## Türk Kadın Sağlığı ve Neonatoloji Dergisi

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Original Article

# **Outcomes of Fertility Sparing Surgery for Borderline Ovarian Tumors**

# Borderline Over Tümörlerinde Fertilite Koruyucu Cerrahi Sonuçları

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### **Abstract**

**Aim:** The aim of this study was to investigate the results of fertility-preserving and/or radical surgery, the effects of fertility-preserving surgery on fertility and the postoperative recurrence rate in patients with borderline ovarian tumors.

**Material and Method:** The study included 138 patients who were diagnosed with borderline ovarian tumors in the oncology clinic of a tertiary institution in Ankara. The patients' data were analyzed retrospectively from the hospital information system. Among 138 patients, age, parity, type of surgery, number of lymph nodes removed, recurrence rates, pregnancy rates after treatment and fertility and recurrence analysis were performed. Recurrence and fertility rates were compared between those who underwent fertility preserving surgery and those who did not.

**Results:** The distribution of the patients' age groups is as follows: 21% of the patients were under the age of 30; 26.1% were between 31-40 years of age, and 21% were between 41-50 years of age. The BMI data of the patients shows that 20.3% of the patients were in normal weight, on the contrary, 44.9% were overweight (25 kg/m2 to 29.9 kg/m2). According to the pathology results of the patients, 63% (n=87) were serous, 31.9% (n=44) mucinous, 5.1% (n=7) endometrioid type borderline ovarian tumors. Spontaneous pregnancy was observed in 31% (n=18) and pregnancy as a result of assisted reproductive techniques in 5.2% (n=3) of the patients who underwent fertility preserving surgery. According to the results of the study, it is observed that there is a statistical relationship between recurrence and fertility preservation. Recurrence was observed in 2.5% (n=2) of the individuals whose fertility was not preserved while recurrence was observed in 24.1% (n=14) of individuals whose fertility was preserved. Although it was observed that recurrence increased in patients who underwent fertility preservation surgery, it allowed pregnancy to be achieved at a rate of approximately 36%.

**Conclusion:** Since patients with borderline ovarian tumours are younger than patients with invasive ovarian cancer, fertility-sparing surgery is becoming increasingly important.

Keywords: Epithelial ovarian cancer; recurrence; fertility; surgery

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# Öz

**Amaç:** Bu çalışmanın amacı borderline over tümörüne sahip hastalarda fertilite koruyucu ve/veya radikal cerrahilerin sonuçlarını, fertilite koruyucu cerrahinin fertilite üzerine etkisini ve postoperatif nüks oranlarını araştırmaktır.

**Gereç ve Yöntem:** Çalışmaya Ankara'da yer alan 3. basamak bir sağlık kuruluşunun onkoloji kliniğinde borderline over tümörü tanısı alan 138 hasta dahil edildi. Hastaların verileri hastane bilgi sisteminden retrospektif olarak analiz edilmiştir. 138 hastanın yaş, parite, ameliyat tipi, çıkarılan lenf nodu sayısı, nüks oranları, tedavi sonrası gebelik oranları ve doğurganlık ve nüks analizleri yapıldı. Nüks ve fertilite oranları fertilite koruyucu cerrahi uygulananlar ve uygulanmayanlar arasında karşılaştırıldı.

**Bulgular:** Hastaların yaş gruplarına göre dağılımı aşağıdaki gibidir: Hastaların %21'i 30 yaşın altında; %26,1'i 31-40 yaş arasında ve %21'i 41-50 yaş arasındadır. Hastaların VKİ verileri, hastaların %20,3'ünün normal kiloda olduğunu, buna karşılık %44,9'unun aşırı kilolu (25 kg/m2 ila 29,9 kg/m2) olduğunu göstermektedir. Hastaların patoloji sonuçlarına göre %63'ü (n=87) seröz, %31,9'u (n=44) müsinöz, %5,1'i (n=7) endometrioid tip borderline over tümörüdür. Fertilite koruyucu cerrahi uygulanan hastaların %31'inde (n=18) spontan gebelik, %5,2'sinde (n=3) ise yardımcı üreme teknikleri sonucu gebelik gözlendi. Çalışma sonuçlarına göre, nüks ile fertilite koruma arasında istatistiksel bir ilişki olduğu görülmektedir. Fertilitesi korunmayan bireylerin %2,5'inde (n=2) nüks gözlenirken, fertilitesi korunan bireylerin %24,1'inde (n=14) nüks gözlenmiştir. Fertilite koruma cerrahisi uygulanan hastalarda nüksün arttığı gözlense de yaklaşık %36 oranında gebelik elde edilmesine olanak sağlamıştır.

