cyst formation, vascular injury, venous thromboembolism, and lower limb lymphedema. Accurate preoperative and intraoperative identification of lymph node status will prevent complications.

Various factors such as age, tumor size, LVSI, parametrial invasion, deep stromal invasion, histological type, and grade have been reported as independent prognostic factors for the risk of nodal metastasis, although there are inconsistencies in studies (2,3). Yanaranop et al. identified a lymph node metastasis rate as 11.9% in 251 stage IB1-IIA cervical adenocarcinoma patients. Authors defined in their multivariate analysis that lymphovascular space invasion (LVSI) and a tumor size larger than 2 cm were independent prognostic factors (13).

Recently, Cao et al. conducted a study that involved 975 stage IA-IIA CC patients and lymph node metastasis rate was 14.8%

(14). In their multivariate analysis, tumor size (>4 cm), LVSI, deep stromal invasion, and deep uterine involvement were identified as independent prognostic factors associated with lymph node metastasis. The authors noted that 74.3% of patients with lymph node metastasis had LVSI positivity in biopsy material, while in 5.3% of cases, LVSI was detected in subsequent pathology despite being falsely negative in the initial biopsy material. In a cohort study of stage IB CC patients, Zhao et al. found that parametrial invasion, LVSI and tumor size were associated with lymph node metastasis in multivariate analysis (15).

The number of studies showing an association between uterine involvement and lymph node metastasis, which was not given enough importance in the management of CC patients in the past and was not among the staging criteria, has increased in recent years. In our study, uterine involvement was defined as an independent factor predicting lymph node metastasis in multivariate analysis. Cao et al. categorized uterine involvement into three categories (endometrial, <50% myometrial invasion, ≥50% myometrial invasion). The authors reported that only deep myometrial invasion was an independent prognostic factor for predicting lymph node metastasis (14).

He et al. observed a 30.0% rate of lymph node metastasis in a group of 2212 stage IA-IIB CC patients (16). The rate of lymph node metastasis was 37. 7% in patients with uterine involvement and 27. 7% in those without (p<0. 001). The authors reported in their multivariate analysis that the presence of uterine involvement increased the likelihood of lymph node metastasis by approximately 1.6 times and by 2.3 times in adenocarcinoma histology. Yang et al. determined a lymph node metastasis rate of 15.8% in stage IA-IIA CC patients (17). The authors reported that lymph node metastasis was 44. 3% in the presence of uterine involvement and 5. 8% in the absence of uterine involvement (p<0. 001). Uterine involvement was defined as an independent prognostic factor in their multivariate analysis.

Due to the use of a clinical staging system instead of surgical staging in the staging and treatment of CC patients, pathologic confirmation of lymph node metastases in every patient is not acceptable. This method may delay a patient's adjuvant treatment and can lead to unnecessary morbidity, adversely affecting the oncological outcome. With the technological advances in recent years, preoperative evaluation of lymph nodes with imaging methods help to predict lymph node metastasis . However, imaging methods can lead to both false positive and false negative results and cause over- or under-treatment. Studies have reported 58%, 56% and 75% sensitivity and 92%, 93% and 98% specificity for CT, conventional MRI and PET-CT to detect lymph node metastasis in CC, respectively (3). Imaging methods have some limitations due to their moderate sensitivity.

The main limitation of our study is its retrospective design. Since the study cohort consisted of pure non-SCCC patients, it is more valuable in terms of outcomes in non-SCCC patients compared to heterogeneous patient groups in the literature. Other advantages of our study are that all surgical procedures were performed by expert gyneco-oncologists, lymphadenectomy was performed as complete pelvic plus paraaortic lymphadenectomy in almost all patients and pathology results were reported by experienced gynecopathologists.

In conclusion, LVSI and uterine involvement were independent predictors of lymph node metastasis in early stage non-SCCC patients undergoing surgery. These factors can be identified with high accuracy in biopsy specimens and imaging methods in the preoperative period. Due to the subjective nature of clinical staging in CC and limitations in imaging methods, in order to identify lymph node metastasis with a higher accuracy rate in the preoperative period, it would be useful to create models that include clinicopathologic factors and imaging methods. In this way, patients at high risk for lymph node metastasis can be directed to chemoradiotherapy, avoiding unnecessary surgical treatment and possible complications.

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Maternal Aritmi Tanısıyla Beta Bloker Tedavisi Alan Gebe Kadınlarda Obstetrik ve Fetal Sonuçlar

Obstetrics and Fetal Outcomes in Pregnant Women with Beta-blocker Treatment in Maternal Arrhythmia

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ÖZ

Amaç: Bu çalışmanın amacı, maternal kardiyak aritmi tedavisi için beta-bloker kullanan hastaların gebelik prognozlarının incelemesidir.

Gereçler ve Yöntem: Bu çalışma, 1 Ocak 2020-1 Ocak 2022 arasında Ankara Şehir Hastanesi' ne başvuran 50 aritmi tanısı olan gebe ile 55 sağlıklı gebenin katıldığı retrospektif gözlemsel bir çalışmadır. Beta blokerler; metaprolol, propranolol ve bisoprolol olarak 3 gruba ayrılmıştır. Beta bloker kullanımı durumu yüksek doz ve düşük doz olarak iki grupta incelenmiştir. Gebelik prognozu için doğum haftası, doğum kilosu ve doğum kilosunun Z skoru, beta human koryo gonadotropik hormon (bHCG) MoM ve gebelikle ilişkili plazma protein-A (PAPP-A) MoM, yenidoğanların APGAR skoru ve yoğun bakıma gidiş oranları belirlendi.

Bulgular: Beta bloker alan hasta grubunun, beta bloker kullanmayan gruba göre istatistiksel olarak anlamlı bir erken doğum haftası vardı (p= <0.001). Primer sezaryen doğum oranı çalışma grubunda daha yüksekti (p=0,007). Doğum ağırlığı ve beşinci dakika APGAR skoru çalışma grubunda anlamlı olarak düşük, yoğun bakıma yatış oranı anlamlı olarak yüksekti (sırasıyla p=0.006, p=<0.001ve p=<0.001).

Sonuç: Maternal aritmiler için birinci basamak tedavi olan beta-blokerler, fetal gelişimi ve gebelik sonuçlarını etkileyebilir. Uygulanacak bu ilaçların, uygun alt gruplara ve en düşük etkili dozlara sahip olacak şekilde titizlikle seçilmesi önerilir.

Anahtar kelimeler: aritmi, beta-bloker, doğum ağırlığı, anne/fetal sonuçlar Obstetrics and fetal outcomes in pregnant women with beta-blocker treatment in maternal arrhythmia

ABSTRACT

Abstract

Aim: The aim of this study was to investigate the pregnancy outcome of patients taking beta-blockers for the treatment of maternal cardiac arrhythmias.

Materials and Method: This study was a retrospective observational study involving 50 pregnant women with cardiac arrhythmias and 55 healthy pregnant women, admitted between January 1, 2020 and January 1, 2022, to Ankara City Hospital. Beta-blockers were classified into three groups: metaprolol, propranolol, and bisoprolol. The use of beta-blockers was examined in two groups: high-dose and low-dose. For pregnancy outcome, birth week, birth weight and birth weight Z-score, beta human chorionic gonadotrophin (bHCG) MoM and pregnancy-associated plasma protein A (PAPP-A) MoM, neonatal APGAR score, and neonatal intensive care unit admission (NICU) rates were determined.

Results: The patient group taking beta-blockers had a statistically significant earlier delivery week than the group without beta-blocker use (p= <0.001). The rate of primary cesarean deliveries was higher in the study group (p= 0.007). Birth weight and APGAR score at the fifth minute was significantly lower in the study group, and NICU admission rate was significantly higher (p= 0.006, p= <0.001and p= <0.001, respectively).

Conclusion: Beta-blockers, a first-line therapy for maternal arrhythmias, may affect fetal development and pregnancy outcomes. İt is recommended that these drugs to be administered are meticulously selected for appropriate subgroups, with lowest effective doses.

Keywords: arrhythmia, beta-blocker, birth weight, maternal/fetal outcomes

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INTRODUCTION

Maternal arrhythmias in pregnancy are common, with or without structural abnormalities. We see maternal arrhythmias frequently for reasons such as maternal adaptation to pregnancy, pregnancies at advanced ages, and the increasing success of cardiac surgery in infancy (1). The heart conduction system mainly consists of the sinoatrial node, the atrioventricular node, and specialized myocytes (2). Conditions such as structural anomalies, inappropriate automaticity, abnormal electrolyte level in the blood, and thyroid dysfunction cause arrhythmia by affecting the conduction system. The 12-lead electrocardiogram (ECG) test is the primary step in diagnosing arrhythmia. Also, increased heart rate, left axis shift, and different P and QRS waveforms could be seen in the ECG during pregnancy (3).

Beta-blockers are used as first-line agents in treating cardiac arrhythmias, especially tachyarrhythmia, but there are studies suggesting cause pregnancy complications (4, 5). Beta-blockers affect the fetus by crossing the placental barrier and altering maternal cardiac output and uteroplacental flow (4). In addition, studies show that maternal arrhythmia is associated with poor obstetric outcomes (6). The aim of this study was to investigate the pregnancy outcome of patients taking beta-blockers for the treatment of cardiac arrhythmias.

MATERIALS AND METHOD

This study was a retrospective observational study involving 50 pregnant women with cardiac arrhythmias and 55 healthy pregnant women, admitted between January 1, 2020 and January 1, 2022, to Ankara City Hospital Department of Obstetrics and Gynaecology. The Ministry of Health of Republic of Turkey and the Medical Research Ethics Department of Ankara City Hospital approved the study protocol (ethics committee number: E2.23.3586). Participants who applied to the cardiology department with complaints such as heart palpitation, dizziness, and syncope were diagnosed with arrhythmia using the 12-lead ECG or 24-hour Holter monitor. The arrhythmia was defined as heart rates above 100 beats per minute (10–20 beats higher than resting during pregnancy) and abnormal P or QRS waves (7). Treatment was started with the beta-blocker diagnosis of supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, long QT syndrome, and ventricular arrhythmias. Patients diagnosed with cardiac arrhythmias, who had taken beta-blockers for at least six months before pregnancy and had no structural cardiac abnormalities were included in the study group. Multiple pregnancies, pregnant women with chronic hypertension, abnormal thyroid stimulating hormone (TSH) levels, anemia, structural heart abnormalities, smoking, and pregnant women with a body mass index (BMI) > 35 were not included in the study. Also, participants with comorbidities in the study group take no medication except beta blockers. Pregnant women with active comorbidity and using different drug groups were not included in the study to not affect the results.

The study recorded maternal age, pregestational BMI, gravidity, parity, additional maternal diseases, type and dose of beta-blocker used, and pregnancy outcomes. The gestational week was determined by last menstrual period or measurement of crown-rump length in the first trimester. Beta-blockers were classified into three groups: Metaprolol, propranolol, and bisoprolol. The use of beta-blockers was examined in two groups: high-dose and low-dose. The dosage of the drugs was calculated on the basis of expert opinions for pregnancy. High dosage was defined as > 75 mg/day for metoprolol, > 80 mg/day for propranolol, and > 10 mg/day for bisoprolol (4, 8). For pregnancy outcome, birth week, birth weight and birth weight Z-score, neonatal APGAR score, and neonatal intensive care unit (NICU) admission rates were determined (9, 10). In addition, beta human chorionic gonadotropin (bHCG) multiple of the median (MoM) and pregnancy associated plasma protein-A (PAPP-A) MoM levels were compared during the first-trimester screening tests of the pregnant women in the study and control groups.

Statistical analysis was performed using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA). Shapiro-Wilk and Kolmogorov-Smirnov tests were both used to evaluate normality of variables. Groups were compared using the Student t-test and the Mann-Whitney U test. P-values < 0.05 were considered as statistically significant. With a confidence interval of 95%, power of 80%, and sample size of 1:1, samples of at least 40 patients per group were planned (5).

RESULTS

The study enrolled 105 subjects whose baseline characteristics are given in Table 1.

Table1. Demographic data of study [median (IQR)]

	Patient (n=50)	Control (n=55)	P Values
Maternal age (years)	29 (10)	30 (8)	0.535
Maternal body mass index before pregnancy (kg/m2)	27.6 (4.5)	27.5 (6.4)	0.434
Gravidity	3 (2)	3 (2)	0.267
Parity	1 (2)	1 (2)	0.278
Nulliparity (n,%)	16 (32)	11 (20)	0.253
Assisted reproductive techniques (n,%)	1 (2)	1 (1.8)	0.946

There was no significant difference between the two groups for demographic data. The vast majority (n=39, 78%) of pregnant women taking beta-blockers used metoprolol. The number of pregnant women taking propranolol was 6 (12%), and the number of pregnant women taking bisoprolol was 5 (10%). Seventy percent of patients in the study group were using high-dose medication. In the study group, thyroid disease, asthma, and rheumatological disease were observed as maternal comorbidities (10%, 10%, and 8%, respectively).

The pregnancy and birth outcomes of the two groups are shown in Table 2.

Table2. Pregnancy and birth outcomes

	Patient (n=50)	Control (n=55)	P Values
Gestational age at birth (week)	38 (2)	39 (2)	**<0.001**
Primary cesarean delivery (n,%)	21 (42)	11 (20)	**0.007**
Emergency cesarean delivery (n,%)	8 (16)	7 (12.7)	0.542
APGAR score, first minute	8 (1)	8 (1)	0.139
APGAR score, fifth minute	8 (1)	9 (0)	**<0.001**
Birth weight (g)	3190 (745)	3370 (682)	**0.006**
Birth weight Z score	-0.11 (1.07)	-0.3 (1.44)	0.965
Neonatal intensive care unit (n,%)	12 (24.0)	1 (1.8)	**<0.001**
PAPP-A MoM	1.15 (0.63)	0.96 (0.72)	0.673
bHCG MoM	1.09 (0.72)	1.24 (0.93)	0.725

The patient group taking beta-blockers had a statistically significant earlier delivery week than the group without beta-blocker use (p= <0.001). While the rate of emergency cesarean deliveries did not differ between the two groups, the rate of primary cesarean deliveries was significantly higher in the group taking beta-blockers (p=0.007). Although birth weight was significantly lower in the beta-blocker group, no difference was found in terms of the birth weight Z-score (p=0.006 and p=0.965, respectively). APGAR score at the fifth minute was significantly lower in the study group, and NICU admission rate was significantly higher (p= <0.001 and p= <0.001, respectively). When first-trimester biomarkers were examined in both groups, no difference was found for bHCG MoM, and PAPP-A MoM levels (p=0.752 and p=0.673, respectively).

Maternal and fetal complications in the group taking beta-blockers are given in Table 3.

Table3: Maternal and fetal complications

	Patient (n=50)
Preterm delivery (n,%)	6 (12)
Pre-eclampsia (n,%)	6 (12)
Hospitalization in intensive care (n,%)	6 (12)
Fetal growth restriction (n,%)	1 (2)
Oligohydramnios (n,%)	2 (4)
Embolism (n,%)	1 (2)

The most common pregnancy complications were preterm labor, preeclampsia, and postpartum maternal admission to the intensive care unit.

In this study, the patients taking beta-blockers were divided into two groups: low-dose and high-dose beta-blocker users. Participants taking low-dose and high-dose beta-blockers were compared in terms of pregnancy and birth outcomes (Table 4). The birth weeks of the two groups were similar. Almost half (n=17, 48.5%) of the high-dose beta-blocker users underwent primary cesarean section, and 1 in 5 underwent emergency cesarean section. However, the two groups did not differ significantly in the rate of primary and emergency cesarean sections (p=0.148 and p=0.241, respectively). The mean APGAR scores at the first and fifth minutes were similar in both groups. Although birth weight was lower in the group taking high-dose beta-blockers, this difference was not statistically significant (p=0.443). The birth weight Z-score in the high-dose beta-blocker user group was -0.18, while the Z-score in the low-dose beta-blocker user group was 0.09 (p=0.323). Rates of pregnancy complications and NICU admission were also higher with high-dose beta-blocker exposure (p=0.524 and p=0.674, respectively).

DISCUSSION

Cardiac adaptation to pregnancy is one of the most important causes of maternal arrhythmias. Already in the early stages of pregnancy, plasma volume increases under the influence of the renin-angiotensin-aldosterone system (11). Ion channels are stimulated by the increase in cardiac output and tension in the cardiac structure (12). In response to the increase in plasma, there is a decrease in systemic and pulmonary vascular resistance, and vascular remodeling occurs with vasodilation (11). Systemic vascular pressure tends to decrease in the first trimester of pregnancy (13). Consequently, mean arterial pressure also changes. In addition, hormonal changes and increased sympathetic activity during pregnancy also cause an increase in heart rate (14). All these maternal changes predispose pregnant women to cardiac arrhythmias or cause pre-existing cardiac arrhythmias to worsen and become symptomatic.

The most common arrhythmias in pregnancies without structural heart anomalies are atrial fibrillation, supraventricular tachycardia, and ventricular tachycardia (15). Beta-blockers are the most commonly used drugs in treating cardiac arrhythmias in pregnancy. These drugs are divided into selective and non-selective blockers of beta receptors. The mechanisms of beta blockers are on the sympathetic system, intracellular calcium release, and nitric oxide production (16). Fetal perfusion may be affected by reduced blood pressure and the negative inotropic/chronotropic effects of beta-blockers (17). The placental barrier is a priority in protecting the fetus, but the passage of beta-blockers through this barrier also affects the fetus.

A meta-analysis showed an increased risk of fetal heart anomalies, neural tube defects, and cleft palate-lip in pregnant women using beta blockers in the first trimester (18). However, our study detected no fetal structural anomalies in pregnant women using beta-blockers.

Previous studies pointed out an increase in the rate of small for gestational age (SGA) babies, low birth weight, preterm birth, and perinatal mortality in pregnancies with beta-blocker exposure (4, 17, 19). Other studies found that the risk of preeclampsia/eclampsia, neonatal bradycardia, and hypoglycemia was increased in pregnancies taking beta-blockers (17, 20). Similar to previous studies, pregnant women with a history of drug use were found to have significantly lower birth weight and gestational week in our study. In the study group, preterm births and preeclampsia were observed, as 12% and 12% , respectively. At the same time, a high number of NICU admissions, low APGAR scores, and a high rate of primary cesarean deliveries were observed in the group of newborns with beta-blocker exposure.

