ORIGINAL ARTICLE

Eastern Journal of Medicine
East J Med 30(2): 318-325, 2025
DOI: 10.5505/ejm.2025.95815

Effect of Both Preserving Fertility and Preventing Surgical Menopause on Recurrence in Borderline Ovarian Tumors

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ABSTRACT

The impact of fertility-sparing surgery on the recurrence rates of borderline ovarian tumors has been extensively documented in the literature. Moreover, fertility-sparing surgery is associated with favorable pregnancy outcomes for women wishing to conceive.
This current dilemma in the literature has led us to investigate our own clinical experience.
This study retrospectively analyzed 86 patients who underwent surgical procedures at our clinic from November 2008 to May 2022, with pathology results indicating borderline ovarian tumors.
In the present study, 25(29%) out of 86 patients had a desire for fertility and underwent fertility-preserving surgery. Pregnancy was achieved in 13(52%) of these 25 patients. Live birth was achieved in 9(36%) of these 13 patients. Recurrence was observed only in 3(4%) of our patients.
Our study found no statistically significant effect of fertility-sparing surgery on the recurrence of borderline ovarian tumors. Furthermore, the favorable outcomes noted during pregnancy and the mitigation of early surgical menopause represent additional benefits of this treatment approach.
Given these favorable outcomes, fertility-sparing surgery may be regarded as the primary treatment option for patients with borderline ovarian tumors.

Keywords: Borderline Over Tumor, Fertility Sparing Surgery, Recurrence Factors

Introduction

Borderline ovarian tumors (BOTs) possess low malignant potential and represent a rare category of gynecologic tumors, comprising 10% to 15% of epithelial ovarian tumors (1). The incidence is low, with rates between 1.5 and 2.5 occurrences for each 100,000 women in the United States and 4.8 cases per 100,000 in Europe. The 5-year survival rate for early stage diseases is approximately 99%, while the 10-year survival rate is 97% (3-4).

International Ovarian Tumor Analysis (IOTA) criteria on transvaginal ultrasound show that BOTs clinically presents similarly to other adnexal tumors with often typical characteristics (5). The measurement of CA 125 can be advantageous for diagnosis and follow-up purposes (6).The main treatment choices for BOTs are still surgical staging techniques, including bilateral salpingo-oophorectomy, hysterectomy, peritoneal washing, omentectomy, repeated biopsies, and appendectomy for mucinous BOTs. Bilateral adnexectomy is the recommended surgical procedure for BOTs (7).

BOTs is often identified in younger populations and at an initial stage. Fertility-sparing surgery (FSS) is a common alternative that includes unilateral or bilateral cystectomy and unilateral adnexectomy, which may or may not be associated with contralateral cystectomy.

Nevertheless, there is insufficient proof to support the necessity of a systematic lymphadenectomy and hysterectomy. In order to treat BOTs, the National Comprehensive Cancer Network (NCCN) recommends either monitoring without surgical intervention or consideration of options such staging surgery, comprehensive

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Received: 07.11.2024, **Accepted:** 28.03.2025

surgery, and fertility-sparing surgery, depending on the patient's desire for fertility (8).

It has been demonstrated that after fertility-sparing surgery, the recurrence rate is higher (up to 20%) (9). BOTs exhibit histological features including complex papillary structures, multilayered epithelium, modest nuclear atypia, and increased mitotic activity, while lacking significant stromal invasion (10). Because there is no harmful stromal invasion, BOTs has a far better prognosis than invasive epithelial ovarian cancer (11). Overall survival rates have not been demonstrated to increase with adjuvant chemotherapy or radiation. Regardless of the stage of the International Federation of Obstetrics and Gynecology's (FIGO) Ovarian Cancer Classification, the current guidelines do not recommend adjuvant treatment for women with BOTs (11-12). The first FIGO stage and the existence of peritoneal implants, especially invasive implants, are the biggest risk factors for relapse (12).

The literature raises questions regarding the significant likelihood of recurrence in borderline ovarian tumors after fertility-sparing surgery. Is it possible to perform fertility-sparing surgery on the patient a second time? The response to these inquiries remains ambiguous. Our goal in publishing this study is to provide the findings from our own tertiary cancer treatment center, which can assist answer these concerns in the literature.

Material and Methods

Between November 2008 and May 2022, a total of 86 patients who underwent surgery for adnexal mass at Bakırköy Dr. Sadi Konuk Training and Research Hospital, with final pathology results indicating borderline ovarian tumor, were included in this study. This study is a single-center, retrospective, and descriptive analysis.

The study was accepted by the institutional review board at the University of Health Sciences, Bakırköy Dr. Sadi Konuk Education and Research Hospital in Turkey on July 3, 2023 (Approval no. 2023/07-13).