**Sonuç:** Borderline over tümörlü hastalar invaziv over kanserli hastalardan daha genç olduğundan, fertilite koruyucu cerrahi giderek daha önemli hale gelmektedir.

Anahtar Kelimeler: Epitelyal over kanseri; rekürrens; fertilite; cerrahi

### 1. Introduction

Borderline ovarian tumors (BOT) are neoplasms of epithelial origin characterized by increased cell proliferation and the presence of mild nuclear atypia, but without destructive stromal invasion (1). This group of tumors was first described by Taylor in 1929 as "semi-malignant" ovarian tumors with peritoneal involvement but surprisingly good prognosis and later recognized by the International Federation of Gynecology and Obstetrics (FIGO) in 1971 as tumors with "low malignant potential" in contrast to ovarian carcinomas (2), followed by the WHO in 1973 (3). The current 2014 WHO classification of tumors of the female reproductive organs uses the term "borderline tumor", which is interchangeable with "tumor with atypical proliferation" (4), while the previously proposed synonym "tumor of low malignant potential" is no longer recommended (5,6). The six histological subtypes of BOT are differentiated according to epithelial cell type, similar to invasive carcinomas. These include serous (50%) and mucinous (45%) and less common subtypes such as endometrioid, clear cell, seromucinous and borderline Brenner tumors (1,5).

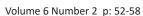
BOTs usually have an asymptomatic course and patients are often diagnosed by pathologic examination of the intraoperative specimen. Surgical treatment of BOTs is the same as for malignant ovarian tumors except for lymphadenectomy during

surgical staging (7,8). In addition to radical surgical treatment, fertility preserving conservative surgery is another option. In young women with early stage (FIGO I-II) tumors, conservative treatments are appropriate for fertility preservation as long as close follow-up is performed (9). Recurrence rates seem to have reached 75% in patients who underwent oophorectomy and cystectomy for fertility preservation (10). Prognostic factors affecting the recurrence rate include advanced stage disease, the presence of invasive tumor implants resembling low-grade serous carcinoma in serous tumors, residual tumor in fertility preserving procedures such as cystectomy or unilateral salpingo-oophorectomy, incomplete surgical staging and tumor pathologies with microinvasive or micropapillary histology (11).

As the cancer rates accelerate, more and more young people are being diagnosed with cancer. Therefore, the interest in fertility-sparing surgery is increasing. The aim of this study is to compare the patients who underwent fertility-sparing and those who underwent non-fertility-sparing surgery along with the effect of fertility-sparing surgery on survival and postoperative recurrence rates.

### 2. Material and Method

Patients were diagnosed with borderline ovarian tumor between the dates 01.01.2001 and 31.12.2020 in the Gynecologic Oncology Surgery Clinic of the Ministry of Health,





Health Sciences University Etlik Zübeyde Hanım Gynecological Diseases Training and Research Hospital between 01.01.2001 and 31.12.2020. The patients' treatment and follow-up were performed in the same hospital, so patients whose information could be accessed in the database were evaluated. Patients whose surgery and follow-up were outside this hospital and patients with synchronous or metastatic tumors were excluded from the study.

The examined patients include those who underwent fertility-sparing and those who underwent non-fertility-sparing surgeries. Fertility-sparing surgical procedures consisted of unilateral salpingo-oophorectomy (USO), in which the uterus and other ovary were preserved, and cystectomy, in which only the cyst was removed, while hysterectomy, bilateral salpingo-oophorectomy (BSO), pelvic and paraaortic lymphadenectomy, omentectomy and peritoneal biopsy were non-fertility-sparing procedures. The largest postoperative residual tumor diameter less than or equal to 1cm (R≤1cm) was considered optimal cytoreduction.