In a study examining maternal arrhythmia and pregnancy prognosis, although the number of patients was small, fetal growth restriction and placental abruption were more common in the study group (6). A previous study about treated and untreated maternal cardiac arrhythmias has shown lower preterm births and higher birth weight in the treated group (21). Untreated arrhythmia is also a significant risk factor for adverse obstetric outcomes. Therefore, treatments during pregnancy should be started by considering maternal and fetal benefits.

In a previous study that examined pregnancy outcomes as a function of beta-blocker dose, high-dose drug exposure was found to increase SGA rates (4). This result is comparable to that of our study. In addition, although more primary and emergency cesarean deliveries were observed in pregnant women with high-dose beta-blocker exposure in our study, this difference was not significant, which may be due to the small number of participants.

The limitations of this study are the insufficient number of participants and the inability to examine subgroups of beta-blockers.

CONCLUSION

Beta-blockers, a first-line therapy for maternal arrhythmias, may affect fetal development and pregnancy outcomes. For this reason, it is recommended that these drugs to be administered are meticulously selected for appropriate subgroups, with lowest effective doses.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Endometriomanın preoperatif tanısında nötrofil lenfosit oranı ve platelet lenfosit oranının yararı var mıdır?

Is there any benefit of neutrophil lymphocyte ratio and platelet lymphocyte ratio in preoperative diagnosis of endometrioma?

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ÖZ

Amaç: Nötrofil lenfosit oranı ve platelet lenfosit oranı birçok hastalıkta inflamatuar ve koagülatif süreci yansıtabileceği düşüncesiyle bazı hastalıkların tanısında kullanılabileceği araştırılmıştır. Endometrioziste benzer süreçlerin rol aldığı bilinmektedir. Dolayısıyla, birçok retrospektif çalışmada bu oranların endometrioma hastalarında bir noninvazif tanı aracı olarak kullanılabilmesi yönünden incelenmiştir. Bu prospektif çalışmada nötrofil lenfosit ve platelet lenfosit oranlarının endometriomayı diğer adneksiyel kitlelerin preoperatif ayırıcı tanısında kullanılmasının yararı araştırmaya amaçlanmıştır.

Gereçler ve Yöntem: Bu çalışma Çukurova Üniversitesi Tıp Fakültesi Balcalı Hastanesi Kadın Hastalıkları ve Doğum Anabilim Dalında Jinekoloji Bölümünde Ocak 2016 ve Ocak 2023 tarihleri arasında gerçekleştirilmiştir. Çalışma prospektif gözlemsel karşılaştırmalı olarak tasarlanmıştır. Benign adneksiyel kitle ön tanısı ile operasyon planlanan hastalardan dahil edilme ve çıkarma kriterlerinden geçirildikten sonra çalışmanın analizi toplam 240 hasta ile gerçekleştirildi. Hastalar endometrioma ve diğer benign kitleler (kontrol grubu) olarak sınıflandırıldı. İki grup arasında kan tablosu değerleri, ferritin, demir ve demir bağlama kapasitesi, Nötrofil lenfosit, platelet lenfosit ve monosit lenfosit oranları istatiksel yöntemlerle karşılaştırıldı.

Bulgular: Hastaların 58'i endometrioma ve 182'si endometrioma dışı benign lezyonlar teşkil etti. Endometrioma grubunun ortalama yaşı 35.5 ± 8.52, kontrol grubunun ortalama yaşı 35.5 ± 13.8 idi (p=0.994). Endometrioma ve kontrol grubunun ortalama platelet lenfosit, nötrofil lenfosit ve monosit lenfosit oranları sırasıyla, 153.8 ± 65.84, 3.0 ± 2.30, 0.29 ± 0.14 ve 152.3 ± 90.13, 3.0 ± 2.48, 0.31 ± 0.20 olarak saptandı (p=0.910, p=0.947, p=0.481).

Sonuç: Nötrofil lenfosit ve platelet lenfosit oranlarının endometrioma ile endometrioma dışı benign adneksiyel kitlelerin arasında anlamlı bir fark tespit edilmemiştir. Dolayısıyla, çalışmamız bu parametrelerin endometriomanın preoperatif tanısında kullanılması yararlı olmayabileceğini göstermiştir.

Anahtar Kelimeler: Endometrioma, endometriozis, nötrofil lenfosit oranı, platelet lenfosit oranı. Is there any benefit of neutrophil lymphocyte ratio and platelet lymphocyte ratio in preoperative diagnosis of endometrioma?

ABSTRACT

Aim: Using neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in the diagnosis of many diseases has been investigated with the idea that it can reflect the inflammatory and coagulative process. It is known that similar processes are involved in endometriosis. Therefore, using these ratios as a noninvasive diagnostic instrument in endometrioma patients were examined in many retrospective studies. In this prospective study, it was aimed to investigate the use of NLR and PLR in the preoperative diagnosis of endometrioma.

Materials and Method: This study was carried-out between January 2016 and January 2023 in the Gynecology Department of Cukurova University. It was designed as a prospective observational comparative study. After reviewing the inclusion/exclusion criteria of the patients with a preliminary diagnosis of benign adnexal mass, the analysis was realized with 240 patients. Patients were classified as endometrioma and other benign masses (control group). Values of the blood parameters, NLR, PLR, and monocyte-lymphocyte ratio (MLR) were compared between the two groups.

Results: Fifty-eight patients were endometrioma and 182 were non-endometrioma benign lesions. The mean age of the endometrioma and control groups was 35.5 ± 8.52 and 35.5 ± 13.8, respectively (p = 0.994). The average of PLR, NLR, and MLR of the endometrioma and control groups were 153.8 ± 65.84, 3.0 ± 2.30, 0.29 ± 0.14, and 152.3 ± 90.13, 3.0 ± 2.48, 0.31 ± 0.20, p = 0.910, p = 0.910, p = 0.47 81), respectively.

Conclusion: No significant difference in neutrophil-lymphocyte or platelet-lymphocyte ratio was found between the endometrioma and non-endometrioma patients. Therefore, our study showed that these parameters may not be useful in the preoperative diagnosis of endometrioma cases.

Keywords: Endometrioma, endometriosis, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio.

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GİRİŞ

Endometriozis, endometrial dokunun endometrium dışında herhangi bir yerde görülmesi olarak tanımlanmaktadır. Overdeki formu endometrioma ve myometriumdaki adenomyozis olarak adlandırılmaktadır. Reprodüktif dönemdeki tüm kadınların %10 kadarını ve infertil kadınların %20-50'sini etkilediği tahmin edilmektedir (1-3). Endometriozis, hormonal multisistemik ve inflamatuar kronik bir hastalıktır (4). Patogenezinde immünolojik ve inflamatuar süreçlerin etkili olduğu düşünülmektedir. Endometriozisin tanısı genellikle laparoskopide yapılan gözlem ve alınan dokuların histopatolojik incelenmesi ile konulmaktadır (1, 4, 5). Çalışmalar invazif olan bu tanı işlemine alternatif bulmak için yoğunlaşmıştır. Bu amaçla birçok çalışmada rolünün olabileceği düşünülen markır ve belirteçler araştırılmıştır.

Sistemik inflamatuar ve koagülatif yanıta kan tablosunda platelet ve rölatif dolaşan beyaz küre hücrelerinde artış, nötrofili ve rölatif lenfositopeni eşlik etmektedir (5, 6). Nötrofil lenfosit oranı (NLO) ve platelet lenfosit oranı (PLO) birçok hastalıkta tanıda kullanılması açısından çalışılmıştır (7, 8). NLO ve PLO çeşitli benign ve malign jinekolojik hastalıklarda da araştırılmıştır. Endometrioziste bu inflamatuar markırların noninvazif tanı için faydalı olabileceğini kaydeden çalışmalara karşın, yarar sağlamadığını ifade eden çalışmalar da mevcuttur (3-6, 9-14). Literatürdeki bu çalışmalar farklı tasarımlara sahip ve çoğu retrospektif özelliktedir. Literatürdeki bu ikilemi gidermek için katkı sağlaması adına, prospektif kontrol grubu karşılaştırmalı dizayna dayalı bu çalışmayı planladık.

GEREÇ VE YÖNTEMLER

Bu çalışma Çukurova Üniversitesi Tıp Fakültesi Balcalı Hastanesi Kadın Hastalıkları ve Doğum Anabilim Dalında Jinekoloji Bölümünde Ocak 2016 ve Ocak 2023 tarihleri arasında gerçekleştirilmiştir. Çalışma prospektif gözlemsel karşılaştırmalı olarak dizayn edilmiştir. Çukurova Üniversitesi Tıp Fakültesi Etik Kurul Komitesinden onay alındı. Benign over kisti ön tanısı ile operasyon planlanan tüm hastalar çalışma için değerlendirildi. Gebelik tespit edilen, pelvik inflamatuar hastalık, tüberkülöz veya aktif enfeksiyon geçiren, endokrin veya immünolojik hastalığı bulunan, kronik akciğer, karaciğer veya böbrek hastalığı, Kronik inflamatuar hastalığı, bilinen kanser öyküsü ve Covid döneminde son 1 ay içinde covid-19 geçirme öyküsü olan hastalar çalışmaya dahil edilmedi. Geriye kalan tüm hastalardan operasyondan en fazla yedi gün önce preop değerlendirme kapsamında istenen kan sayımı tetkiki baz alındı. Operasyon sırasında veya sonrasında borderline veya malign patoloji tespit edilen hastalar çalışmadan çıkarıldı. Sonuçta, çalışma 58 endometrioma ve 182 diğer benign over kisti vakası olmak üzere toplamda 240 hasta ile yürütüldü.

Hastaların yaşı, başvuru nedeni ve lezyon çapı gibi klinik, operasyon şekli ve yapılan cerrahi işlem gibi operatif, patoloji ve laboratuvar bilgileri incelendi ve endometrioma ile kontrol grubu (diğer) arasında karşılaştırıldı. İki grup arasında kan tablosunda hemoglobin, hematokrit, ortalama korpus volümü, ferritin, demir ve demir bağlama kapasite değerleri, total beyaz küre, platelet, monosit, nötrofil ve lenfosit sayıları, NLO, PLO ve monosit lenfosit oranı (MLO) karşılaştırıldı. NLO mutlak nötrofil sayısının mutlak lenfosit sayısına oranı, PLO mutlak platelet sayısının mutlak lenfosit sayısına oranı ve MLO mutlak monosit sayısının mutlak lenfosit sayısına oranı olarak tanımlandı.

İstatistiksel analizler için SPSS 23.0 versiyonu kullanıldı. Tanımlayıcı analizlerin sonuçları sayı, yüzde, ortalama ± standart sapma, medyan, minimum ve maksimum değerler olarak sunulmuştur. Kategorik değişkenler arasındaki karşılaştırmalar Ki-kare ve Fisher kesin testleri kullanılarak yapıldı. Sürekli değişkenlerin karşılaştırmalarında t testi kullanıldı.

BULGULAR

Çalışma sürecinde toplam 240 hasta incelendi. Bunların 58'i endometrioma ve 182'si endometrioma dışı benign kistik lezyonlar teşkil etti. Hastaların ortalama yaşı 35.5 ± 12.78 idi. Tüm hastalara ait kan tablosu parametreleri yanı sıra klinik, cerrahi ve histopatolojik karakteristikler Tablo 1'de özetlenmiştir.

Tablo 1. Hastaların karakteristikleri.

Parametre	Ortalama±SS	Median (Minimum-Maximum)
Yaş	35.5 ± 12.78	33.5 (15 - 75)
Fe (μg/dL)	52.8 ± 27.84	54.0 (3 - 126)
Fe baglama kapasitesi (μg/dL)	322.5 ± 84.22	322.0 (113 - 505)
Hemoglobin (g/dl)	12.2 ± 1.60	12.4 (5.8 - 16.0)
Hematokrit (%)	36.5 ± 4.16	36.8 (19.3 - 47.0)
Beyaz küre sayısı, 10^3/μL	8.73 ± 5.52	7.90 (3.20 - 79.00)
Platelet sayısı, 10^3/μL	283.3 ± 92.1	275.5 (150.0 - 811.0)
Monosit sayısı, 10^3/μL	0.562 ± 0.197	0.500 (0.20 - 1.40)
MCV (fL) μm^3	81.03 ± 11.62	83.90 (3.4 - 95.7)
Nötrofil sayısı 10^3 /μL	5.37 ± 2.52	4.67 (1.43 - 15.30)
Lenfosit sayısı 10^3/μL	2.09 ± 0.735	2.10 (0.40 - 4.00)
PLO	152.6 ± 84.85	132.2 (8.2 - 901.1)
NLO	3.04 ± 2434	2.36 (0.66 - 22.75)

MLO	0.30 ± 0.189	0.25 (0.09 - 175)
		N (%)
Patoloji	**Endometrioma**	58 (24.2)
	Seröz	51 (21.3)
	Dermoid	27 (11.3)
	Müsinöz	33 (13.8)
	Diğer	71 (29.4)
Yer	**Sağ**	84 (35.0)
	Sol	119 (49.6)
	Bilateral	37 (15.4)
Ameliyat Şekli	**Laparoskopi**	140 (58.3)
	Laparatomi	100 (41.7)
Yapılan Operasyon	**Biyopsi**	6 (2.5)
	Kistektomi	141 (58.8)
	Ooferektomi	86 (35.8)
	Diğer	7 (2.9)
Basvuru Nedeni	**Pelvik Ağrı**	135 (56.5)
	İnfertilite	22 (9.2)
	Şişkinlik/Kitle	73 (30.5)
	Diğerleri	10 (3.8)
Boyut	**<5 cm**	54 (22.5)
	5-10 cm	126 (52.5)
	>10 cm	60 (25.0)

SS: Standart sapma, Fe: demir, PLO: Platelet lenfosit oranı, NLO: Nötrofil lenfosit oranı, MLO: Monosit lenfosit oranı.

Sırasıyla medyan hemoglobin ve hematokrit değerleri 12.4 ve 36.8 idi. Ortalama platelet sayısı 283.3 ± 92. 1 bin idi. Ortalama nötrofil sayısı 5.37 ± 2.52 bin idi. Ortalama lenfosit sayısı 2.09 ± 0.735 bin idi. Kasık veya alt karın ağrısı en sık kaydedilen başvuru şikayeti idi. Endometrioma dışı patolojilerden en sık 51 vaka (%21.3) ile seröz kist adenomlar tespit edildi. Ardından müsinöz kistadenomlar (%13.8) ve dermoid kistler (%11.3) yer aldı. Hastaların yaklaşık yarısının (%52.5) lezyon çapları 5-10 cm olarak ölçüldü. Lezyonların yaklaşık yarısı kadar (%49.6) sol over kökenli ve %15.4'ü bilateral idi. Hastaların yarısından fazlasında laparoskopik cerrahi uygulandı ve kistektomi en çok tercih edilen cerrahi yöntem idi.

Yaş, demir, demir bağlama kapasitesi, ferritin değerleri ve kan tablosu parametrelerinin yanı sıra klinik ve cerrahi özelliklerinin endometrioma ve kontrol grubu arasındaki karşılaştırmaları Tablo 2'te gösterilmiştir.

Tablo 2. Endometrioma ve kontrol grubunun karşılaştırılması.

Parametre	Endometrioma	Diğer	P	
	Ortalama±SS			
Yaş	35.5±8.52	35.5±13.88	0.994	
Demir (μg/dL)	50.0±32.82	53.8±26.38	0.700	
Demir_bağlama (μg/dL)	336.6±104.23	318.0±78.18	0.552	
ferritin	47.141±59.2250	35.959±41.5247	0.501	
Hemoglobin (g/dl)	12.06±1.482	12.25±1.644	0.431	
Hematokrit (%)	36.57±3.946	36.52±4.242	0.929	
Beyaz Küre Sayısı 10^3/μL	8.343±2.5707	8.856±6.1744	0.539	
Platelet Sayısı 10^3/μL	297.2±97.28	278.9±90.27	0.187	
Monosit Sayısı 10^3/μL	.554±.1664	.564±.2072	0.717	
MCV (fL) μm^3	81.57±7.555	80.86±12.667	0.687	
Nötrofil sayısı 10^3 /μL	5.367±2.3835	5.377±2.5766	0.980	
Lenfosit sayısı 10^3 /μL	2.164±.7637	2.076±.7270	0.447	
PLO	153.804±65.8490	152.305±90.1358	0.910	
NLO	3.022±2.3044	3.047±2.4805	0.947	
MLO	0.293±.1441	0.314±.2016	0.481	
		N (%)		
Boyut	**<5cm**	22 (37.9)	32 (17.8)	0.003
	5-10cm	98 (54.4)		
	>10cm	51 (27.8)		
	28 (48.3)			
	9 (13.8)			
Yer	**Sağ**	19 (32.8)	65 (35.7)	0.104
	Sol	94 (51.6)		
	Bilateral	23 (12.6)		
	25 (43.1)			
	14 (24.1)			
Ameliyat Şekli	**Laparoskopi**	37 (63.8)	103 (56.6)	0.333
	Laparatomi	79 (43.4)		
	21 (36.2)			
Operasyon	**Tanısal+ Biyopsi**	1 (1.7)	5 (2.7)	0.623
	Kistektomi	103 (56.6)		
	Ooferektomi	69 (37.9)		
	Diğer	5 (2.7)		
	38 (65.5)			
	17 (29.3)			
	2 (3.4)			
Başvuru nedeni	**Kasık Ağrısı**	31 (53.4)	104 (57.5)	<0.001
	İnfertilite	7 (3.9)		
	Şişkinlik/Kitle	61 (33.6)		
	Diğerleri	10 (5.0)		
	15 (25.9)			
	12 (20.7)			
	0 (0.0)			

SS: Standart sapma, PLO: Platelet lenfosit oranı, NLO: Nötrofil lenfosit oranı, MLO: Monosit lenfosit oranı

Karşılaştırılan tüm parametrelerde, gruplar arasında anlamlı farklılık saptanmamıştır. Endometrioma grubunun ortalama yaşı 35.5 ± 8.52, kontrol grubunun ortalama yaşı 35.5 ± 13.8 idi (p=0.994). Ortalama hemoglobin değerleri sırasıyla, endometrioma grubunda 12.0 ± 1.48 ve kontrol grubunda 12.2 ± 1.64 olarak ölçüldü (p= 0.431). Endometrioma ve kontrol grubunun PLO, NLO ve MLO değerleri sırasıyla, 153.8 ± 65.84, 3.0 ± 2.30, 0.29 ± 0.14 ve 152.3 ± 90.13, 3.0 ± 2.48, 0.31 ± 0.20 olarak saptandı ve bu oranlar gruplar arasında anlamlı farklılığa sahip değildi. Lezyonun boyutu, hastaların başvuru nedeni ve cerrahi endikasyonları incelendiğinde gruplar arasında istatistiksel anlamda farklılık saptanırken, lezyonun lokalizasyonu, cerrahinin şekli ve yapılan operasyon açısından farklılık saptanmamıştır.