Our study included patients with comprehensive surgical and pathology information, as well as medical follow-ups, in our hospital's software system. We did not include patients whose data were not sufficient in our study.

Medical history and clinical data were gathered from records, including demographics such as age, menopausal status, body mass index (BMI), fertility desire, tumor localization, tumor size, preoprative CA 125 level, surgical intervention history, adjuvant medication, and follow-up time. The histopathological evaluation was performed by a gynecologist pathologist with at least 10 years of experience working in our center.

We scheduled fertility-preserving surgery for all patients wishing to conceive prior to the procedure and advised a 40-day abstention from coitus following surgery. Our patients who were unable to obtain spontaneous pregnancy within one year of surgery and who had conditions that could result in male or female infertility were referred to the assisted reproductive department. The formation of a live intrauterine fetus was documented as a live pregnancy during the patients' follow-up, and the birth of a live baby was recorded as a live birth.

Surgical management of patients is tailored to their age, fertility desire and menopausal status. Radical surgery was also performed on patients who had entered menopause or completed their fertility. Additionally, staging surgery was conducted on patients whose frozen section results indicated at least BOTs during the procedure. Radical surgery for BOTs encompasses surgical staging procedures, including bilateral salpingo-oophorectomy, hysterectomy, peritoneal washing, omentectomy, multiple biopsies, and appendectomy. These remain the primary therapeutic options, with bilateral salpingo-oophorectomy being performed with or without hysterectomy. The BOTs were classified according to the FIGO 2014 system.

Statistical Analysis: The data was statistically analyzed using SPSS 24.0. The study used chi-squared or Fischer's exact tests to evaluate the association between important variables, in addition to their distributions. The effect magnitude was determined in accordance with Cohen's guidelines and the research conducted by Pecorino B et al. and others (17). In order to preserve the study's efficacy, 1-beta was set at 0.95. The minimal number of patients required for each group was established to be 80. Statistical significance was established at $p<0.05$.

Results

Pregnancy outcomes in patients with borderline ovarian tumors and the factors influencing probable recurrence were assessed, as were the possible effects of fertility-sparing surgery. In the present study, 25(29%) out of 86 patients had a

Table 1: Demographic Characteristics of Patients with Borderline Ovarian Tumors

	N or Median	Percentage or Range
Age (median, range) (years)	48.9	(19-80)
Premenopausal	63	(73%)
Postmenopausal	23	(27%)
BMI* (Kg/M2)	25.8	(21-34)
<25	38	(44%)
>25	48	(56%)
CA-125 level (median, range) (U/mL)	108	(9-2520)
≤ 35	60	(70%)
> 35	26	(30%)
Tumor Size (median, range) (cm)	13	(4-21)
Tumor Laterality		
Unilateral	72	(84%)
Bilateral	14	(16%)
Tumor Histology		
Serous	52	(60%)
Mucinous	29	(33,5%)
Endometrioid	1	(1,5%)
Clearcell	1	(1,5%)
Mix Type	3	(3,5%)
FIGO stage		
IA	66	(76%)
I B	17	(19,5%)
I I B	1	(1,5%)
I I IC	2	(3%)
Fertility-Sparing Surgery (FSS)	25	(28%)
Radical Surgery (RS)	61	(72%)
Surgical Approach		
Laparoscopy	36	(42%)
Laparotomy	50	(58%)
Postoperative chemotherapy	3	(4%)

desire for fertility and underwent fertility-preserving surgery. Live pregnancy was achieved in 13 (52%) of these 25 patients. Live birth was achieved in 9(36%) of these 13 patients. Recurrence was observed only in 3(4%) of our patients.

There were only 23 patients (27%) going through the postmenopausal phase, and the patients' average age was 48.9 years (range: 19–80). Additionally, 48 patients (56%) had a BMI exceeding 25. The mean preoperative CA-125 level was 108 U/mL (range 9-2520), while the average tumor size measured 13 cm (range 4-21). Furthermore, 14 patients (16%) presented with bilateral tumors. Upon evaluating the tumor histology of our patients, we found that 52 (60%) exhibited serous type, 29 (33.5%) displayed mucinous type, 3 (3.5%) presented mixed type, 1 (1.5%) had endometrial type, and 1 (1.5%) demonstrated clear cell histology of borderline ovarian tumors. Based review of the FIGO stages of our patients, 66 (76%) were classified as stage 1A, 17 (19.5%) as stage 1B, 1 (1.5%) patient as stage 2B, and 2 (3%) as stage 3C. Fertility-preserving surgery was conducted on 25 patients, representing 28% of the total cohort. The patients' demographic information is encapsulated in Table 1.