Demographic characteristics, pathology results, FIGO stages, medical and surgical treatment modalities, controls, progression-free or disease-free survival and overall survival rates of the patients were retrospectively analyzed from patient data registered in the system or electronic database and patient council files.

Postoperative treatment and follow-up of the patients were performed by the gynecology-oncology outpatient clinics in the Gynecologic Oncology Clinic of Ankara Etlik Zübeyde Hanım Training and Research Hospital Clinical examination, ultrasonography and serum CA-125 levels were measured every 3 months for the first year after the operation, every 6 months for 2 years and then annually. Patients whose last follow-up period was more than 24 months were considered lost to follow-up.

Ethics committee approval of the study was obtained from Local Ethics Committee on 21.01.2022 (Decision no: 2022/11 Date: 21.01.2022).

### Statistical analysis

SPSS 24.0 was used for the statistical analysis of the data. In addition to the distributions for the variables within the scope of the study; chi-square test or Fischer's Exact test was used to test the relationship between the relevant variables. Logistic regression analysis was used to examine the presence of fertility preservation. Statistical significance was defined as p<0.05.

#### 3. Results

The study included 138 patients with BOT. Of the 138 patients included in the study, 58 patients underwent fertility preserving surgery and the remaining 80 patients underwent non-fertility preserving surgery.

According to the results of the analysis, when the distribution of the demographic characteristics of the individuals was analyzed, it was seen that 21% (n=30) of the patients were under 30 years of age, 26.1% (n=36) of the patients were between 31-40 years of age at diagnosis, and 21% (n=29) of the patients were between 41-50 years of age. According to BMI data, 20.3% of the patients were of normal weight, whereas 44.9% were overweight (25 kg/m2 to 29.9 kg/m2).

Among the patients, 14 patients underwent cystectomy, 44 patients underwent USO, 79 patients underwent BSO with total abdominal hysterectomy and 1 patient underwent BSO with total laparoscopic hysterectomy. On the other hand, 60.9% (n=84) of the individuals underwent lymphadenectomy. 59.4% (n=82) underwent pelvic lymphadenectomy and 5.8% (n=7) of these patients had metastatic lymph nodes. 60.1% (n=81) of the patients underwent paraaortic lymphadenectomy. Metastatic lymph nodes were detected in 5.1% (n=6) of these patients.

When frozen histology types were analyzed, 61.6% (n=85) were serous, 34.1% (n=47) mucinous, and 4.3% (n=6) endometrioid. The final pathology result of 63% (n=87) of the individuals was serous, 31.9% (n=44) mucinous, and 5.1% (n=7) endometrioid. 76.9% (n=108) of the patients were stage IA, 1.4% (n=2) were stage IB, 11.6% (n=17) were stage 1C, 8.9% (n=5) were stage 3C. 94.9% (n=131) of the patients were followed up after the operation and 5.1% (n=7) received adjuvant CT.

Spontaneous pregnancy was observed in 31% (n=18) and pregnancy as a result of assisted reproductive techniques in 5.2% (n=3) of patients who underwent fertility preserving surgery.

In this study, demographic characteristics such as age, gravida and parity were found to be statistically significant with fertility preservation. This was considered to be due to the fact that fertility preservation surgery was more preferred in patients with younger age at diagnosis and patients with no previous gravida or parity (Table 1).

The number of patients who underwent fertility sparing surgery was fifty-eight. USO was performed in 44 of those patients and 10 of them developed recurrence. Cystectomy was performed in the remaining 14 patients and recurrence developed in 4 of



Sarıkaya Kurt et al.