TARTIŞMA

Bu çalışma endometrioma vakaları ile diğer overyan benign kitleleri arasında demir, ferritin, hemoglobin ve hematokrit değerleri, nötrofil, monosit, lenfosit ve platelet sayıları açısından fark olmadığını göstermiştir. Ayrıca, inflamatuar ve koagülatif süreçleri işaret edebileceği varsayılan NLO ve PLO arasında da fark bulunmadığını ortaya koymuştur.

Cho ve arkadaşları, 231 endometriozis, 145 benign over tümörü ve 384 sağlıklı kontrol hastası ile yapılan retrospektif çalışmalarında, NLO'nun endometriozis grubunda diğer benign over tümörü ve sağlıklı bireylere göre daha yüksek saptadıklarını raporlamışlar ve NLO'nun endometriozis tanısında bir tanı aracı olarak kullanılabileceğini savunmuşlardır (3). Benzer tasarımda bir başka çalışmada, evre 3-4 endometriozis hastalarında diğer benign tümörlü ve normal sağlıklı hastalara göre NLO'nun daha yüksek olduğu ve evre 3-4 endometriozis tanısında değerli olduğu rapor edilmiştir (11). Bu çalışmaların retrospektif olması en önemli dezavantajı ve çalışmamızdan en önemli farkıdır. Yavuzcan ve arkadaşları 33 endometrioma, 28 endometrioma dışı benign adneksiyel kitle ve 33 tubal ligasyon amacıyla yapılan laparoskopi vakalarını incelemiş ve karşılaştırmışlar. Tüm gruplar karşılaştırıldığında, NLO ve PLO değerleri arasında anlamlı fark saptamamış ve sonuç olarak NLO ve PLO'nun ileri endometriozis hastalarında yararlı olmadığı görüşüne varmışlardır (14). Kim ve arkadaşları, 419 endometrioma hastası ile yaptıkları çalışmada hastaları laparoskopide evresine göre sınıflandırıp NLR ile endometriozisin şiddeti arasında korelasyonun olmadığı sonucuna varmışlar (4). Bu çalışmaların sonuçları bizim çalışmanın sonuçları ile uyumludur. Diğer yandan, PLO özellikle CA-125 değerleri ile kombine edildiğinde yapışıklıkların olduğu şiddetli endometriozis vakalarında noninvazif tanı aracı olarak kullanılabileceği raporlayan çalışmalar mevcuttur (15, 16). Yine de bu çalışmaların retrospektif olması, sonuçlarının bağlayıcılığı hususunda önemli handikap olarak karşımıza çıkmaktadır.

Sonuç olarak, NLO ve PLO endometriozis tanısında kullanılması bakımından literatürün önemli karışıklık barındırdığı aşikardır. Bizim çalışmamızın nispeten yeterli hasta içermesi ve prospektif tasarımı ile bu karışıklığın giderilmesi yönünde önemlidir. Çalışmamız sağlıklı kadın grubu içermemesi bir eksiklik olarak düşünülebilir, ancak bu markırların özellikle adneksiyel kitlesi olan hastaların ayırıcı tanısında kullanılması konsepti göz önünde bulundurulduğunda, sağlıklı kadınların dahil edilmesinin yararı olmadığı düşüncesindeyiz.

Sonuç

Çalışmamız, NLO ve PLO'nun endometriomayı diğer benign kitlelerden bir preoperatif ayırıcı tanı aracı olarak kullanılması yararlı olmadığı göstermiştir.

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Jinekolojik Maligniteler Sebebiyle Yapılan Distal Pankreatektominin Erken Dönem Komplikasyonlarının İncelenmesi

Investigation of Early Complications of Distal Pancreatectomy Performed For Gynecologic Malignancies

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ÖZ

Amaç: Bu çalışmada jinekolojik maligniteler sebebiyle distal pankreatektomi yapılan hastaların erken dönem komplikasyonlarının sunulması amaçlandı.

Gereçler ve Yöntem: Kliniğimizde jinekolojik kanserler nedeniyle distal pankreatektomi yapılan sekiz hasta çalışmaya dâhil edildi. Hastaların demografik, klinik, cerrahi ve patolojik özellikleri, adjuvan tedavi durumu ve rekürrens/sağkalım sonuçları hasta dosyalarından, patoloji raporlarından ve elektronik kayıt sistemi üzerinden retrospektif olarak elde edildi. Pankreatik fistül tanısı hastaların klinik bulguları, laboratuvar ve görüntüleme yöntemleri ile tanımlandı.

Bulgular: Yedi (%87.5) hastada tümör overden, bir (%12.5) hastada ise endometriumdan köken almaktaydı. Tümörün histolojik tipi over kanseri hastalarında yüksek dereceli seröz ovarian karsinom (high grade serous ovarian cancer; HGSOC) ve endometrium kanseri hastasında seröz karsinomdu. İki (%25) hastada operasyona sekonder pankreatik fistül gelişti. Bu iki hastada pankreatik fistül, drenaj ve antibiyotik tedavisi ile çözüldü.

Sonuç: Metastatik ileri evre jinekolojik kanserlerde rezidü tümörsüz sitoredüksiyon sağlayabilmek için gerektiğinde distal pankreatektomi yapılabilir. Pankreatik fistül distal pankreatektomi sonrası ortaya çıkabilen nispeten yaygın bir komplikasyondur. Bu durumun zamanında ve doğru teşhis edilmesi ve minimum morbiditeyle başarılı bir şekilde tedavi edilmesine olanak sağlar.

Anahtar kelimeler: Distal pankreatektomi, jinekolojik malignite, pankreatik fistül

ABSTRACT

Aim: To present the early complications of patients who underwent distal pancreatectomy for gynecologic malignancies.

Materials and Method: Eight patients who underwent distal pancreatectomy for gynecologic cancers in our clinic were included in the study. Demographic, clinical, surgical and pathological characteristics of the patients, adjuvant treatment status and recurrence/survival results were obtained retrospectively from patient files, pathology reports and the electronic record system. The diagnosis of pancreatic fistula was defined by the patients' clinical findings, laboratory and imaging methods.

Results: The tumor developed from the ovary in seven (87.5%) patients and from the endometrium in one (12.5%) patient. The histological type of the tumor was high-grade serous ovarian cancer (HGSOC) in ovarian cancer patients and serous carcinoma in endometrial cancer patients. Two patients (25%) had a pancreatic fistula as a result of the surgery. In these two patients, pancreatic fistula resolved with drainage and antibiotic treatment.

Conclusion: Distal pancreatectomy can be performed when necessary to achieve cytoreduction without residual tumor in metastatic advanced gynecological cancers. Pancreatic fistula is a relatively common complication that can occur after distal pancreatectomy. This allows the condition to be diagnosed timely and accurately and treated successfully with minimal morbidity.

Keywords: Distal pancreatectomy, gynecologic malignancy, pancreatic fistula

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GİRİŞ

Jinekolojik malignitelere bağlı ölümlerin başında ileri evre over kanseri gelmektedir (1). İleri evre hastalıkta sağkalım sonuçlarını iyileştiren en önemli faktörün cerrahi sonrasında 1 cm altı rezidü tümör ya da rezidü tümörsüz sitoredüksiyon olduğu gösterilmiştir (2, 3).

Rezidü tümörü en aza indirmek için kapsamlı sitoredüktif cerrahi prosedürler, primer veya nüks jinekolojik kanserin cerrahi tedavisinde önemlidir (4). Bu nedenle, kalın ve ince barsak rezeksiyonunun, diyafragmanın soyulmasının ve/veya rezeksiyonunun, distal pankreatektominin, splenektominin ve diğer solid organ rezeksiyonlarının cerrahi prosedüre eklenmesi sıklıkla gerekli olmaktadır.

Over kanseri peritoneal yayılım gösterdiğinden pankreas metastazı sık olup yaklaşık %7 oranında görülebilmektedir (5-9). Endometrium kanserinin pankreasa yayılımı ise çok nadirdir ve çoğunlukla olgu sunumları şeklindedir (10-12). Pankreasın kuyruğu anatomik olarak dalak hilusuna uzanım göstermektedir. Dalak hilusunu tutan tümörlerde tümörsüz cerrahi alan elde edebilmek için splenektomiye ilave distal pankreatektomi gerekebilmektedir (13). Bu nedenle jinekolojik onkoloji cerrahisi pratiğinde distal pankreatektominin yeri önemlidir. Ancak, distal pankreatektomi sonrası pankreatik fistül, hemoraji, kalıcı diabet gelişmesi, gecikmiş mide boşalması, pankreatit gibi komplikasyonlar görülebilmektedir (14).

Bu çalışmada jinekolojik maligniteler sebebiyle distal pankreatektomi yapılanların erken dönem komplikasyonlarının sunulması amaçlandı.

GEREÇ VE YÖNTEMLER

Eylül 2019 ile Aralık 2023 tarihleri arasında kliniğimizde opere edilenlerin sonuçları retrospektif olarak incelendi. Sitoredüktif cerrahi için ek prosedür olarak distal pankreatektom yapılanlar çalışmaya dahil edildi. Jinekolojik orjin dışı maligniteye sahip olanlar çalışma dışı bırakıldı. Çalışma için Etik Kurul'dan onay alındı (E2-23-5427).

Jinekolojik kanserler nedeniyle distal pankreatektomi yapılan dokuz hastanın sonuçları incelendi. Bir hastada postoperatif 24 saat içinde pulmoner tromboemboliye bağlı ölüm gerçekleşmesi nedeniyle çalışma dışı bırakıldı ve sekiz hasta dahil edildi. Hastaların demografik özellikleri, preoperatif ve/veya neoadjuvan kemoterapi öncesi CA 125 değeri (IU/ml), tümörün primer organı ve tümör tipi, preoperatif neoadjuvan kemoterapi durumu, ameliyat özellikleri ve yapılan cerrahi girişimler, postoperatif hastanede kalış süresi, adjuvan tedavi durumu ve rekürrens/sağkalım sonuçları hasta dosyalarından, patoloji raporlarından ve elektronik kayıt sistemi üzerinden retrospektif olarak elde edildi. Pankreatik fistül tanısı hastaların klinik bulguları, laboratuvar ve görüntüleme yöntemleri (bilgisayarlı tomografi) ile tanımlandı.

Tüm istatistiksel analizler, SPSS (Statistical Package for the Social Sciences) Windows 22.0 sürümü ile yapıldı. Tanımlayıcı değerler aritmetik ortalama±standart sapma, ortanca ve yüzde olarak ifade edildi.

BULGULAR

Hastaların ortanca yaşı 60 yıldı (aralık, 56-75). Tedavi öncesi ortanca CA 125 değeri 1452 IU/ml'ydi (aralık, 5-5404). Yedi (%87.5) hastada tümör overden, bir (%12.5) hastada ise endometriumdan köken almaktaydı. Tümörün histolojik tipi over kanseri hastalarında yüksek dereceli seröz ovarian karsinom (high grade serous ovarian cancer; HGSOC) ve endometrium kanseri hastasında seröz karsinomdu. Bir (%12.5) hastaya rekürrens, yedi (%87.5) hastaya primer hastalık nedeniyle sitoredüksiyon cerrahisinin uygulanmış olduğu belirlendi. Ek olarak, dört (%50) hastanın neoadjuvan kemoterapi almış olduğu saptandı (Tablo 1).

Tablo 1. Distal pankreatektomi yapılan hastaların genel özellikleri

Özellikler		Ortanca	Aralık
Tanı anında yaş (yıl)		60	56-75
Tedavi öncesi CA 125 değeri (IU/ml) [1]		1452	5-5404
Hastanede kalış süresi (gün)		11	8-55
		n	**%**
Primer organ	Endometrium	1	12.5
	Over	7	87.5
Neoadjuvan kemoterapi	Uygulanmadı	4	50
	Uygulandı	4	50
Hastalık durumu	Primer hastalık	7	87.5
	Rekürren hastalık	1	12.5
Postoperatif antibiyotik ihtiyacı	Hayır	2	25
	Evet	6	75
Pankreasta tümör mevcudiyeti	Hayır	3	37.5
	Evet	5	62.5
Splenektomi	Uygulanmadı	1	12.5
	Uygulandı	7	87.5
Dalakta tümör mevcudiyeti [2]	Hayır	2	28.58
	Evet	5	71.42
Kardiyofrenik lenfadenektomi	Hayır	5	62.5
	Evet	3	37.5
Ek solid organ rezeksiyonu [3]	Yok	-	-
	Var	8	100
Pankreatik fistül	Hayır	6	75
	Evet	2	25

[1]: Preoperatif ya da neoadjuvan kemoterapi
[2]: Splenektomi yapılan 7 hasta değerlendirildi
[3]: Splenektomi hariç

Distal pankreatektomi yapılan sekiz hastanın beşinde (%62.5) pankreasta tümör mevcuttu. Yedi (%87.5) hastaya splenektomi uygulandı ve bunların beşinde (%71.42) dalakta tümör saptandı. Sekiz (%100) hastada splenektomi dışında ek solid organ rezeksiyonuna ihtiyaç duyuldu. İki (%25) hastada operasyona sekonder pankreatik fistül gelişti. Bu iki hastada pankreatik fistül, drenaj ve antibiyotik tedavisi ile çözüldü. Hastalardan biri 19 gün sonunda, diğeri ise 55 gün sonunda sağlıklı olarak taburcu oldu (Tablo 1, Tablo 2).

Tablo 2. Hastaların klinik, patolojik ve cerrahi özelliklerinin dökümü

Hasta no	Yaş	CA 125 değeri[1]	Primer organ	Tümör tipi	Hastalık durumu	Neoadjuvan kemoterapi	Pankreasta tümör mevcudiyeti	Splenektomi	Ek solid organ rezeksiyon	Pankreatik fistül
1	56	5404	Over	HGSC	Primer	Uygulandı	Hayır	Evet	Karaciğer metastezektomi, kolektomi	Hayır
2	75	2010	Over	HGSC	Primer	Uygulandı	Evet	Evet	Kolektomi, kardiofrenik lenfadenektomi, apendektomi	Hayır
3	72	5	Over	HGSC	Rekürren	Uygulanmadı	Hayır	Evet	Karaciğer metastezektomi, kolektomi, kolesistektomi	Hayır
4	60	1777	Over	HGSC	Primer	Uygulandı	Evet	Evet	Kolektomi	Hayır
5	57	341	Over	HGSC	Primer	Uygulanmadı	Evet	Evet	Kolektomi, kardiofrenik lenfadenektomi, apendektomi, diafram tam kat rezeksiyon	Evet
6	60	1128	Endometrium	SC	Primer	Uygulanmadı	Hayır	Evet	Apendektomi	Evet
7	71	2591	Over	HGSC	Primer	Uygulandı	Evet	Evet	Kolektomi, ileum rezeksiyonu	Hayır
8	57	913	Over	HGSC	Primer	Uygulanmadı	Evet	Hayır	Karaciğer metastezektomi, kardiofrenik lenfadenektomi, apendektomi	Hayır

SC: Seröz karsinom

[1] Preoperatif ya da neoadjuvan kemoterapi

Hastaların tedavi ve sağkalım sonuçları tablo 3'te detaylı olarak sunuldu. Neoadjuvan tedavisi verilen dört hastanın kemoterapi kombinasyonu olarak karboplatin ve paklitaksel almış olduğu belirlendi. Altı hastanın adjuvan tedavi verilerine ulaşıldı. Beş hastaya karboplatin-paklitaksel ve bir hastaya karboplatin-paklitaksel-etoposid kemoterapi kombinasyonunun verilmiş olduğu görüldü. Takiplerinde üç hastada pankeas dışı solid organlarda rekürrens gelişti. Takiplerde dört hastada mortalite izlendi.

Tablo 3. Hastaların neoadjuvan tedavi, adjuvan tedavi, sağkalım ve rekürrens verileri

Hasta no	Neoadjuvan kemoterapi	Neoadjuvan kür sayısı	Adjuvan tedavi	Rekürrens	Rekürrens yeri	Mortalite	Takip süresi (ay)
1	Karboplatin- paklitaksel	3	Karboplatin- paklitaksel	Yok	-	Hayır	41
2	Karboplatin- paklitaksel	3	Karboplatin- paklitaksel	Var	Aksillar lenf nodu ve karaciğer	Evet	9
3	-	-	Karboplatin- paklitaksel	Yok	-	Hayır	3
4	Karboplatin- paklitaksel	4	*	Yok	-	Evet	1
5	-	-	Karboplatin- paklitaksel	Yok	-	Hayır	6
6	-	-	Karboplatin- paklitaksel-etoposid	Var	Paratrakeal lenf nodu ve subrakinal lenf nodu	Evet	22
7	Karboplatin- paklitaksel	3	Karboplatin- paklitaksel	Var	Akciğer, karaciğer, kemik ve mide	Evet	14
8	-	-	*	Yok	-	Hayır	1

*Dış merkezde tedavisini devam ettirdiğinden bilgilerine ulaşılamadı

TARTIŞMA

Over ve endometrium kanseri hastalarında sağkalım sitoredüksiyonla elde edilen sonuçla doğrudan ilişkilidir. Rezidü tümörün bırakılmadığı sitoredüksiyon sağlanabilmesi için solid organ rezeksiyonunu içeren majör cerrahi girişim gerekebilmektedir. Distal pankreatektomi bu amaçla cerrahi prosedüre eklenmektedir. Sunduğumuz çalışmada, tümörün hastaların %87.5'inde overden, %12.5'inde ise endometriumdan köken aldığı ve hastaların %62.5'inde pankreasta tümörün mevcut olduğu belirlendi. Distal pankreatektom hsonrası %25 hastada pankreatik fistülün geliştiği ve bu durumun drenaj ve antibiyotik tedavisiyle çözüldüğü görüldü.