In evaluating patients who underwent fertility-sparing surgery, BMI (over/under 25) (p:0.665),

Table 2: Patient Outcomes Following Fertility-Sparing Surgery (n:25)

Characteristics	Non pregnancy (n:12 (48%))	Pregnancy (n:13(52%))	Total (n:25(100%))	P value
Age (years)				0.658
≤ 40	8(44%)	10(56%)	18	
> 40	3(43%)	4(57%)	7	
BMI* (Kg/M^2)				0.665
<25	4(57%)	3(43%)	7	
>25	8(44%)	10(56%)	18	
Surgery Type				0.656
Laparoscopy	5(50%)	5(50%)	10	
Laparotomy	8(54%)	7(46%)	15	
Unilateral Cystectomy	3(43%)	4(57%)	7	0.373
Bilateral Cystectomy	-	1	1	
Unilateral Salpingo-Oophorectomy (USO)	9(56%)	7(44%)	16	0.502
USO and Contralateral Cystectomy	-	1	1	
FIGO Stage				0.218
IA	12(55%)	10(45%)		
IB	-	2		
II	1	-		

type of surgery (unilateral cystectomy (p:0.373), bilateral cystectomy, unilateral salpingo-oophorectomy (USO) (p:0.502), USO and contralateral cystectomy), method of surgery (laparoscopic/laparotomy) (p:0.656), and FIGO stage (p:0.218) of disease were assessed. These parameters, which can influence fertility, demonstrated no statistical significant effect on the fertility outcomes of the patients. The effects of these parameters are summarized in Table 2.

During the evaluation of recurrence processes and the follow-up period, only 3 (4%) individuals experienced disease recurrence. 2 (8%) patients underwent radical surgery, whereas 1 (4%) patient underwent fertility-preserving surgery. The average follow-up duration for the patients was 42 (19-165) months. Despite the fact that this rate appears to be twice as high when expressed as a percentage, it lacks statistical significance. At least equivocal serous ovarian tumor was the primary pathology result of these 3 patients. The patients' recurrence was evaluated during standard follow-up by using TVUSG to identify newly developed cystic or solid formations and MR imaging of these structures. Furthermore assessed were CA-125 levels of those considered to have recurrence. The patients' lesions were operable and oligometastatic, necessitating a seconder cytoreduction. The recurrence pathology of one patient was identified as low-grade ovarian cancer. The tumor committee has determined to administer adjuvant therapies to these three patients experiencing recurrence. Table 3 provides a summary of the patients with recurrences.

In our study, a comparison between fertility-sparing surgery and radical surgery revealed no statistically significant difference (p=0.097). The presence of the micropapillary variant (p=0.560), invasive implants (p=0.554), with a tumor length exceeding 10 cm (p=0.117) and bilaterality (p=0.068), preoperative CA-125 values exceeding 35 (p=0.866), and lymphadenectomy (p=0.097), revealed no statistically significant association with recurrence rates. The expected statistically significant increase in recurrence was observed in advanced stage tumors according to FIGO (p= 0,002). In Table 4, you can see an overview of the parameters that would impact the recurrence discussed earlier.

Discussion

Due to the earlier manifestation of BOTs compared to other invasive ovarian tumors, it is crucial to manage patients with this condition in a manner that preserves fertility and postpones surgical menopause.

Table 3: Characteristics of Patients With Recurrence

Patient	Age (year)	FIGO Stage	Frozen Pathology	Preoperative CA125 level(U/mL)	Surgery	DFS* (Months)	OAS** (Months)	First histological result	Treatment after Recurrence	Adjuvant Treatment	Recurrence Histology Outcome
1	19	IIB	Serous Borderline	123	†USO +omentectomy +peritonectomy	24	39	Serous Borderline	RSS††	Paclitaxel + platinum;	LGSOC‡
2	58	IIIC	Serous Borderline	472	RSS	48	92	Serous Borderline	SS¥	Paclitaxel + platinum;	Invasive implants
3	50	IIIC	Serous Borderline	25	RSS	124	142	Serous Borderline	SS	Paclitaxel + platinum;	Invasive implants

*DFS : Disease-Free Survival
**OAS : Over All Survivaş
†USO : Unilateral Salpingo-Oophorectomy
††RS. :Radical Sitoredüktive Surgery
‡LGSOC :Low Grade Serous Ovarian Carcinoma;
¥SS. : Seconder Cytoredüctive Surgery

Some recent studies have shown that fertility-sparing surgery increases the risk of BOT recurrence (13,14). There was no correlation between fertility-sparing surgery and increased recurrence in our statistical analysis. Researchers have found no evidence that fertility-sparing surgery increases the risk of recurrence or adverse effects, which provide credence to our findings (15,16). Additionally, a literature review found that patients undergoing BOTs who experience a recurrence after fertility-sparing surgery can still undergo attentive follow-up and have the procedure repeated if they so desire (2). Based on our research, we found that our recurrence rate was 3.5% (3 cases). This rate aligns closely with existing literature (17).