Table 1. Relationship	Between Demo	graphic Charac	teristics and Fei	rtility Sparing			
			Fertility	Chi-Square	р		
		No				Yes	
		n	%	n	%		
Age at Diagnosis	Less than 30	2	2,5	28	48,3		0,000*
	31-40	12	15	24	41,4		
	41-50	24	30	5	8,6	76,541	
	51-60	32	40	1	1,7		
	More than 60	10	12,5	0	0		
Gravidity (Number of Pregnancy)	0	7	8,8	21	36,2		0,000*
	1	4	5	11	19		
	2	16	20	10	17,2	27.014	
	3	18	22,5	13	22,4	37,914	
	4	15	18,8	3	5,2		
	More than 5	20	25	0	0		
Parity (Number of Births)	0	8	10	24	41,4		0,000*
	1	5	6,3	12	20,7		
	2	24	30	11	19	38,302	
	3	21	26,3	11	19		
	More than 4	22	27,5	0	0		

10

7,5

28,8

27,5

26,3

23

13

12

10

0

39,7

22,4

20.7

17,2

0

them. In the group of patients who did not undergo fertility sparing surgery, recurrence developed in 2 patients. 3 of our 14 patients who underwent fertility sparing surgery and had recurrence had peritoneal implants. In 11 patients, recurrence was seen in the contralateral ovary, 1 patient had recurrence in the ipsilateral ovary, and 2 patients had recurrence in bilateral ovaries.

0

1

2

3

More than 4

Alive

\*p<0,05

8

6

23

22

21

According to the results of the study, it is observed that there is a statistical relationship between recurrence and fertility preservation. While 2.5% (n=2) of individuals without fertility preservation had recurrence, 24.1% (n=14) of individuals with fertility preservation had recurrence. The incidence of recurrence is 12 times higher in those with fertility sparing compared to those without fertility sparing. The pathologies of the patients who recurred in this study show that while the pathologies of 14 of 16 patients were reported as serous borderline tumors, the recurrent pathologies of these patients were reported as serous borderline tumors. While 2 of them were reported as mucinous borderline tumors, their recurrent pathologies were reported as mucinous bordeline tumors. While 9 of the patients who developed recurrence after fertility sparing surgery developed recurrence within the first 1 year, 1 of the 2 patients who did not undergo fertility sparing surgery developed recurrence after 17 years, and the other patient developed recurrence after 9 years (Table 2).

0.000\*

36,207



Table 2. Relationship Between Recurrence and Fertility Sparing											
			Fertility	Sparing	Total	Chi-Square	р				
			No	Yes	lotai						
Recurrence	No	n	78	44	122		0,000*				
		%	97,5%	75,9%	88,4%	13,320					
	Yes	n	2	14	16						
		%	2,5%	24,1%	11,6%						
Total n		80	58	138							
		%	100,0%	100,0%	100,0%						
*p<0,05											

### 4. Discussion

BOTs are more common in young women and have a much better prognosis than invasive tumors (12). The fact that most of the patients are young increases the interest in fertility sparing surgery. In this study, 47% (n=66) of the patients with BOTs were under 40 years of age. In a Swedish study investigating the diagnosis age patients diagnosed with BOT between 1960 and 2005, 34% of the patients were found to be under 40 years of age (13). In another study conducted by Boran et al. 56% of the study group consisted of patients whose age at diagnosis was below 40 years (14). BOTs generally have a low malignant potential. Most of them are diagnosed at early stages and are seen as stage-I according to FIGO staging (12). Being confined to the ovary and hiding invasion is the reason behind this phenomenon. In the study, 89.9% of the patients were stage-1 and 10.1% were stage 2-3. The pathology results of the patients were reported as serous borderline in 63%, mucinous borderline in 31.9% and endometrioid borderline in 5.1%. In the study by Tinelli et al. 80% of the patients were reported as stage-1, while the rate of patients reported as stage-3 was 8% (15).

In this study, 60.9% of the individuals underwent lymphadenectomy. 59.4% underwent pelvic lymphadenectomy and 5.8% of these patients had metastatic lymph nodes. 60.1% of the patients underwent paraaortic lymphadenectomy. Metastatic lymph nodes were detected in 5.1% of these patients. In this study, there was no significant difference in terms of recurrence between patients who underwent lymphadenectomy and those who did not. Whether or not lymphadenectomy should be performed in patients is still controversial. In a meta-analysis of 12503 patients in 25 studies by Fan et al., lymph node metastasis was found to affect recurrence but not survival. Similarly, it was concluded that lymphadenectomy did not affect recurrence rates (16).