Distal pankreatektomiye bağlı postoperatif pankreatik fistül %22-26 oranında görülmektedir (15, 16). Risk faktörleri preoperatif, intraoperatif ve postoperatif olarak üç gruba ayrılabilir. Preoperatif risk faktörleri; ileri yaş, diyabet, kronik pankreatit, obezite, yumuşak pankreas dokusuna sahip olmak, intraoperatif risk faktörleri; uzamış operasyon süresi, artmış kan kaybı, cerrahi deneyim, postoperatif risk faktörleri; pankreatit geçirmek olarak tanımlanabilir (17). Sunulan çalışmamızda pankreatik fistülün geliştiği iki hastada ileri yaş, uzamış operasyon süresi ve artmış kan kaybı risk faktörü olarak bulunmaktaydı.

Uluslararası pankreas cerrahisi çalışma grubu postoperatif pankreatik fistül tanımını drenaj sıvısında amilaz değerinin yükselmesi olarak tanımlar ve ciddiyetine göre A, B ve C olarak derecelendirir (18). "A", klinik olarak anlamlı kabul edilmez ve sadece biyokimyasal sızıntı olarak tanımlanır. "B", antibiyoterapi ve drenaj ihtiyacının olması olarak tanımlanır. "C" ise tekrar operasyon ihtiyacı gelişmesi, organ kaybı gelişmesi ve mortalite ile tanımlanır. Ertürk ve ark.'larının yaptığı 13 distal pankreatektomi yapılan over kanseri hastasının sonuçlarının incelendiği çalışmada, hastaların birinde relaparatomi ihtiyacı olan pankreatik fistül gelişmiş ("C") (8). Sunulan çalışmamızdaysa, iki hastada distal pankreataektomiye bağlı fistül gelişti. Bu iki hastada sorun antibiyoterapi ve drenajla çözüldü. Fistülün derecesi, "B" olarak tanımlandı.

Çalışmanın en önemli kısıtlayıcı noktası hasta sayısıdır. Bu nedenle özellikle fistül için risk faktörleri istatistiksel olarak değerlendirilememiştir. Ancak rezidü tümörsüz sitoredüksiyon sağlanması için deneyim gerektiren üst batın cerrahilerinin yapılabilirliğini ve komplikasyonlarının yönetimini vurgulaması yönünden önemli katkılar sağlamaktadır.

SONUÇ

Metastatik ileri evre jinekolojik kanserlerde rezidü tümörsüz sitoredüksiyon sağlayabilmek için gerektiğinde distal pankreatektomi yapılabilir. Pankreatik fistül distal pankreatektomi sonrası ortaya çıkabilen nispeten yaygın bir komplikasyondur. Bu durumun zamanında ve doğru teşhis edilmesi ve minimum morbiditeyle başarılı bir şekilde tedavi edilmesine olanak sağlar.

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Gebeliğin İntrahepatik Kolestazında Serum Midkine Düzeyinin Değerlendirilmesi: Üçüncü Basamak Bir Merkezde Vaka-Kontrol Çalışması

Evaluation of serum midkine level in intrahepatic cholestasis of pregnancy: a case-control study in a tertiary center

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ÖZ

Amaç: Gebeliğin intrahepatik kolestazı (ICP) tanısı alan kadınlarda midkine düzeylerini araştırmak.

Gereç ve Yöntem: Bu çalışma 40'ı ICP (çalışma grubu) ve 72'si kontrol grubu olmak üzere toplam 112 gebe üzerinde yapıldı. İki grup demografik özellikler, obstetrik veriler, laboratuvar parametreleri ve serum midkine düzeyleri açısından karşılaştırıldı. Ayrıca, çalışma grubunda midkine düzeyi ile aspartat aminotransferaz (AST), alanin aminotransferaz (ALT) ve serum safra asidi (SBA) değerleri arasında bir korelasyon analizi yapıldı.

Bulgular: Midkine değeri çalışma grubunda 0.495 ng/ml ve kontrol grubunda 0.275 ng/ml olarak tespit edildi. Midkine düzeyi kolestazlı hastalarda istatistiksel olarak anlamlı derecede yüksekti ($p<0.001$). Midkine düzeyi ile SBA veya transaminaz değerleri arasında korelasyon bulunmadı. ROC analizine göre, ICP için midkine kesme değeri 0,345 ng/ml alındığında; özgüllük: %70; duyarlılık: %70 bulundu.

Sonuç: Kolestazlı gebelerde serum midkine düzeyi daha yüksek bulundu, ancak maternal midkine düzeyi ile SBA düzeyi arasında korelasyon bulunmadı.

Anahtar Kelimeler: Serum Safra Asidi, Kolestaz, ICP, Karaciğer Enzimleri, Midkine

ABSTRACT

Aim: To investigate midkine levels in women diagnosed with intrahepatic cholestasis of pregnancy (ICP).

Materials and Method: This study was conducted with 112 pregnant women, 40 of whom had ICP (study group) and 72 were in the control group. The two groups were compared regarding demographic characteristics, obstetric data, laboratory parameters, and serum midkine levels. In addition, a correlation analysis was undertaken between the midkine level and aspartate aminotransferase (AST), alanine aminotransferase (ALT), and serum bile acid (SBA) values in the study group.

Results: The midkine value was determined to be 0.495 ng/ml in the study group and 0.275 ng/ml in the control group. It was statistically significantly higher in the patients with cholestasis ($p<0.001$). No correlation was found between the midkine level and the SBA or transaminase values. According to the receiver operating characteristic analysis, the midkine cut-off value for ICP was 0.345 ng/ml (specificity: 70%; sensitivity: 70%).

Conclusion: The serum midkine level was found to be higher in pregnant women with cholestasis, but there was no significant relationship between the maternal midkine level and the SBA level.

Keywords: Serum Bile Acid, Cholestasis, ICP, Liver Enzymes, Midkine

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease in pregnancy. It usually presents in the form of itching that starts in the last trimester of pregnancy. It is characterized by increased liver enzymes and increased serum bile acid (SBA≥ 10 µmol/L) in laboratory tests (1). In addition to many factors such as environmental effects, hormonal changes, and genetic variations, the activation of inflammatory cells and uptake of proinflammatory cytokines into the liver also plays a role in the pathogenesis of ICP (2,3). ICP is associated with adverse pregnancy outcomes. Furthermore, many hepatobiliary diseases and hepatocellular carcinoma have been reported to be more common in women with a history of cholestasis during pregnancy (4). So, knowing the underlying pathology in cholestasis patients can shed light on liver diseases that may occur in the future.

Midkine was first identified in 1988, being defined as the product of the retinoic acid-responsive gene involved in embryogenesis (5). Midkine is a heparin-binding secreted growth factor protein that plays an important role in cell growth and angiogenesis (6). It promotes the migration of macrophages and neutrophils, which is crucial for inflammation. In addition, midkine suppresses the development of regulatory T cells, and therefore it may be a molecular target for treating or preventing inflammatory diseases (7).

In the present study, we aimed to investigate midkine levels in women diagnosed with ICP and evaluate its correlation with the SBA level.

MATERIALS AND METHOD

This prospective study was conducted with a total of 112 participants. Pregnant women diagnosed with ICP according to the diagnostic criteria (study group) (n = 40) were compared with a control group of gestational age-matched pregnant women without any identified risk factors (n = 72). Written informed consent was obtained from all the participants. Approval for the study was obtained from the local ethics committee (E2-21-725), and the study was conducted in accordance with the ethical standards and principles of the Declaration of Helsinki. The two groups were compared in terms of demographic characteristics, obstetric data, laboratory parameters, and midkine levels. In addition, a correlation analysis was performed between midkine and the aspartate aminotransferase (AST), alanine aminotransferase (ALT), and SBA values in the study group.

Patient selection

The diagnostic criteria for ICP were defined as follows: unexplained pruritus develops during pregnancy and abnormal liver function tests and/or bile acids are elevated, both of which resolve after delivery (8). While evaluating all the cases, viral hepatitis serology screening and abdominal ultrasonography were undertaken to rule out other liver diseases. Patients with chronic liver or skin disease, allergic diseases, symptomatic cholelithiasis, elevated liver enzymes after viral hepatitis, preeclampsia, or acute fatty liver of pregnancy were excluded from the study.

Biological samples and analyses

Venous blood samples were obtained from each participant by venipuncture at the gestational week of diagnosis time. Blood samples were collected from all participants at a similar gestational week before delivery. Immediately after the blood sample was taken, it was centrifuged at 3,000 g for 15 minutes. Plasma was aliquoted in plastic tubes and stored at -80 °C until the analysis day. Midkine level measurements were made using the enzyme-linked immunosorbent assay method (Human Midkine Elisa Kit, Bioassay Technology Laboratory) following the manufacturer's instructions for the use of the commercial kit. The researcher who performed the tests evaluated the results of clinical data in a blinded manner.

Statistical analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS v. 22, IBM SPSS Statistics for Windows, Version 22.0 Armonk, NY: IBM Corp.). Visual and analytical methods (Kolmogorov-Smirnov test) were used to determine whether the variables were normally distributed. Descriptive statistics were presented as median and interquartile range values for non-normally distributed variables. Since continuous variables were not normally distributed, the Mann-Whitney U-test was conducted to compare the median values between the groups. A correlation analysis was undertaken using Spearman's rho test. The receiver operating characteristic (ROC) curve was constructed to evaluate the performance of the midkine in women diagnosed with ICP. A two-tailed p-value of <0.05 was considered statistically significant.

RESULTS

A total of 112 pregnant women were included in the study (40 patients with ICP in the study group and 72 controls). When the

study and control groups were examined in terms of demographics and obstetrics, they were found to be similar (p> 0.05). The AST and ALT values were significantly higher in the study group (p <0.001). The mean midkine value was 0.275 ng/ml in the control group and 0.495 ng/ml in the study group. The midkine value was statistically significantly higher in the patients with ICP (p <0.001) (Table 1).

Table 1: Comparison of demographic, obstetric, and laboratory parameters of the groups

	Control group (n = 72)		Study group (n = 40)		p
	Median	IQR	Median	IQR	
Age (year)	**29**	**10.75**	**28**	**7**	**0.959**
Body mass index (kg/m2)	**29.3**	**7.63**	**26.9**	**6.15**	**0.216**
Gravity	**2**	**3**	**2**	**2**	**0.095**
Parity	**1**	**2**	**0**	**2**	**0.156**
Miscarriage	**0**	**1**	**0**	**0**	**0.227**
Gestational age at diagnosis (weeks)	**36**	**7.75**	**36**	**2.75**	**0.959**
Estimated fetal weight (g)	**2492**	**945**	**2594**	**598**	**0.597**
Single deepest vertical pocket (mm)	**52**	**16**	**50**	**14.75**	**0.595**
AST (U/L)	**16**	**4.8**	**59**	**44**	**<0.001**
ALT (U/L)	**14**	**6.2**	**75**	**68**	**<0.001**
Serum Midkine level (ng/ml)	**0.275**	**0.21**	**0.495**	**0.51**	**<0.001**

Mann-Whitney U

IQR: Interquartile range, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

The correlations between the midkine, SBA, AST, and ALT values were examined. Although there was a positive significant correlation between AST and ALT, no correlation was observed between midkine and SBA, or between these two parameters and AST or ALT (Table 2).

Table 2: Non-parametric correlations between midkine, SBA, AST, and ALT

		Midkine	SBA	AST	ALT
Midkine	Correlation coefficient	1.000	-.066	.093	.043
	Sig. (two-tailed)	-	.688	.568	.790
SBA	Correlation coefficient	-.066	1.000	.242	.216
	Sig. (two-tailed)	.688	-	.133	.181
AST	Correlation coefficient	.093	.242	1.000	.912**
	Sig. (two-tailed)	.568	.133	-	.000
ALT	Correlation coefficient	.043	.216	.912**	1.000
	Sig. (two-tailed)	.790	.181	.000	-

**Correlation significant at the 0.01 level (two-tailed). Spearman's rho

SBA: Serum bile acid, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase,

n the receiver operating characteristic (ROC) analysis, at a cut-off of 0.345 ng/ml, midkine had specificity and sensitivity values of 70% and 70%, respectively for ICP (Table 3).

	Cut-off	AUC	P	95% CI	Sensitivity	Specificity
Midkine	0.345	77.3	<0.001	0.686-0.86	70%	70%

AUC: Area under the curve, CI: Confidence interval

DISCUSSION

In this study, we investigated the maternal serum midkine level in a group of patients with ICP and compared the results with a control group with uncomplicated pregnancies. We found that when compared to the healthy control group, the midkine levels were statistically significantly higher in the patients with ICP, which develops on an inflammatory basis and is the most common liver disease in pregnancy. In our ROC analysis to determine the increased risk of ICP, we determined the cut-off value as 0.345 ng/ml, at which specificity and sensitivity were 70% and 70%, respectively. When we examined the correlation of the midkine level with SBA, AST, and ALT, we found no significant correlation.

Midkine is a biochemical marker found in small amounts in the plasma of healthy individuals and is detected at elevated levels in some inflammatory and malignant conditions (9). Previous studies on cholestasis and inflammation have shown that ICP is an inflammatory process. In addition, they claim that there is a relationship between inflammation markers and the severity of the disease (10,11). Increasing bile acids are considered to cause inflammation and stimulate the secretion of proinflammatory mediators through their direct effects on hepatocytes (12). In the present study, although we found higher serum midkine levels in the study group, we did not find a correlation between serum midkine levels and SBA.

ICP is characterized by itching and elevated serum bile acid concentrations, which typically develop in the late second and/or third trimester and resolve rapidly after delivery (8,13). Although the incidence of ICP varies depending on the regional and ethnic structure, it has been reported to range from 0.5 to 1.5% in Europe (14). Increased bile acids may pass through the placenta and accumulate in the fetus and amniotic fluid (15). Pregnant women with cholestasis have an increased risk of intrauterine death, meconium-containing amniotic fluid, premature birth (spontaneous and iatrogenic), and neonatal respiratory distress syndrome (16,17). In a meta-analysis, adverse perinatal outcomes were observed more frequently as serum bile acid increased (16). In a similar systematic review, fetal

death rates were found to be 0.4, 0.3, and 6.8% in pregnant women with total bile acid concentrations of <40 micromole/L, 40-99 micromole/L, and ≥100 micromole/L, respectively (18). It is considered that increased bile acids lead to fetal death by causing fetal arrhythmia and sudden vasospasm in placental chorionic vessels (19). Fortunately, since fetal death usually occurs in the last weeks of pregnancy, planning the timing of delivery according to bile acid concentration reduces negative perinatal outcomes (16,18). Fetal death was not observed in any of our patients because delivery was scheduled in accordance with current treatment protocols in our clinic. Since we had no cases with adverse perinatal outcomes, we evaluated a correlation between serum midkine levels and SBA to examine the correlation with disease severity. In the correlation analysis, there was no correlation between the midkine level and SBA. Therefore, we were not able to establish a relationship between the maternal serum midkine level and the severity of ICP.

According to previous studies, the risk of liver, biliary tract, and pancreatic diseases and hepatobiliary cancer is increased in women with a history of ICP during pregnancy (4). Although the serum midkine level may be elevated in many cancer cases, such as esophagus, stomach, bladder, and lung, the most investigated type of cancer is hepatocellular carcinoma (2,22). In a cohort study conducted in Sweden evaluating 125,281 women who gave birth, liver cancer risk was 3.61 times higher and bile cancer 2.62 times higher in women with a history of cholestasis during pregnancy (23). In other studies, it was shown that an increased midkine level could be used as a tumor marker even in the early stages of hepatocellular carcinoma (24,25). In a study in which hepatectomy was performed on mice, liver regeneration was found to be slower in those whose midkine gene was suppressed (26). In another study, it was reported that midkine secretion increased in liver cells damaged by cadmium and reduced this tissue damage (27). Based on these results, we can refer to a potential relationship between liver damage and repair and midkine levels. Long-term cohort studies are needed to establish a relationship between the risk of hepatobiliary disease or cancer and high midkine levels in pregnant women.

ICP, the most common liver disease of pregnancy, is associated with adverse perinatal outcomes. In addition, women with a history of ICP in pregnancy have an increased risk of liver disease and cancer later in life. Therefore, understanding the mechanism underlying ICP pathology may shed light on many diseases. We believe that future studies may elucidate this hypothesis thanks to this study in which we have shown an association between ICP and elevated serum midkine levels. However, in this study, we could not show a correlation between serum midkine level and disease severity.

To the best of our knowledge, this is the first study to investigate the midkine level in pregnant women with cholestasis, and therefore we consider that our results will make a significant contribution to the literature. However, this study also had certain limitations, including the small number of patients and the absence of perinatal and long-term maternal outcomes. In this context, there is a need for randomized controlled studies with a large number of participants.

Conclusion

We found a higher serum midkine level in pregnant women with cholestasis. There was no correlation between the midkine level and SBA or transaminases. When the cut-off value of midkine was taken as 0.345 ng/ml for the prediction of ICP, specificity and sensitivity were determined as 70% and 70%, respectively.

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Özgün Araştırma / Original Article

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Erken Başlangıçlı Fetal Büyüme Kısıtlamasını (FGR) Öngörmede İlk Trimester CRL (baş popo mesafesi) Ölçümünün NT (ense saydımlığı) Ölçümlerine Oranının Rolü

The role of the ratio of first trimester CRL (crown rump length) measurement to NT(nuchal translucency) measurements in predicting early-onset fetal growth restriction (FGR)

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ÖZ

Amaç: Amacımız, ilk trimester CRL (baş popo mesafesi) ölçümünün NT (ense saydamlığı) ölçümlerine oranının erken başlangıçlı fetal büyüme kısıtlamasını (FBK) öngörmedeki rolünü değerlendirmek ve mevcut literatüre katkıda bulunmaktır.

Yöntemler: Mevcut vaka-kontrol çalışmasında, erken başlangıçlı FBK'lı fetüsler, frekans eşleştirilmiş düşük riskli kontrol grubuyla karşılaştırıldı. Bu çalışma, 2020-2023 yılları arasında Ankara Bilkent Şehir Hastanesi Perinatoloji kliniğinde gerçekleştirildi. Erken başlangıçlı FBK'lı gebe kadınlar (n=39) ve FBK'sı olmayan hamile kadınlar (n=50) arasında anne yaşı, gravida , parite, baş popo mesafesi (CRL) ve ense saydamlığı (NT) ölçümleri karşılaştırıldı.