Our analysis found no statistically significant relationship between histological recurrence and the presence of invasive implants and micropapillary structures in BOTs, which were previously thought to be the leading cause of histological recurrence (18). Our results show that oophorectomy and cystectomy do not reduce the risk of recurrence after fertility-sparing procedures, which contradicts the findings in the literature (19). Just like in the previous study (19), when it came to recurrence, we didn't find any statistically significant difference between radical surgery and fertility-sparing surgery on BOT patients. This suggests that laparoscopic procedures, in comparison to laparotomy, would lead to a rise in recurrence. Previous research indicated that tumor histology (serous, mucinous, endometrioid) might affect pregnancy outcomes after fertility-sparing surgery; however, this was not the case when the effects of tumor histology on these outcomes were examined (17-20).

Contrary to earlier literature (13–19), the study found no statistically significant difference in recurrence rates between tumors with a diameter larger than 10 cm, bilateral tumors, and CA-125 values below 35 IU. The recurrence rate increased significantly as the patients' FIGO stage progressed, as has been observed in previous study (13).

Table 4: Potential Influencing Factors for Recurrence

	N:86(100%)		
	Non recurrent:83(96%)	*Recurrent:3(4%)*	P value
Age (years)			0.104
≤ 40	27(32,5%)	1(33,3%)	
> 40	56(67,5%)	2(66,7%)	
BMI* (Kg/M2)			0.227
<25	37(45%)	1(33,3%)	
>25	46(55%)	2(66,7%)	
Menopausal Status			0.371
Premenopausal	62(74%)	1(33,3%)	
Postmenopausal	21(26%)	2(66,7%)	
CA125 level(U/mL)			0.866
≤ 35	52	1(33,3%)	
> 35	21	2(66,7%)	
Size (median, range) (cm)			0.117
≤ 10	43(53%)	1(33,3%)	
> 10	40(48%)	2(66,7%)	
Tumor Laterality			0.068
Unilateral	71(85%)	1(33,3%)	
Bilateral	12(15%)	2(66,7%)	
Histology			0.845
Serous	49(59,5%)	3(100%)	
Mucinous	28(34%)	-	
Endometrioid	1(1,5%)	-	
Clearcell	1(1,5%)	-	
Mix Type	3(3,5%)	-	
FIGO stage			0.002
IA	65(78%)	-	
IB	17(21,5%)		
IIB	1(1,5%)	1(33,3%)	
III	-	2(66,7%)	
Surgical approach			0.097
Fertility Sparing Surgery	24(29%)	1(33,3%)	
Radical Surgery	59(71%)	2(66,7%)	
Surgical Technique			0.611
Laparoscopy	32(38,5%)	-	
Laparotomy	51(61,5%9	3(100%)	
Lymphadenectomy			0.097
yes	20(24%)	2(66,7%)	
no	63(76%)	1(33,3%)	
Excistent of İnvazive			0.554

İmplant			
yes	78(94%)	2(66,7%)	
no	5(6%)	1(33,3%)	
Excistent of Noninvazive Implant			0.008
Yes	3(4%)	1(33,3%)	
No	80(96%)	2(66,7%)	
Excistent of Micropapillary Pattern			0.561
Yes	3(4%)	1(33,3%)	
No	80(96%)	2(66,7%)	
Surgical Rupture			0.931
Yes	2 (2.4%)	-	
No	81(97.6%)	3(100%)	
Spontaneous Rupture			-
Yes	-	-	
No	83(100%)	3(100%)	

* BMI: Body Mass Index

Consistent with the literature, one of our patients' pathology results at the site of recurrence following secondary cytoreduction showed low grade ovarian cancer (20,21). Despite the fact that serous BOTs have the potential to develop into malignant tumors from the start, they more commonly advance to low-grade ovarian cancer, and because they are typically diagnosed early, their 5-year survival rate is more than 90% (21). Therefore, early and close follow-up surveys are highly successful, even if BOTs return or become malignant.

The limited number of patients with recurrence, which was just three, constrained the statistical analysis of our study. Another drawback of our study was that it was retrospective in nature. Our study's strength is that it is a single-center investigation that follows up with patients over an extended period of time.

Fertility-sparing surgery is a primary treatment option for borderline ovarian tumors (BOTs) due to its lack of impact on recurrence rates, favorable pregnancy outcomes, and ability to delay surgical menopause. Prospective studies with larger patient populations are necessary for this subject.

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