In another study by Camatte et al., patients diagnosed with early stage BOT were compared with those who had completed and incomplete staging. While a recurrence rate of 8% was observed in patients with incomplete staging, no recurrence was observed in patients with complete staging. However, in this study, it was observed that staging had no effect on survival in patients with significant stage-1 disease. As suggested at the end of the study, staging may not be performed in patients who are sure that there is no micropapillary pattern and who are suitable for follow-up (17). In other studies, it was observed that routine staging in stage-1 patients did not make a significant difference on recurrence and survival (18). For now, the best approach seems to be to explain the options to the patient and share the responsibility.

Fertility sparing surgery was performed in 58 patients in the study. Pregnancy was observed in 21 of the patients who underwent fertility sparing surgery. Of these patients, 18 conceived spontaneously and 3 conceived with assisted reproductive techniques. When the pregnancy outcomes were analyzed, it was observed that 12 pregnancies reached live birth, 8 pregnancies had no follow-up information and 1 pregnancy resulted in abortion. In another study by Donez et al. pregnancy rates were found to be 63.6% (19). As in this study, the possibility of learning the fertility wishes of the patients in prospective studies makes the studies more valuable than retrospective studies. The main aim of conservative surgery is to preserve the fertility potential in young women. According to the results of the study, pregnancy rates obtained after treatment were high in BOTs.

There are many studies evaluating recurrence after treatment of BOTs. Fertility-sparing surgery may be considered as a valid treatment option because of the good prognosis of patients with early-stage ovarian cancer. Many studies have shown that



although conservative surgery increases recurrence rates, it does not worsen survival. 24.1% of the patients in the study who underwent fertility-sparing surgery had recurrence. In another study conducted by Boran et al. among 142 patients, recurrence was observed in 6.5% of patients who underwent fertility-sparing surgery, while this rate was 0.0% in patients who did not undergo fertility-sparing surgery (14). Compared to radical surgery, fertility sparing surgery increased the recurrence rates, similar to other reports in the literature. If we look at the rates in the literature, the recurrence rate after fertility sparing surgery is between 5% and 34%, while the recurrence rate after radical surgery is between 3.2% and 7% (20,21).

In a prospective study by Zanetta et al. 35 of 189 patients who underwent fertility-sparing surgery recurred, while only 7 of 150 patients who underwent radical surgery developed recurrence. Although the recurrence rate seems to be higher in fertility-sparing surgery, the recurrent patients were detected in stage-1 (22). In our study, the number of patients in whom we performed fertility-sparing surgery was 58. Among these patients, the recurrence rate after cystectomy was 28.5%, while the recurrence rate after unilateral oophorectomy was 22.7%. In a meta-analysis by Vasconcelos et al. the recurrence rates after cystectomy and unilateral oophorectomy were 25.3% and 12.5%, respectively (23). In the literature, the recurrence rate after cystectomy varies between 12% and 36.3%. The recurrence rate after unilateral oophorectomy also varies between 7.2% and 25% (24-26).

The weakness of the study is that the fertility intention of the patients could not be determined precisely because it was retrospective. Another weakness of the study is the limited follow-up period and the limited information obtained from the referrals when evaluating the development of recurrence. If we talk about the strengths of the study; it is aimed to contribute to the literature by studying a subject such as fertility preservation, which is still open to controversy, with the largest and homogeneous patient group possible.

## 5. Conclusion

Since patients with BOTs are younger than patients with invasive ovarian cancer, fertility-sparing surgical approaches are becoming increasingly important when discussing treatment options. With the widespread use of conservative surgery, issues such as reducing postoperative morbidity, and recurrence complicate the management of this treatment option. As a result of despite the high live pregnancy rates in patients undergoing fertility preserving surgery, the most appropriate approach should be planned by explaining all options to the

patient, when the increased recurrence rate in these patients is considered.

#### **Author contribution**

Study conception and design: DSK, NB, ASDÇ; data collection: DSK, AK; analysis and interpretation of results: DSK, AK; draft manuscript preparation: DSK. All authors reviewed the results and approved the final version of the manuscript.

### **Ethical approval**

The study was approved by the Ethics Committee for Noninterventional Studies of Etlik Zubeyde Hanım Women Health Education Research Hospital (Protocol no. 1/11 - 21.01.2022).

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### **Conflict of interest**

The authors declare that there is no conflict of interest.

#### Yazar katkısı

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