Bulgular: Çalışmaya katılan FBK'lı gebelerin yaş ortalaması 27,1±0,8, FBK olmayan gebelerin yaş ortalaması 26,3±0,6 olup iki grup arasında istatistiksel olarak anlamlı fark saptanmadı (p=0,4)). Ortalama CRL FBK'lı grupta 54,98±1,08 mm, FBK'sız grupta ise 56,99±1,11 mm idi; iki grup arasında anlamlı fark yoktu (p=0,2). NT değeri FBK grubunda 1,11±0,04 mm, FBK olmayan grupta 1,13±0,02 mm olup iki grup arasında anlamlı fark yoktu (p=0,73). Erken başlangıçlı FBK'lı grupta ortalama CRL/NT oranı 52,00±2,33, FBK'sız grupta ise 51,46±1,48 olup iki grup arasında istatistiksel olarak anlamlı fark yoktu (p=0,83).

Erken gelişen FBK grubu kendi içinde değerlendirildiğinde ortalama tanı yaşı 31,7±0,3 hafta idi. Tanı anındaki EFW ortalama persantil 4,5±0,6 ve AC persantil 2,9±0,4 idi. Ortalama umbilikal arter sistol/diyastol oranı (UA-SD) 2,9±0,16 ve ortalama umbilikal arter pulsatilite indeksi (UA-PI) 1,02±0,05 idi.

Sonuç: Baş popo mesafesi/ense saydamlığı oranı, erken başlangıçlı FBK'yı tahmin etmede klinik olarak yararlı değildir.

ABSTRACT

Objective: Our aim is to evaluate the role of the ratio of first-trimester CRL (crown rump length) measurement to NT (nuchal translucency) measurements in predicting early-onset fetal growth restriction (FGR) and to contribute to the existing literature.

Methods: In the present case-control study, fetuses with early-onset FGR were compared with a gestational age-matched low-risk control group. This study was conducted in the perinatology clinic of Ankara Bilkent City Hospital between 2020 and 2023. Maternal age, gravidity, parity, crown-rump length (CRL), and nuchal translucency (NT) measurements were compared between pregnant women with early onset FGR (n=39) and pregnant women without FGR (n=50).

Results: The mean age of pregnant women with FGR who participated in the study was 27.1±0.8, and the mean age of pregnant women without FGR was 26.3±0.6, and no statistically significant difference was found between the two groups (p=0.4)). Mean CRL was 54.98±1.08 mm in the group with FGR and 56.99±1.11 mm in the group without FGR; there was no significant difference between the two groups (p=0.2). The mean NT value was 1.11 ± 0.04 mm in the FGR group and 1.13 ± 0.02 mm in the without FGR group, there was no significant difference between the two groups (p=0.73). The mean CRL/NT ratio was 52.00±2.33 in the group with early onset FGR and 51.46±1.48 in the group without FGR and there was no statistically significant difference between the two groups (p=0.83).

When the early developing FGR group is evaluated within itself, the mean gestational age at diagnosis was 31.7±0.3 weeks. The mean estimated fetal weight (EFW) percentile at diagnosis was 4.5±0.6 and AC percentile was 2.9±0.4. The mean umbilical artery systole/diastole ratio (UA-SD) was 2.9±0.16 and the mean umbilical artery pulsatility index (UA-PI) was 1.02±0.05.

Conclusion: Crown-rump length to nuchal translucency ratio is not clinically useful to predict early-onset FGR.

Keywords: CRL, NT, crown-rump length, nuchal translucency, fetal growth restriction, FGR

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INTRODUCTION

Normal growth of the fetus is a multifactorial process and genetic, placental, and maternal factors affect the process (1). Disruption of this multifactorial cycle prevents the fetus from reaching its genetic growth potential and fetal growth restriction occurs. In FGR, the nutritional resources of the fetus are compromised The fetus responds to this situation by reducing its overall size and maintaining brain growth, accelerating lung development, and increasing erythrocyte production (2). In the fetus, blood is directed to the more vital organs: the heart, brain, adrenal gland, and placenta. Total fat tissue and bone mineralization decrease, leading to a weakened appearance in babies with FGR (3). Nitrogen and protein levels are low due to reduced muscle mass. Liver and muscle glycogen levels are reduced due to low glucose and insulin levels (4). The determining factor in early and late fetal development restriction is the placenta. It plays an important role in the development of early onset FGR, such as placental insufficiency, as a result of abnormal trophoblastic invasion of spiral arterioles in the first and second trimester. It is more common in patients with autoimmune diseases, hypertensive disorders, and patients where placental vessels are affected. While early FGR and preeclampsia are usually seen together, late FGR is not accompanied either. Early onset fetal growth restriction (FGR) is defined as an abdominal circumference (AC) or estimated fetal weight (EFW) below the 3rd percentile or absence of end-diastolic flow in the umbilical artery (UA-AEDF) before 32 weeks of gestation. AC and EFW below the 10th percentile and a concomitant uterine artery pulsatility index (UtA-PI) or umbilical artery pulsatility index (UA-PI) above the 95th percentile are also used to make the diagnosis (5). Although there are different criteria for defining fetal growth restriction, none of them are successful in fully predicting adverse neonatal outcomes (6). Babies with developmental delay are usually born preterm and therefore may lead to morbidity, mortality, and short and long-term sequelae (7). The most commonly associated long-term effects of FGR are neurodevelopmental disorders in childhood and cardiovascular disorders, glucose intolerance and diabetes, and blood lipid profile disorders in adulthood (8, 9).

During the first trimester of pregnancy, Nuchal Translucency (NT) refers to the sonographic observation of subcutaneous fluid accumulation in the posterior part of the fetal neck. NT measurement is a sensitive method used in chromosomal abnormality screening. Cardiac malformations, extracellular matrix disorders, and unusual or delayed development of the lymphatic system may also lead to the thickening of the NT, in addition to chromosomal abnormalities. NT measurements above the 95th percentile are considered abnormal. Increased NT is associated with chromosomal and non-chromosomal abnormalities, but also with miscarriage, fetal structural malformations, and fetal death (10-12).

Prenatal diagnosis of fetal growth restriction is a key place to disseminate new strategies and prevent stillbirths, which can reach up to 30%. This study aims to try to predict early-onset fetal growth restriction as early as the first trimester and to organise prospective strategies and to prevent adverse factors that can be prevented in this multifactorial process.

MATERIALS AND METHOD

This study was designed retrospectively in the perinatology clinic of Ankara Bilkent City Hospital. Pregnant women who were followed up for early onset FGR and pregnant women with similar demographic characteristics and without FGR between 2020 and 2023 were included in the study. The study protocol was approved by the ethics committee with the reference number E2-23-5657 and all participants gave written consent. Crown-rump length (CRL), nuchal translucency (NT) measurements in the first trimester, biparietal diameter (BPD), Head circumference (HC), abdominal circumference (AC) percentage, femur length (FL), Estimated fetal weight (EFW) percentage, umbilical artery pulsatility index (UA-Pİ) percentage, uterine artery pulsatility index (UtA-Pı), percentage were reported.

All ultrasound evaluations were performed by the same perinatologist (A.T.) using Voluson E8 with a 2-9 Mhz abdominal convex probe.The first fetal ultrasound scan was performed at 11-14 weeks of gestation, with further ultrasound scans performed at 2-week intervals until the time of delivery. The Delphi procedure was adopted as a consensus criterion for FGR (5). Early-onset FGR is defined as pregnancies that occur before 32 weeks of gestation and have either an estimated fetal weight (EFW) or abdominal circumference (AC) below the 3rd percentile or loss of end-diastolic flow in the umbilical artery. According to the same consensus, other diagnostic criteria include an AC or EFW below the 10th percentile and an accompanying umbilical artery or uterine artery pulsatility index above the 95th percentile.

The statistical analysis was performed by SPSS 22 (IBM Corp., NY). Kolmogrov-Smirnov test was used to assess whether the

data is normally distributed. Mean and standard deviation values were used for normally distributed continuous variables. Categorical variables were presented as numbers and percentages. A p-value <0.05 is considered as statistically significant.

RESULTS

A total of 89 patients, including 39 pregnant women with early onset FGR and 50 pregnant women without FGR, were included in the study. Demographic characteristics and first-trimester CRL and NT measurements were summarised in Table 1.

Table 1: Demographic characteristics and first-trimester CRL and NT measurements

	With FGR (n=39)	Without FGR (n=50)	p
Age	27.1±0.8	26.3±0.6	0.4
Gravidity	1.92±0.21	1.76±0.14	0.51
Parity	0.51±0.1	0.6±0.12	0.58
CRL (mm)	54.98±1.08	56.99±1.11	0.2
CRL (week)	11.46±0.8	11.56±0.9	0.45
NT (mm)	1.11 ± 0.04	1.13 ±0.02	0.73
NT (mom)	0.79±0.035	0.76±0.022	0.58
CRL (mm) /NT (mm)	52.00±2.33	51.46±1,48	0.83

FGR: Fetal growth restriction, CRL: Crown-rump length, NT: nuchal translucency

The mean age of pregnant women with FGR who participated in the study was 27.1±0.8, and the mean age of pregnant women without FGR was 26.3±0.6, and no statistically significant difference was found between the two groups (p=0.4). The mean gravidity of the FGR group was 1.92±0.21, the mean gravidity of the without FGR group was 1.76±0.14, and no significant difference was detected between the two groups (p=0.51).

Table 2: Ultrasonographic measurements in the group with early-onset FGR

EFW (percentile)	4.5±0,6
AC (percentile)	2.9±0.4
UA-SD	2.9±0,16
UA-PI	1.02±0.05
Gestational age of diagnosis (week)	31.7±0.3

EFW: Estimated fetal weight, AC: Abdominal circumference, UA-SD: Umbilical artery systole/diastole ratio, UA-PI: Umbilical artery pulsatility index

The mean parity was 0.51±0.1 in the group with FGR and 0.6±0.12 in the group without FGR, and there was no significant difference between the two groups (p = 0.58). Mean CRL was 54.98±1.08 mm in the group with FGR and 56.99±1.11 mm in the group without FGR; there was no significant difference between the two groups (p=0.2). CRL measurement time was 11.46±0.8 weeks in the group with FGR, and 11.56±0.9 weeks in the group without FGR, and there was no significant difference between the two groups (p = 0.45). The NT value was 1.11 ± 0.04 mm in the FGR group and 1.13 ± 0.02 mm in the without FGR group, there was no significant difference between the two groups (p=0.73). The mean CRL/NT ratio was 52.00±2.33 in the group with early onset FGR and 51.46±1.48 in the group without FGR and there was no statistically significant difference between the two groups (p=0.83).

When the early developing FGR group is evaluated within itself, the mean age at diagnosis was 31.7±0.3 weeks. Ultrasonographic measurements in the group with early-onset FGR were summarised in Table 2. EFW mean percentile at diagnosis was 4.5±0.6 and ac percentile was 2.9±0.4. The mean umbilical artery systole/diastole ratio (UA-SD) was 2.9±0.16 and the mean umbilical artery pulsatility index (UA-PI) was 1.02±0.05.

DISCUSSION

In the present study, CRL to NT ratio was not found to be clinically useful in the prediction of early-onset FGR.

In a single-center retrospective study, the prediction of first-trimester crown-rump length (CRL), pregnancy-related plasma protein-A (PAPP-A), and nuchal translucency (NT) values for adverse pregnancy outcomes were investigated. A total of 12592 pregnant women were included in the study There were preterm labour in 852 (6.8%) and preeclampsia in 352 (2.8%) patients. Small for gestational age (SGA) occurred in 1824 (14.5%), and miscarriage occurred in 73 (0.6%) patients. Stillbirths occurred in 37 (0.3%), perinatal deaths occurred in 73 (0.6%) and neonatal death occurred in 38 (0.30%) patients. It was concluded that PAPP-A, NT, and CRL are independent prognostic factors for unfavorable pregnancy outcomes, especially the risk of SGA increases with low PAPP-A (13).

In a cohort study including 8012 patients, the relationship between the first trimester (free human chorionic gonadotropin-β [hCG], pregnancy-associated plasma protein A [PAPP-A], NT and adverse pregnancy outcomes was investigated. PAPP-A values below the 1st and 5th percentiles and free β-hCG below the 1st percentile values were associated with an increased risk of developing FGR. PAPP-A values below the 5th percentile and NT values above the 99th percentile were associated with an increased risk of preterm birth before 34 weeks. As a result of the study, it was concluded that extreme values of first-trimester free β-hCG, PAPP-A, and NT were all associated with adverse pregnancy outcomes, and especially PAPP-A levels below the 1 percentile have a particularly high predictive value for FGR (14).

In a prospective study including 6026 patients, the relationship

between unexplained nuchal translucency thickness increase and pregnancy adverse outcomes was investigated. Pregnant women with comorbidities, and fetuses with fetal chromosomal or structural abnormalities were excluded from the study. The NT of 277 fetuses in the study was found to be above the 95th percentile, and the NT of 5749 fetuses was below the 95th percentile. The miscarriage rate was significantly higher in the group with NT above the 95th percentile; 18/277 (6.5%) versus 55/5749 (1.0%). Preeclampsia, premature birth, fetal growth restriction, and low birth weight rates were found to be slightly but significantly higher in the group with NT above the 95th percentile. It was concluded that increased NT measurements above the 95th percentile in the first trimester are associated with a significantly increased risk of miscarriage, fetal growth restriction, preterm birth, low birth weight, and preeclampsia (15).

In a study involving 427 pregnant women, the association with adverse outcomes was investigated in fetuses with normal karyotype and increased NT. The patient groups were divided into 3 groups: nt ≥ 3 mm, ≥ 3.5 mm, and ≥ 4.5 mm, it was concluded that high NT values in fetuses with normal karyotypes do not reliably discriminate between normal and unfavorable outcomes (16). However, in the present study, no significant difference was present between the control and early-onset FGR groups in terms of CRL to NT ratio.

The main strength of the present study was its novelty. However, retrospective design and a relatively low number of cases were the main limitations.

CONCLUSION

In conclusion, CRL to NT ratio is not clinically useful to predict early-onset FGR.

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Servikal Kanserde Prognozu Etkileyen Faktörler ve Neoadjuvan Tedavinin Prognoza Etkisi
Factors Affecting Prognosis in Cervical Cancer and the Effect of the Neoadjuvant Therapy on Prognosis

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ÖZ

Amaç: FIGO 2009 Evre 1B2 ve üzeri lokal ileri evre serviks kanserli hastalarda tedavi seçeneği olarak Radikal Histerektomi ile neoadjuvan kemoterapi sonrası Radikal Histerektominin genel ve hastalıksız sağkalıma etkisi araştırıldı.

Gereç ve Yöntem: Çalışma Şubat 2007 – Ocak 2015 tarihleri arasında Başkent Üniversitesi Jinekolojik Onkoloji Bölümünde tedavi edilen 119 FİGO 2009 evre 1B2 ve üzeri lokal ileri serviks kanserli hastaları içermekte olup retrospektif olarak düzenlendi. Hastalar jinekolojik muayene ile klinik olarak evrelendirilip, görüntüleme tetkikleri ile değerlendirildikten sonra, tedavi planlarına göre 2 gruba ayrıldı. Primer olarak cerrahi yapılacak hastalara (grup1) Radikal histerektomi ve lenf nodu diseksiyonu yapıldı. Neoadjuvan kemoterapi uygulanan hastalarda ise (grup 2) 3 kür kemoterapi verildikten sonra radikal histerektomi ve lenf nodu diseksiyonu uygulandı. Çalışmada bu iki grup arasında genel ve hastalıksız sağkalım süreleri araştırıldı. Ayrıca genel ve hastalıksız sağkalımı etkileyen faktörler araştırıldı.

Bulgular: Hastaların ortalama yaşı 56 (32-85) idi, ortalama takip süresi ise 35(1-100) aydı. 119 hastanın 36'sına neoadjuvan kemoterapi uygulanırken, 83 hasta primer cerrahi grubundaydı. 5 yıllık genel sağkalım neoadjuvan kemoterapi grubunda %51,7 (56,3 ay), primer cerrahi uygulanan grupta ise %73,5 (79,2 ay) olarak bulundu (p=0,03). Hastalıksız sağkalım ise neoadjuvan alan grupta %48,2 (49,2 ay) bulunurken bu oran primer cerrahi grubu için %61,4 (67,7 ay) olarak hesaplandı (p=0,17). Primer cerrahi yapılan grubunun genel sağ kalım hızı, neoadjuvan kemoterapi sonrası cerrahi uygulanan hastalardan anlamlı olarak yüksekti (p=0.036).

Sonuç: Çalışmamızda servikal kanserli hastalarda uygulanan 2 farklı tedavi şekli karşılaştırılmış olup, primer olarak radikal histerektomi ve lenf nodu diseksiyonu yapılan hastalarda genel sağkalım hızının, neoadjuvan kemoterapi sonrası radikal histerektomi ile lenf nodu diseksiyonu uygulanan hastalardan istatiksel olarak daha iyi olduğu saptanmıştır. Neoadjuvan kemoterapi tedavisi lokal ileri evre serviks kanserli hastalarda standart bir tedavi şekli olmayıp çalışmamızda da genel ve hastalıksız sağkalıma etkisi olmadığı saptanmıştır. Neoadjuvan kemoterapinin lenf nodu tutulumuna ve tümör çapına etkisi olduğu bulunmuştur.

Anahtar kelimeler: Servikal kanser, Evre IB2, 2A1, 2A2, Neoadjuvan Kemoterapi

ABSTRACT

Aim: The effects of Radical Hysterectomy and Radical Hysterectomy after neoadjuvant chemotheraphy on overall and disease-free survival were investigated in FIGO 2009 Stage 1B2 and higher locally advanced cervical cancer.

Materials and Methods: This retrospective study included 119 FIGO 2009 stage 1B2 and locally advanced cervical cancer patients treated in Baskent University Department of Gynecological Oncology between February 2007 and January 2015. The patients were divided into 2 groups according to their treatment plans after they were clinically stratified by gynecological examination and evaluated with imaging techniques. Radical hysterectomy and lymph node dissection were performed in group 1, who would undergo primary surgery. Radical hysterectomy and lymph node dissection were performed after 3 cycles of neoadjuvant chemotherapy in group 2. In the study, overall and disease-free survival between these two groups were investigated. In addition, factors affecting overall and disease-free survival were investigated.

Results: The mean age of the patients was 56 (32-85), and the mean follow-up period was 35 (1-100) months. While neoadjuvant chemotherapy was applied to 36 of 119, 83 patients were primary underwent surgery.

The 5-year overall survival was 51.7% (56.3 months) in the neoadjuvant group and 73.5% (79.2 months) in the primary surgery group (p=0.03). Disease-free survival was 48.2% (49.2 months) in the neoadjuvant group, while this rate was 61.4% (67.7 months) in the primary surgery group (p=0.17). The overall survival rate of the primary surgery group was significantly higher than that of the patients who underwent surgery after neoadjuvant chemotherapy (p=0.036).

Conclusion: In our study, 2 different treatment modalities applied in patients with cervical cancer were compared, and it was determined that the overall survival rate in patients who had primarily radical hysterectomy and lymph node dissection was statistically better than those who underwent radical hysterectomy and lymph node dissection after neoadjuvant chemotherapy. Neoadjuvant chemotherapy treatment is not a standard treatment in patients with locally advanced cervical cancer, and it was found that it had no effect on overall and disease-free survival in our study. Neoadjuvant chemotherapy was found to have an effect on lymph node involvement and tumor diameter.

Key words: Cervical cancer, Stage IB2 , 2A1, 2A2, Neoadjuvant Chemotherapy

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GİRİŞ

Servikal kanser en sık görülen jinekolojik maligniteler içerisinde üçüncü sıradadır. Globacan 2020 verilerine göre insidansı 604.107'dir (1). Yaşam boyu servikal kansere yakalanma riski %0,7 ve median görülme yaşı 50'dir (2, 3)

Lokal ileri evre servikal kanser vakalarında ise standart tedavi konkomitan cisplatin ve radyoterapi ile brakiterapidir (4) (5) . Neoadjuvan kemoterapi tedavisi standart olmayıp özellikle evre 1B2 ve 2B hastalar için alternatif tedavi olarak sunulmuştur (2) (6) (7). 1990lardan itibaren neoadjuvan kemoterapi tedavisiyle ilgili birçok çalışma yapılmıştır.

Neoadjuvan kemoterapi tedavisinin tümör boyutunu, stromal invazyon derinliğini, parametrial tutulumunu, lenfovaskuler alan invazyonunu ve lenf nodu metastazını azalttığı saptanmıştır (2, 5) (7) (8) (9) , fakat yine de genel sağkalıma etkisinin bulunmadığı gösterilmiştir (8, 9). Neoadjuvan kemoterapi tedavisine yanıtsız olgularda progresyon görülmesi ise tedavi süresinin uzamasına neden olmuştur. Hematolojik yan etkiler ise neoadjuvan kemoterapinin diğer dezavantajıdır. Neoadjuvan kemoterapide etkinliği gösterilmiş ve yaygın olarak kullanılan platin bazlı rejimdir (8) .

Çalışmamızın amacı lokal ileri evre serviks kanseri tanısı almış neoadjuvan kemoterapiden sonra cerrahi uygulanan hastalar ile primer olarak cerrahi yapılan hastaların genel ve hastalıksız sağkalım oranlarını karşılaştırmaktı. Ayrıca neoadjuvan kemoterapinin cerrahi sonrası patolojik bulgulara olan etkisi incelendi.

GEREÇ VE YÖNTEM

Bu çalışma Şubat 2007- Ocak 2015 tarihleri arasında Başkent Üniversitesi Ankara Hastanesi Kadın Hastalıkları ve Doğum Ana Bilim Dalı Jinekolojik Onkoloji Bölümünde retrospektif olarak yürütülmüştür. Şubat 2007 ile Ocak 2015 tarihleri arasında tedavi edilen evre 1B2,2A1,2A2 serviks kanserli hastalar araştırma kapsamına alındı. Çalışma retrospektif, iki gruplu ve tek merkezli olarak tasarlandı.

Hastalar merkezimizde jinekolojik muayene, patoloji sonuçları ve görüntüleme yöntemleri (MR, CT ve PET) ile beraber değerlendirildi. Tümör boyutları, lenf nodu tutulumları ile parametrium tutulumu görüntüleme metodlarından kaydedildi. İleri muayene gerektiren hastalarda genel anestezi altında pelvik muayene yapıldı. Postoperatif patolojik bulgular ve tümör boyutları ise patoloji raporlarından kaydedildi.

Hastaların tümü FIGO 2009 evre 1B2,2A ve 2Bidi. Klinik evrelendirme sonrası olgular 2 gruba ayrıldı. 36 olguya cerrahi öncesi neoadjuvan kemoterapi planlandı. 83 hastada primer cerrahi kararı alındı. Neoadjuvan kemoterapi, cerrahi öncesinde 3 hafta arayla 3 kür olarak şekilde uygulandı. İlaç olarak Paklitaksel, Sisplatin ve Karboplatin verildi. Toplam 119 hastaya Radikal histerektomi ile bilateral pelvik ve paraaortik lenf nodu diseksiyonu yapıldı. Cerrahi sonrası yapılan patolojik değerlendirmede yüksek risk faktörü bulunan hastalara adjuvant tedavi kemoradyasyon veya radyoterapi eklendi.

Çalışmamızda hastalıksız sağkalım ameliyat tarihi ile belgelenmiş ilk nüks arasındaki süre olarak tanımlandı. Genel sağ kalım ise ilk tanı tarihi ile son vizit arasındaki süre olarak ölçüldü. Olguların cerrahi sonrası takipleri ilk bir sene içerisinde iki ayda bir, bir sene sonrası üç ayda bir ve sonraki senelerde 6 ayda bir pelvik muayene, smear testi ve görüntüleme ile değerlendirme şeklinde planlandı.

İSTATİKSEL ANALİZ:

Araştırma verisi "SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc, Chicago, IL)" aracılığıyla bilgisayar ortamına yüklendi ve değerlendirildi. Tanımlayıcı istatistikler ortalama±standart sapma, ortanca (minimum-maksimumu), frekans dağılımı ve yüzde olarak sunuldu. Kategorik değişkenlerin değerlendirmesinde Pearson Ki-Kare Testi, Yates Düzeltmeli Ki-Kare Testi, Fisher'in Kesin Testi ve McNemar Testi uygulandı. Değişkenlerin normal dağılıma uygunluğu görsel (histogram ve olasılık grafikleri) ve analitik yöntemler (Kolmogorov-Smirnov/Shapiro-Wilk Testi) kullanılarak incelendi. Normal dağılıma uymayan değişkenler için; iki bağımsız grup arasındaki anlamlılıklarda Mann-Whitney U Testi, iki bağımlı grup arasında Wilcoxon İşaretli Sıralar Testi istatistiksel yöntem olarak uygulandı. Sağkalımın tek değişkenli analizlerde incelenmesi Log Rank testiyle yapıldı. Çok değişkenli analizde önceki analizlerde belirlenen olası faktörler kullanılarak sağkalımı öngörmedeki bağımsız etkenler Cox regresyon analizi kullanılarak incelendi. Sağkalım hızları Kaplan-Meier yöntemiyle hesaplandı. İstatistiksel anlamlılık düzeyi $p<0,05$ olarak kabul edildi.

BULGULAR

Ortalama yaş 56 (32-85), ortalama takip süresi 35(1-100) aydı. Serviks biyopsilerinin %89,8'i (n=88) squamoz hücreli kanserdi. Ortalama eksize edilen pelvik lenf nodu sayısı 29, paraaortik lenf nodu sayısı ise 10 idi.

Neoadjuvan kemoterapi alan hastalar ile primer cerrahi uygulanan hastalar arasında invazyon derinliği, parametrium invazyonu ve parametrial cerrahi sınır tutulumu arasında farklılık yoktu (p=0.16, p= 0.20, p=0.99). Lenfovasküler invazyon, vajen ve vajinal cerrahi sınır tutulumları her 2 grupta benzerdi (p=0.43, p=0.20, p=0.25). Ayrıca lenf nodu tutulumu, adjuvan tedavi alma durumu, nüks ve grade 3-4 komplikasyonlar oranlarında iki grup arasında benzerlik bulunmaktaydı (p= 0.76, p=0.25, p=0.39, p=0.76) (Tablo 1).

Tablo 1: Olguların Patolojik Sonuçları

	Grup1(neoadjuvan tedavi almayan) (n=83)	Grup2(neoadjuvan tedavi alan) (n=36)	p değeri
Yaş	56 (32-81)	56,5 (32-85)	0,488
Takip süresi (ay)	35 (1-100)	35 (1-100)	

Hastalıksız ve genel sağ kalımı etkileyen faktörlerin belirlenmesine yönelik yapılan cox regresyon analizi sonucu, neoadjuvan tedavi alma durumunun, parametrium, vajen ve lenf nodu tutulumunun genel sağ kalımı etkileyen risk faktörleri olduğu görüldü. Hastalıksız sağ kalım hızını ise; lenf nodu tutulumunun etkilediği görüldü (Tablo 2,3).

Tablo 2: Hastalıksız Sağkalımı Etkileyen Faktörlerin Belirlenmesine Yönelik Tek ve Çok Değişkenli COX Regresyon Analizi

Faktör	Univaryant Analiz		Multivaryant analiz		
	P value		HR	95 CI	P değeri
NACT	0.1		1,57	0,84-2,91	0,155
Parametrıal tutulum	0,057		1,74	0,69-4,37	0,240
Vajen invazyonu	0,128		1,50	0,75-3,02	0,250
Lenf nodu invazyonu	**0,039**		1,84	0,98-3,46	0,057
Yaş	0,765				
Gravida	0,601				
Parite	0,380				
Sigara	0,231				
Histology	0,731				
Invazyon derinliği ≥%50 vs <%50 Tam kat vs <%50	0,909 0,813				
LVSI	0,173				
Adjuvan Tedavi	0,204				

Tablo 3: Genel Sağkalımı Etkileyen Faktörlerin Belirlenmesine Yönelik Tek ve Çok Değişkenli COX Regresyon Analizi

Faktör	Univaryant analiz		Multivaryant analiz		
	P value		HR	95 CL	P değeri
NACT	**0,041**		2,21	1,04-4,70	**0,039**
Parametrıal tutulum	**0,002**		1,74	0,69-4,37	0,240
Vajen invazyonu	**0,016**		1,73	0,78-3,89	0,178
Lenf nodu invazyonu	**0,003**		2,16	0,89-5,21	0,089

Yaş	0,440				
Gravida	0,622				
Parite	0,730				
Sigara	0,826				
Histoloji	0,757				
İnvazyon derinliği ≥%50 vs <%50 Tam kat vs <%50	0,787 0,487				
LVSI	0,060				
Adjuvan Tedavi	0,925				

Neoadjuvan tedavisi öncesinde lenf nodu tutulumu olan 22 hastanın %50,0'ında (n=11) tedavi sonrasında da tutulum varken tedavi öncesi lenf nodu tutulumu olmayan 14 hastanın %85,7'sinde (n=12) tedavi sonrası lenf nodu tutulumu yoktu. Neoadjuvan tedavi öncesiyle sonrası arasında lenf nodu tutulum durumu açısından istatistiksel olarak fark saptandı (p=0,022). Tedavi öncesi lenf nodu tutulumu olan hasta sayısı tedavi sonrası yarı yarıya azalmıştı. Diğer taraftan neoadjuvan tedavi öncesi ve sonrası parametrium ve vajen tutulumu açısından anlamlı bir fark saptanmadı (p>0,05) (Tablo 4).

Tablo 4. Neoadjuvan Tedavi Öncesi ve Sonrası Bazı Klinik Özelliklerin Dağılımı

(N=36)		**Neoadjuvan Tedavisi Sonrası**		
Yok		**Var**		**P**
		Sayı (%*)	**Sayı (%*)**	
Neoadjuvan Tedavisi Öncesi	**Parametrium Tutulumu**			
	Yok	11 (78,6)	3 (21,4)	0,057
	Var	11 (50,0)	11 (50,0)	
	Vajen Tutulumu			
	Yok	17 (73,9)	6 (26,1)	0,791
	Var (üst 1/3)	8 (32,0)	5 (38,5)	
	Lenf Nodu Tutulumu			
	Yok	12 (85,7)	2 (14,3)	**0,022**
	Var	11 (50,0)	11 (50,0)	

*Satır yüzdesi

Neoadjuvan tedavi alan hastaların tedavi öncesi tümör çapı ortancası 4,5 (0,5-8,6) cm iken tedavi sonrası 3 (1-11) cm'ydi. Hastaların tedavi öncesi ve sonrası arasında tümör çapı açısından istatistiksel olarak anlamlı fark saptandı (p=0,004). Kemoterapi sonrası tümör çapı tedavi öncesine göre anlamlı olarak azalmıştı.

Hastaların 5 yıllık genel sağ kalım hızı %67,6, hastalıksız sağ kalım hızı ise %57,2'ydi (Şekil 1). Hastaların ortalama genel sağ kalım ve hastalıksız sağ kalım süreleri sırasıyla 74,6 (%95 GA:67,2-82,0) ve 63,8 (%95 GA:55,7-71,8) aydı.

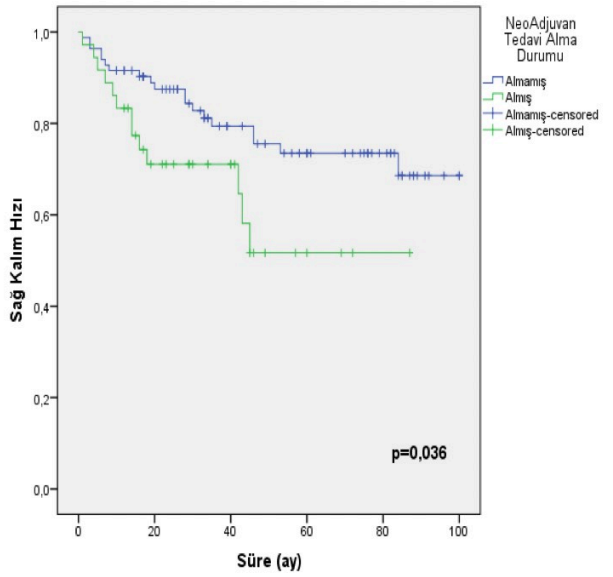
İncelenen hastalarda 5 yıllık genel sağkalım hızı neoadjuvan tedavi almayan grupta %73,5 iken neoadjuvan tedavi alan grupta bu oran %51,7 idi. 5 yıllık hastalıksız sağkalım süresi ise neoadjuvan tedavi almayan grupta %61,4 iken tedavi alan olgularda bu oran %48,2'ydi. Neoadjuvan tedavi almayanların ortalama genel sağkalım süresi 79,2 (%95 GA:71,1-87,3) ay, hastalıksız ortalama

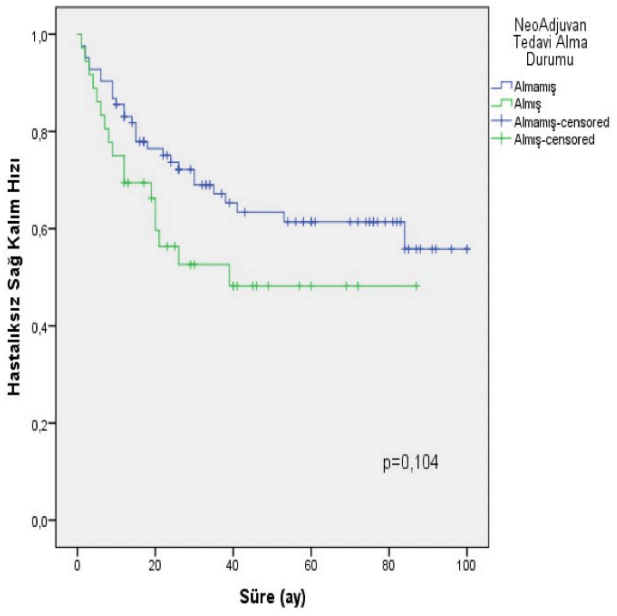
sağ kalım süresi 67,7 (%95 GA:58,4-77,1) ay iken neoadjuvan tedavi alanların ortalama genel sağ kalım

süresi 56,3 (%95 GA:43,4-69,1) ay, hastalıksız ortalama sağ kalım süresi 49,2 (%95 GA:36,3-62,1) ay idi.

Neoadjuvan tedavi alanlar ile almayanların genel sağ kalım hızları arasındaki fark istatistiksel olarak anlamlıyken (p=0,036), hastalıksız sağ kalım hızları benzerdi (p=0,170). Neoadjuvan tedavi almayanların genel sağkalım hızı alanlardan anlamlı olarak yüksekti

Şekil 1: Neoadjuvan Tedavi Alma Durumuna Göre Genel ve Hastalıksız Sağkalım Hızları





TARTIŞMA

Çalışmamızdaki bulgulara göre neoadjuvan kemoterapi alan grup ile almayan grup karşılaştırıldığında alan grubun genel sağkalımı 56,3 hastalıksız sağkalımı 49,2 ay olarak, almayan grubun ise genel sağkalımı 79,2 hastalıksız sağkalımı 67,7 ay olarak bulunmuştur. Neoadjuvan kemoterapi tedavisinin genel ve hastalıksız sağkalıma etkisi istatiksel olarak gösterilememiştir. Neoadjuvan kemoterapi tedavisi alan hastaların genel sağkalımı anlamlı olarak daha düşük bulunmuştur.

Japon jinekolojik onkoloji grubunun lokal ileri evre servikal kanser vakalarında yaptığı çalışmada çalışmamızda olduğu gibi neoadjuvan kemoterapi sonrası cerrahi yapılan ve primer tedavi olarak cerrahi yapılan 2 grup toplam 134 hasta karşılaştırılmıştır. Bu çalışmadan farklı olarak kemoterapi rejimi olarak BOMP (bleomisin, vinkristin, mitomisin, sisplatin) tedavisi uygulanmıştır. Çalışmada 2 grup hasta arasında bizim çalışmamızdan farklı olarak 2 grup arasında genel sağkalımda anlamlı bir fark bulunamamıştır (10) .

2270 hastanın incelendiği bir meta-analizde neoadjuvan kemoterapi sonrası operasyon ile kemoradyasyon tedavisi karşılaştırılmış olup bu vakalarda da neoadjuvan kemoterapi tedavisinin genel sağkalıma herhangi bir fayda sağlamadığı belirtilmiştir (11). 2158 olgunun değerlendirildiği bir başka meta-analizde ise neoadjuvan kemoterapinin daha uzun hastalıksız sağkalımla ilişkisinin gösterilemediği fakat yine de lokal ileri evre servikal kanserde kabul edilebilir olduğundan bahsedilmiştir. Aynı meta-analizde neoadjuvan kemoterapi tedavi kararının cerrahın tecrube ve klinik görüşüne göre alınması gerektiğinden bahsedilmiştir (7).

Lenf nodu tutulumu servikal kanser için en önemli prognostik faktörlerden biri olmakla beraber hem hastalıksız hem de genel sağkalımı etkilediği gösteren birçok çalışma ve yayın mevcuttur. Çalışmamızda neoadjuvan tedavi öncesi ve sonrasında parametrium, vajen, lenf nodu tutulumları ve tümör çapları karşılaştırılmış olup, lenf nodu tutulumları açısından anlamlı fark bulunmuştur. Literaturde çalışmamıza benzer olarak neoadjuvan kemoterapi aldıktan sonra radikal histerektomi yapılan vakalarda, lenf nodu tutulumunun ve mikrometastazların azaldığını belirten çalışmalar vardır (5) (12). Lenf nodu tutulumunun serviks kanserindeki önemi açısından neoadjuvan kemoterapinin lenf nodlarına olan etkisinin daha büyük prospektif vakalarla incelenebilir.

Lokal ileri servikal kanser tanılı 219 hastanın incelendiği bir çalışmada neoadjuvan kemoterapi sonrası cerrahi ile primer cerrahi seçeneği karşılaştırılmış ve araştırmamızdan farklı olarak lenfovaskuler alan tutulumunun ve derin stromal invazyonun neoadjuvan kemoterapi alan grupta anlamlı olarak daha düşük olduğu gözlenmiştir (8). Benzer olarak ise genel ve hastalıksız sağkalım arasında anlamlı bir fark bulunamamıştır. Patolojik parametrelere etki etse de neoadjuvan kemoterapinin sağkalım faydası gösterilememiştir.

Çinde yapılan 163 vaka içeren bir çalışmada 72 hastaya cerrahi uygulanmış, 91 hastaya ise neoadjuvan kemoterapi sonrasında cerrahi uygulanmış, bu 2 grup arasında komplikasyonlar açısından bir fark bulunamamıştır. Aynı şekilde bu çalışmada da komplikasyon oranlarında istatiksel açıdan fark bulunamamıştır (5). Çalışmamızda median takip süresi 35 aydı. Hastaların daha uzun takip süreleri ile değerlendirilmesi uzun dönem komplikasyonların farkedilmesini sağlayabilir.

Bu çalışmanın limitasyonları tek merkezli ve retrospektif bir çalışma olmasıdır. Vaka sayısının az olması diğer bir dezavantajdır. Araştırmamızın güçlü tarafları ise kemoterapi rejimlerinin homojen olması ve tüm hastaların aynı ve deneyimli jinekolog onkolog tarafından muayene edilip değerlendirilmesidir.

SONUÇ

Neoadjuvan kemoterapi seçilmiş vakalarda güncel olarak dünyada ve ülkemizde kullanılmakla birlikte bu çalışmada lenf nodu tutulumuna ve tümör çaplarına anlamlı bir etkisi bulunmakla birlikte, çalışmada genel ve hastalıksız sağkalıma etkisi bulunanamıştır. Bu çalışmada olgu sayıları sınırlıdır, daha kesin sonuçlar elde edebilmek için daha geniş çapta çalışmalara gereksinim vardır.

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THE RELATIONSHIP BETWEEN CIRCULATING BETATROPHIN LEVELS AND INSULIN RESISTANCE IN LEAN AND OVERWEIGHT /OBESE PCOS

ZAYIF VE OBEZ PCOS' DA İNSÜLİN REZİSTANSI VE KAN BETATROFİN DÜZEYLERİ ARASINDAKİ İLİŞKİ

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ÖZ

Amaç: Polikistik over sendromlu (PKOS) kadınların yaklaşık %70'inde insülin direnci ve buna bağlı metabolik bozukluklar vardır, ancak insülin direncine yol açan altta yatan mekanizma bilinmemektedir. Betatrofin, karaciğerde ve yağ dokusunda eksprese edilen ve insülin direnci ve β-hücre proliferasyonu ile ilişkili olduğu bulunan bir proteindir. Bu çalışmanın amacı, PKOS olgularında dolaşımdaki betatrofin düzeyini değerlendirmek ve obezite ve insülin direnci ile ilişkisini araştırmaktır.

Yöntemler: Bu prospektif kesitsel çalışmada, ELİSA test kitleri kullanılarak normo-ağırlıklı 35 tane PCOS vakasında ve 38 tane fazla kilolu/obez PCOS vakasında (BMI≥25) dolaşan betatrofin seviyeleri ölçüldü. Betatrofin seviyeleri, antropometrik ölçümler, açlık kan şekeri, glikoz yüklemesinden 2 saat sonra kan şekeri ve insülin direncinin homeostaz modeli değerlendirmesi (HOMA-IR) değerleri karşılaştırıldı.

Bulgular: Normal ağırlıklı PKOS grubunun dolaşımdaki betatrofin düzeyleri aşırı kilolu/obez PKOS grubuna göre anlamlı derecede yüksek bulundu (p=0,023). Betatrofin ve HOMA-IR seviyeleri arasında anlamlı bir ilişki yoktu.

Sonuç: Betatrofin, aşırı kilolu/obez grupta normo-ağırlıklı PKOS grubuna göre anlamlı derecede düşük bulundu. Betatrofinin PKOS ve insülin direncindeki rolü yeterince aydınlatılamadığından PKOS hastalarında insülin direncinin iyi bir öngörücüsü olmadığı söylenebilir.

Anahtar Kelimeler: Betatrophin; PCOS; obesite; insulin direnci; metabolik sendrom.

ABSTRACT

Objective: About 70% of women with polycystic ovary syndrome (PCOS) have insulin resistance and related metabolic disorders but the underlying mechanism leading to insulin resistance remain unknown. Betatrophin is a protein expressed in the liver and adipose tissue that has been found to be related to insulin resistance and β-cell proliferation. The aim of this study is evaluate the circulating betatrophin level in PCOS cases and to investigate its relationship with obesity and insulin resistance.

Methods: In this prospective cross-sectional study circulating betatrophin levels were measured in 35 PCOS cases with lean and 38 overweight/ obese PCOS cases (BMI≥25) using spesific enzyme-linked immunosorbent assay kits. Betatrophin levels, antropometric measurements, fasting blood glucose, 2 -hour post-glucose load blood glucose and homeostasis model assessment of insulin resistance (HOMA-IR) values were compared.

Results: Circulating betatrophin levels of the lean PCOS group were found to be significantly higher than the overweight/obese PCOS group (p=0.023). There were no significant association between betatrophin and HOMA-IR levels.

Conclusions:Betatrophin was found to be significantly lower in the overweight/obese group than in the lean PCOS group. Since the role of betatrophin in PCOS and insulin resistance has not been sufficiently clarified, it can be said that it is not a good predictor of insulin resistance in PCOS patients.

Key words: Betatrophin; PCOS; obesity; insulin resistance;metabolic syndrome

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INTRODUCTION

PCOS is the most common endocrine disorder in the fertile female age group and hyperandrogenism,oligoanovulation, and polycystic ovarian morphology are the main features of disease(1,2). These features are related to future metabolic risks for the patient such as obesity, insulin resistance (IR), glucose intolerance, diabetes and metabolic syndrome (3-5). The pathogenesis of PCOS is not clear today. According to studies, insulin resistance and hyperinsulinemia have been found together in obese PCOS. (3,4,6). Insulin resistance is thought to be responsible for hormonal and metabolic disorders observed in PCOS. PCOS has two phenotypes, obese and normal weight, the latter being a much less common presentation of the syndrome(7).

Betatrophin is a protein originated from liver and adipose tissue known in the following names refeeding-induced fat and liver protein-RIFL (8, 9), lipasin (8,10) or atypical angiopoetin-like protein 8 (ANGPLT8) (8,11). It is a novel glucolipid metabolic regulation factor and plays a key role in insulin metabolism by controlling beta cell proliferation in pancreatic beta cell islets in mice (3,12). It is also related with glucose homeostasis and lipid metabolism by taking dual roles (13,14). In humans, the role of betatrophin in glucose metabolism is controversial. Several reports indicated that betatrophin levels were increased in insulin resistance (8), obesity and type 2 diabetes (15-18) whereas other data claims the opposite (19,20). Betatrophin was also investigated in PCOS patients in comparison with non-PCOS healthy women (18,20-21). Most of the studies and a current meta-analysis (22) revealed the betatrophin levels increased in PCOS patients as compared to non-PCOS cases and these sudies showed a positive correlation between serum betatrophin concentration and HOMA-IR in women with PCOS (20). On the contrary some other studies showed that a negative correlation between fasting serum betatrophin concentration and HOMA-IR (23).

The aim of the present study was to compare the serum betatrophin levels in patients with overweight/obese and normal weight PCOS and and to investigate the relationship between betatrophin and insulin resistance.

MATERIALS AND METHOD

A total of 73 reproductive age women with PCOS according to 2003 Rotterdam ESHRE/ASRM PCOS Consensus Workshop Group diagnostic criteria were included in this prospective cross-sectional study(24). Patients were recruited from the Reproductive Endocrinology Clinic of Zekai Tahir Burak Women's Health and Research Hospital. This study was approved by the Institutional Review Board of the aforementioned hospital. Informed consent was obtained from every included patient.

Exclusion criteria included the following: Pregnancy and breastfeeding, morbid obesity, an additional systemic disease (i.e.,hyperprolactinemia, thyroid dysfunction, hypertension, liver or kidney diseases, cardiovascular disease, dyslipidemia, type 1 or type 2 diabetes, chronic or acute infection within the previous 30 days), smoking, and using hormonal contraception or antiandrogen therapy.

The patients were divided into two groups according to their BMI values : Group 1 consisted of lean (BMI<25 kg/m2) PCOS cases (n=35) and Group 2 (n=38) consisted of overweight/obese (BMI≥ 25 kg/m2) PCOS cases.

Waist-to-hip ratio(WHR), fasting blood glucose (FBG) and fasting insulin(FI), serum betatrophin concentrations at baseline were estimated. Blood samples were obtained after fasting overnight for at least 10 hours.

The modified Ferriman Gallwey score for the detection of hirsitismus was obtained in all patients. A score of 8 and above was considered significant for hirsutmus(25,26).

A 2-h oral glucose tolerance test was used to evaluate impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) that reveals the presence of IR in clinical practice. After a 12-h overnight fasting, participants ingested 75 g glucose, and glucose and insulin concentrations were determined at baseline and after 120 min. Fasting glucose was measured using a glucose oxidase assay. Impaired glucose tolerance (IGT) was defined as two-hour glucose levels of 140 to 199 mg/dL. Insulin was measured by the immunoradiometric method.

Homeostasis model assessment insulin resistance (HOMA-IR) was calculated using this formula: fasting glucose (mg/dL) x fasting insulin (mU/L)/405. A HOMA-IR value of 2,5 was taken as a cut-off point (27). All results were compared between the groups.

Fasting maternal blood samples were obtained from the mother in the form of venous blood . Serum samples were separated by centrifugation at 5000 revolutions/min (2236 g) for 10 min within 15–20 min of blood sampling. They were frozen immediately and kept at -80 C until final analysis.

Serum betatrophin levels was detected by enzyme-linked immunosorbent assays (CHEMWELL 2900, ALGEN, ELISA) using commercially available kit (Human betatrophin, YL Biont, ELISA.) in duplicate. Results were reported as ng/L. Intraassay and interassay %CV (Coefficient Variation) values are given as <8%, <10%, respectively.

Statistical Analysis

Statistical analyses were perfrmed with IBM SPSS (Statistical Package for Social Sciences) software, version 21.0 (https://www.ibm.com/support/pages/how-cite-ibm-spss-statistics-or-earlier-versions-spss). The normality of the data was evaluated for all of the quantitative variables by using the Kolmogorov–Smirnov test, and the descriptive statistics were expressed as the Mean±Standard deviation or median (min–max). When the data were not normally distributed, a Mann–Whitney U test was used to compare the two groups. The comparison between the categorical variables was performed using the Chi-square test and $p<0.05$ was accepted as significant. Multiple Lineer Regression analisis was used to determine the variables affecting betatrophin. In this regression model, betatrophin was taken as the dependent variable. Age, WHR, HOMA-IR, BMI and IGTT were taken as independent variables.

Power analysis was performed using G-power software (G-power v3.1.9.2, Universitat Kiel, Kiel, Germany). Difference between two independent means (two groups) power analysis demonstrated that we achieved a power of 0.80 with a 5% level of significance. Accordingly, 35 patients from each group were sufficient.This analysis was performed between the two groups using comparison of the Betatrophin values.

RESULTS

A total of 73 cases were included. Mean age, BMI and WHR values of participants were 23.6±4.4 years, 26.11±5.3 kg/m2 and 0.92±1,05 respectively; mean total testosterone concentration, mean baseline plasma glucose concentrations, mean blood glucose values of 2 -hour post-glucose load and mean HOMA-IR values were 0,57 ±0,2 ng/mL, 92.5±7.5 mg/dl, 107±23.6 mg/dl and 2.6±0.5, respectively. Mean betatrophin level and were found 1041±148 ng/L. Only 20% of the all cases had a mFG score of 8 and above.

When the groups were compared, subjects with overweight/obese PCOS had a significantly higher FI, plasma glucose of 2 -hour post-glucose load, HOMA-IR and WHR values. The circulating betatrophin concentration was higher in the lean PCOS patients than in overweight/obese PCOS patients (691,8±996 ng/L vs 1421,4±1279 ng/L, p=0.023).The clinical and biochemical characteristics of the studied groups are presented in Table 1.

Table 1. The clinical and biochemical characteristics of the studied groups

Mean±SD	Lean PCOS (n=35)	Overweight/obese PCOS (n=38)	P value
Age(year)	22,26 ± 3,9	24,7± 4,5	**0,016**
WHR	0,8 ± 0,2	1,02 ±1, 5	**0,000**
FBG (mg/dl)	90 ±7,2	93 ± 7,6	0,140
FI(mIU/mL)	9,2±3,3	13,6±8,9	**0,005**
2-hour post-glucose load blood glucose (mg/dl)	98 ± 19,6	114±24,7	**0,004**
HOMA-IR	2,1±0,8	3,1±2,1	0,008
Betatrophin(ng/L)	1421,4±1279	691,8±996	0,023

SD: Standard deviations;BMI: Body mass index;WHR: Waist/Hip Ratio;FBG: Fasting Blood Glucose;

FI: Fasting ınsulin; HOMA-IR: Homeostasis Model Assessment-Insulin resistance

Clinical indexes with significant differences ($P < 0.05$) are in bold.

To further explore the association of plasma betatrophin level with metabolic characteristics, groups were divided into two sub-groups according to WHR, 2-h post-glucose load blood glucose and HOMA-IR values. In 80 % of the overweight/obese PCOS group, WHR was above 0.85. Comparison of the WHR, 2-hour post-glucose load blood glucose and HOMA-IR values in normal weight and overweight/obese PCOS are presented in Table 2.

Table 2. Comparison of the WHR, 2-hour post-glucose load blood glucose and HOMA-IR values in normal weight and overweight/obese PCOS

	Lean PCOS (n=35)	Overweight/obese PCOS (n=38)	P value
Waist-to-hip ratio			
<0.85	58.5% (n=31)	41.5% (n=22)	
≥0.85	20% (n=4)	80% (n=16)	**0.008**
2-hour post-glucose load blood glucose (mg/dl)			
<140	50.8% (n=33)	49.2% (n=32)	
≥140	25% (n=2)	75% (n=6)	0.264
HOMA-IR			
<2.5	68,57% (n=24)	52,63 % (n=20)	
≥2.5	31,43 % (n=11)	47,37 %(n=18)	0.250

HOMA-IR: Homeostasis Model Assessment-Insulin resistance P-values in bold are statistically significant (p<0.05)

It was found that there was no statistically significant difference in circulating betatrophin levels of those with WHR below and above 0.85 (p=0.097). In terms of serum betatrophin concentrations, no significant association was found between those with 2 -hour post-glucose load <140 and those with ≥140 (p=0.230). There was no significant association between HOMA-IR values (below and above 2.5) and circulating betatrophin concentrations (p=0.420). Associations of clinical and laboratory parameters with serum betatrophin concentration are presented in Table 3.

Table 3. Association of evaluated parameters with serum betatrophin concentration

Mean±SD	Serum betatrophin concentration (ng/L)	P value
Waist-to-hip ratio <0.85(n=53) ≥0.85 (n=20)	1214±1249 583±892	97
2-hour post-glucose load blood glucose (mg/dl) <140 (n=65) ≥140 (n=8)	1090±1214 647±946	230
HOMA-IR <2.5 (n=44) ≥2.5 (n=29)	1290±1379 877.9±1032	420
BMI(kg/m2) <25 (n=35) ≥25 (n=38)	1421±1279 691±996	23

Considering all the other factors affecting circulating betatrophin concentration according to Anova regression analysis, it was concluded that serum betatrophin concentration decreased with increasing age and WHR (p = 0.008 and p = 0.049, respectively). The variables affecting circulating betatrophin concentration are presented in Table 4.

Table 4. Regression analysis of the variables affecting circulating betatrophin concentration: standardized regression coefficients

	Standardized Coefficients	P values
Age	-.326	**0.008**
2-hour post-glucose load blood glucose (mg/dl)	.000	0.999
HOMA-IR	.176	0.137
WHR	-.236	**0.049**
BMI(kg/m²)	-.008	0.952

P-values in bold are statistically significant (p<0.05)

DISCUSSION

In the present study, circulating betatrophin concentrations were found significantly lower in the overweight/obese PCOS group compared to the lean PCOS group. Additionally, circulating betatrophin concentrations in groups were found similar according to the FBG, 2-hour post-glucose load blood glucose, HOMA-IR and WHR values. Considering all the factors affecting circulating betatrophin concentration, it was found that serum betatrophin concentration correlates only with age and WHR.

Previous studies have shown that betatrophin, a protein-derived hormone produced from liver and adipose tissue, plays a role in insulin secretion by pancreatic islet cell induction (28,29). In addition, betatrophin is not only involved in glucose metabolism but also in lipoprotein metabolism(28,30). In animal studies, betatrophin was found to increase insulin production and regulate glucose metabolism by beta cell proliferation (28) and circulating betatrophin was found to be higher in patients with type 2 diabetes (31,32). In the gestational diabetes group, betatrophin was found to be high in the third trimester if the

pregnant were overweight (33,34).

According to the in vivo and in vitro studies it has been emphasized that the regulation of betatrophin is a useful marker for insulin resistance and metabolic diseases (21). Circulating betatrophin has also been examined in PCOS patients. Available studies in the literature have reported conflicting results with elevated (18,20), decreased or similar (8,21) serum concentrations of betatrophin in PCOS patients as compared to controls.

In some studies, serum concentration of betatrophin has been found to be associated with IR and metabolic syndrome in PCOS patients regardless of being obese or lean (8,35). On the contrary, in the study of Kahraman et al., it was stated that in PCOS patients had no relation to insulin resistance and circulating betatrophin concentration Conversely, in the study of Kahraman et al., no significant relationship was found between serum circulating betatrophin and insulin resistance (1). In a different study exploring the association of betatrophin levels with metabolic parameters in lean and overweight/obese women with and without PCOS, it was found that betatrophin level was higher in lean PCOS with compared to overweight/obese PCOS. The authors were stated that the reason for this contradictory situation may be due to different metabolic types of PCOS(3). As a result of a current meta-analysis of 11 studies, circulating betatrophin was significantly higher in PCOS patients than non-PCOS controls most likely regardless of lean or obese BMI (22).

In this meta-analysis, according to the results of subgroup analysis, it was found that the increased betatrophin concentrations were basically due to the presence of PCOS, regardless of BMI. In addition, this meta-analysis suggests that elevated betatrophin levels in PCOS become more prominent with higher age and IR.

Since betatrophin levels were found to be different in patients with PCOS compared to normal individuals in previous studies, we only included obese and normal weight patients with PCOS in this study. Furthermore, based on the hypothesis that the dominant expression site of betatrophin is in adipose tissue, we divided our study population into two groups according to their BMI values and compared lean and overweight/obese PCOS cases. As a result of our study, betatrophin concentration was found to be statistically significantly lower in the overweight/obese PCOS group compared to the lean group. Similarly, in a prospective cross sectional study, it was stated that significantly higher plasma betatrophin levels in lean PCOS compared with overweight/obese PCOS(3).

The IR in patients with PCOS is closely associated with an increase in the amount of abdominal fat and overweight. In our study, 2-hour post-glucose load blood glucose, FI and HOMA-IR values were significantly higher in the overweight/obese group Circulating betatrophin levels were found significantly lower compared to the lean group. Additionally, circulating betatrophin levels were found similar in the subgroup of PCOS patients having HOMA-IR ≥ 2.5 and HOMA-IR<2.5. Multiple linear regression analysis revealed that WHR and age were independently associated with betatrophin levels in our studied group. In the study of Li et al., the circulating betatrophin levels were found to be negatively correlated with WHR and HOMA-IR in PCOS group (3). Based on the results of a current meta-analysis that included the aforementioned study (22) statistical significance was not achieved according to betatrophin levels in obese and lean PCOS. Inconsistent with the results of our study, in this meta-analysis circulating betatrophin levels were found significantly higher in the subgroup of studies with PCOS patients having HOMA-IR >2.5 and this results was interpreted as possibility of association between increased betatrophin and IR in PCOS. As a result of a study, authors were shown that a significant increase of circulating betatrophin in untreated IR women and different effects of elevated insulin on betatrophin in vivo and in vitro which selected only women with IR. They were also found that metformin or rosiglitazone decreases circulating levels and expression of betatrophin (29). Furthermore in aforementioned meta-analysis, it was stated that the significant positive correlations were found betatrophin with age, free androgen index and free testosterone in PCOS cases (22) However, other studies in literature have conflicting results on the correlation between betatrophin and HOMA-IR.

Different opinions in previous studies on betatrophin suggest that there may be mechanisms of batatrophin that have not yet been clarified. Since betatrophin is a hormone that secretes insulin in the pancreas, it is not clear whether increased betatrophin is responsible for glucose intolerance by increasing insulin, or whether increased insulin reduces betatrophin with a negative feedback effect in already glucose intolerance. Conflicting results regarding betatrophin in obese and normal weight patients in PCOS complicates the issue. In our study, although fasting insulin, 2-hour oral glucose loading and HOMA-IR were found to be statistically significantly higher in the obese group, it was found that they did not affect betatrophin levels in the regression analysis.

The fact that we found betatrophin lower in the obese group in our study may be considered as the betatrophin-reducing effect of insulin and HOMA-IR elevation in the obese group with negative feedback. Although this is not a definitive judgment, it is a mechanism that comes to mind.

In our study, the decrease in betatrophin in the obese group suggests that the role of betatrophin not only in insulin resistance but also in fat tissue metabolism may be important. Betatrophin is not fully understood, the current results of our study may lead to some interpretations. Weight appears to be a factor influencing betatrophin levels, but it may not be the sole determinant. Various factors, including hormonal and metabolic aspects, likely contribute to the regulation of betatrophin. The interplay between weight, PCOS, and betatrophin is a complex area that requires further research for a comprehensive understanding. There are contradictory statements on the subject in the literature. There are many studies that are compatible with our results (3) and many that are not.

The inconsistency with some other studies in the literature regarding the possible relationship between IR and betatrophin levels may be related to our patient selection criteria. Most of the patients in our studied group were young, non-hyperandrogenic women with a BMI values close to the overweight limit. And also according to the HOMA-IR results, 68,5% of the lean group and 52,5% of the overweight/obese group were HOMA-IR <2.5. When 2-hour post-glucose load blood glucose levels were evaluated in terms of demonstrating impaired glucose tolerance, those with ≥140 mg/dl were in only 6 cases in the overweight/obese group. HbA1c and FAI were not evaluated in our study and our study group did not consist of full-blown PCOS cases. All these factors can be counted among the limitations of our study.

In conclusion, insulin resistance is at the center of the pathogenesis in PCOS and is responsible for most of the metabolic complications. According to the limited number of studies and meta-analysis results circulating betatrophin may be associated with IR, obesity and dyslipidemia although their results are contradictory. The relationship between betatarofin insulin resistance, betatrophin PCOS and insulin resistance, and the mechanisms related to the relationship between obesity and PCOS betatrophin have not yet been adequately clarified.In this respect, it can be said that betatrophin is not a biomarker to adequately explain insulin resistance in obese and normal weight PCOS. However, more studies are needed on which of these have a more significant relationship with circulating betatrophin.

Declaration of interest statement: The authors have no conflict of interest.

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Olgu Sunumu | Case Report

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Amniyotik Sıvı Embolisi Olgusunun Başarılı Yönetimi

Successful Management of a Case with Amniotic Fluid Embolism

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ÖZ

Amniyotik sıvı embolisi (AFE), yüksek maternal ve fetal mortalite ve morbiditeye sahip obstetrik acil bir durumdur. Prognozu belirleyen en önemli faktör erken tanı ve tedavidir. Erken tanı ve zamanında müdahale ile başarıyla tedavi edilen bir amniyotik sıvı embolisi olgusunu sunuyoruz.

Fetal böbrek anomalisi nedeniyle 10 gün önce ürinom drenajı ve kordosentez yapılan 20 yaşındaki hastada doğum sırasında solunum durması gelişti ve ardından vajinal doğumdan yaklaşık 90 dakika sonra yoğun kanama meydana geldi. AFE tanımızla masif kan transfüzyonu, fibrinojen replasmanı ve intrauterin balon hızla uygulandı. AFE tanısı klinik olarak ve ayırıcı tanılar dışlanarak konulmuştur. Hastamız, komplikasyonsuz bir şekilde taburcu edildi.

Anahtar Kelimeler: amniyotik sıvı embolisi, yüksek riskli gebelik, maternal risk, doğum öncesi tanı.

ABSTRACT

Amniotic fluid embolism (AFE) is an obstetric emergency with high maternal and fetal mortality and morbidity. The most important factor in determining the prognosis is early diagnosis and treatment. We present a case of amniotic fluid embolism that was successfully treated with early diagnosis and intime management.

Respiratory arrest developed during labor in a 20-year-old patient who underwent urinoma drainage and cordocentesis for fetal renal anomaly 10 days ago and then profuse bleeding occurred approximately 90 minutes after vaginal delivery. With our definition of AFE, massive blood transfusion, fibrinogen replacement and intrauterine balloon were applied quickly. The diagnosis of AFE was made clinically and excluding differential diagnoses. She was discharged without complications.

Keywords: amniotic fluid embolism, high risk pregnancy, maternal risk, prenatal diagnosis.

BACKGROUND

Amniotic fluid embolism (AFE) is a rare obstetric emergency that can lead to sudden death. Amniotic fluid and fetal components that pass into the maternal circulation activate the maternal complement system, causing an anaphylactic reaction and as a result, sudden cardiopulmonary collapse and early-onset disseminated intravascular coagulation (DIC) develops(1, 2). Amniotic fluid embolism was first described by Meyer in 1926(3). The mortality rate is associated with early diagnosis and rapid resuscitation, and when more than 17 million births and 751 AFE cases in eight countries were analyzed, the overall maternal mortality rate was found to be 20.3%(4). Informed consent was obtained from the patient to present a case of amniotic

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fluid embolism, which was treated with an early diagnosis and multidisciplinary approach.

CASE PRESENTATION

The patient was 20 years old, gravida 2, parity 1 and had a history of COVID-19 infection at the 7th week of her pregnancy. During the fetal ultrasonographic scan, fetal left kidney dimensions and parenchymal echo together with a thin-walled, anechoic cyst of 46x32 mm significantly increased was detected. Therefore, an invasive prenatal diagnostic procedure was recommended to the patient, but the patient refused. In the control examination performed 1 week later, the cyst in the left kidney was measured as 54x39 mm. Thereupon, urinoma drainage and cordocentesis were performed after the betamethasone dose and there were no early complications due to the procedure. The patient was admitted to hospital with 4 cm cervical dilatation 10 days after the procedure. Her blood pressure was 114/66 mmHg, heart rate was 97/min, oxygen saturation (SpO2) was 96%, body temperature was 36.5°C, and fetal heart rate was 120-130/min. Antibiotic and neuroprotective magnesium treatments were applied to the patient with high C-Reactive Protein (CRP) and cervical dilation. The patient delivered 9 hours after her hospitalization. During the straining, her breathing became shallow and she lost consciousness. An Emergency Code was given for the patient who developed respiratory arrest at 13:50 and then an oropharyngeal airway was inserted. Oxygen was given at a rate of 12 L/min, she was monitored and blood analysis was requested. The first venous blood gas analysis result showed pH 7.27, base excess (BE) -9.4, lactate 4.06.

Her blood pressure dropped to 62/43 mmHg and SpO2 to 73%. Within 10 seconds, at 13:50, a 950 gram male infant was delivered vaginally with APGAR scores of 3 and 7 at one and five minutes, respectively. Following delivery, the placenta and its appendages were completely separated. Postpartum 10 units of oxytocin intramuscularly and 20 units of oxytocin infusion were given intravenously at a rate of 125 ml/hour. Active vaginal bleeding was not observed and the uterus was contracted. At 13:58, the patient was intubated and taken to the intensive care unit (ICU). Post-intubation blood pressure was 48/35 mmHg, heart rate was 138/min, SpO2 was 80% and body temperature was 37.6°C. Fluid resuscitation was started, she was monitored and blood analysis was requested. The patient was administered 80 mg of methylprednisolone intravenously daily for 3 days. Misoprostol was given 2 tablets rectally. Considering the possibility of DIC due to the presence of hematuric urine, 2 g of fibrinogen was given intravenously. Following fluid resuscitation, systolic blood pressure values increased to 90, 110, 120 mmHg, respectively and SpO2 to 98%. The patient started to move and it was observed that she had limited range of motion in her right upper extremity. Upon the normalization of blood pressure and oxygen saturation values, emergency Cranial-Thorax-Abdominal Computed Tomography (CT) was performed on the patient. CT results were evaluated as normal. During the vaginal examination performed on the patient who came back to the ICU at 15:25, it was observed that the patient had excessive vaginal bleeding consistent with DIC. Abdominal ultrasound was performed, bleeding focus was not observed. 2 units of red blood concentrates (RBCs) and 4 units of freshly frozen plasma (FFP) were immediately transfused. Another 2 g of fibrinogen was given. An intrauterine balloon was applied to the patient and the balloon was inflated to 300 cc. Abdominal ultrasound was repeated and no bleeding was observed. In the meantime, it was observed that the patient's bleeding decreased. A left femoral catheter was inserted into the patient. COVID PCR was studied and the result was negative. Control blood tests were repeated and another 2 g of fibrinogen was given at 16:50 (fibrinogen 0.85 g/dL). Methylergonovine ampoule was administered intramuscularly. 40 units of oxytocin infusion were continued at a rate of 50 ml/hour. Broad-spectrum antibiotic treatment was started due to suspicion of antenatal subclinical chorioamnionitis. As a result of echocardiography at 18:30, the right atrium and ventricle were observed as slightly dilated. Elevated cardiac markers (troponin I 4213 ng/L, nt-pro BNP 506 ng/L, CK-MB mass 5.95 µg/L, myoglobulin 158 µg/L) and changes in electrocardiography (sinus tachycardia and anterior t negativity) was thought to be secondary to hypoxia that developed after DIC as a result of the patient's follow-up. According to results of the repeated blood test at 18:00, 20 units of cryoprecipitate, 3 units of FFP, 5 ampoules of calcium and 8 ampoules of potassium were given (fibrinogen 1.08 g/dL, potassium 2.9 mEq/L, calcium 7.7 mg/dL). 2 units of RBCs were inserted as a result of the blood tests performed at 20:00 (hemoglobin 7.5 g/dL).

The patient was extubated on the second day. Oxygen was given by mask at 6 L/min.

Diffusion magnetic resonance imaging was requested from the patient due to loss of consciousness during delivery, loss of strength in the right extremity and slowness of speech. As a result, acute infarction was detected in the left capsula externa

and posterior capsula interna. Therefore enoxaparin sodium was started subcutaneously.

On the third day, 1 unit of RBCs and 8 ampoules of potassium were given (hemoglobin 8.9 g/dL, potassium 3.1 mEq/L).

The time series results of blood sampling, vital signs and oxygen saturations are shown in Table 1.

Table 1: Laboratory Data, Vital Signs and Oxygen Saturation

	During hospitalization	Postpartum 1st minute	After 2nd hour	After 4th hour	After 6th hour	After 2nd day	After 3rd day	After 4th day
Laboratory Data								
Hemoglobin (g/dL) [12-15.6]	11.3	11.8	10.2	9.5	7.5	9.7	8.9	10.1
Hematocrit (%) [35.5-45.5]	34.5	32.9	29.1	28.5	21.7	27.2	27.7	31.5
WBC ($x10^6$/L) [3900-10200]	12200	23010	26070	20280	12060	13140	9570	6880
PLT ($x10^9$/L) [150-400]	234	142	188	158	142	155	152	160
Fibrinogen (g/L) [1.7-4.2]	5.22	N/A	0.85	1.08	2.65	3.36	3.79	3.50
D-dimer (mg/L) [<0,55]	N/A	1.49	N/A	>35.2	N/A	>35.2	12.48	N/A
Calcium (mg/dL) [8.7-10.4]	8.1	7.5	7.4	7.7	8.0	9.0	8.4	8.6
Magnesium (mg/dL) [1.3-2.7]	1.7	3.7	2.5	2.2	2.1	1.7	1.6	1.7
Potassium (mEq/L) [3.5-5.5]	3.7	3.6	2.5	2.9	3.1	4	3.1	3.6
pH [7.37-7.45]	N/A	7.28	7.29	7.33	7.40	7.42	7.45	7.43
BE (mmol/L) [(-2)-(+3)]	N/A	-9.4	-6.8	-3.6	-1.2	-2.8	-3	-1.4
Lactate (mmol/L) [4.5-20]	N/A	4.06	5.48	3.44	3.22	1.04	0.67	0.68
Vital Signs								
Blood Pressure (mmHg)	114/66	62/43	118/62	77/45	116/62	103/75	101/56	117/81
Pulse Rate (beats/min)	97	133	113	110	116	93	65	63
Body Temperature (°C)	36.5	37.6	36.8	36.6	37	36.5	36.4	36.2
Respiration Rate (breaths/min)	16	0	20	18	16	18	16	14
Oxygen Saturation								
SpO2 (%)	96	73	98	97	99	96	95	96

In total, 5 units of RBCs, 20 units of cryoprecipitate, 7 units of FFP and 6 g of fibrinogen were given to the patient. She was discharged from the hospital on the 14th postnatal day without any complications.

DISCUSSION

AFE is a complication of labor that usually results in death. The classic triad of AFE is sudden onset hypotension, hypoxia and coagulopathy. Body temperature should be normal and symptoms should have appeared during labor, placental delivery or up to 30 minutes later. The diagnosis of AFE is made clinically and excludes pulmonary embolism, peripartum cardiomyopathy, septic shock, myocardial infarction, venous air embolism, eclampsia, anaphylaxis, cephalad spread of spinal anesthetic(5).

The main risk factors for the development of AFE are advanced maternal age, placenta previa, placenta accreta, ablatio placenta, preeclampsia, eclampsia, gestational diabetes, multiple pregnancies, polyhydramnios, cerebrovascular, heart and kidney diseases, multiparity, male fetuses, trauma such as uterine rupture, cervical laseration, amniocentesis, cordocentesis, amnioinfusion, amniotomy, labor, labor induction, cesarean delivery, dilatation and curettage (5, 6). Regardless of the etiology, early diagnosis and treatment of AFE can be lifesaving.

In our case, the risk factors for AFE were male fetus, history of invasive prenatal diagnostic procedure, labor and multiparity. Our patient did not suffer from chronic hypoxia, as the patient who developed respiratory arrest during delivery was intubated in the early period. Bleeding was controlled with uterotonic treatments, intrauterine balloon, replacement of depleted blood products and electrolytes applied rapidly in the postpartum period. With this approach we could effectively manage two serious complications of AFE, hypoxia and DIC.

There is no specific diagnostic test or treatment for AFE. The main cause of mortality and morbidity associated with AFE is DIC and its complications. In the present case, early diagnosis, intensive and serial fibrinogen replacement are the main factors behind the patient's sequela-free survival.

DISCLOSURE

No potential conflict of interest was reported by the authors.

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