

Original Article

The recurrence and fertility rates in patients with borderline ovarian tumor treated by conservative treatment; A retrospective cohort

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Abstract: Background: Borderline Ovarian Tumors (BOT) are epithelial tumors characterized by a lack of stromal invasion. These tumors mainly affect younger females, making fertility preservation crucial in disease management. In this article, we investigated recurrence and fertility in BOT patients treated with conservative surgery. Methods: Patients with BOT who underwent conservative surgery were retrospectively assessed for recurrence and fertility. Data from 101 patients were collected from their medical records. Patients were categorized into two groups based on recurrence. Data analysis was performed using SPSS version 20 to compare the two groups, with a significance level set at $P < 0.05$. Results: The mean age of patients with recurrent BOT was significantly higher than those without it ($P = 0.001$). Also, the frequency of infertility and abortion in patients with recurrent BOT were significantly higher than those without it ($P < 0.05$). However, there were no significant associations between recurrence rate and marital status, positive family history for cancer, positive cancer history, side of tumor, OCP use, AMH, CA125 or follow-up duration ($P > 0.05$). Moreover, the mean level of FSH, and LH in patients with recurrent BOT were significantly higher than those without it ($P < 0.05$). Also, there were significant differences between the two groups based on the FIGO stage, surgical type, and histopathology type ($P < 0.05$). Conclusion: Patients with recurrent BOT tended to be older and had a higher incidence of infertility, abortion, and altered hormone levels (FSH, LH, and AMH) compared to those without recurrence. Most patients with recurrent BOT had undergone unilateral or bilateral cystectomy.

Keywords: Borderline ovarian tumor, infertility, recurrence, conservative surgery, fertility-sparing surgery

Introduction

Epithelial tumors consist of 60% of ovarian cancers. Among different ovarian epithelial tumors, borderline tumors (BOTs) account for a 10-20% frequency between all other types of ovarian tumors [1, 2]. BOTs were described in 1929 for the first time characterized mainly by lack of stromal invasion in pathological evaluation [2-5].

The diagnostic standard for benign ovarian tumors (BOTs) typically involves a combination of medical history assessment, physical examination, imaging studies such as ultrasound or MRI, and sometimes biopsy for definitive diagnosis [2]. Typical clinical features include abdominal pain or discomfort, bloating, irregular menstruation, and in some cases, palpable abdominal masses. Treatment options for BOTs

depend on various factors including the type, size, and symptoms. Common treatments include observation with regular monitoring, surgical removal (either laparoscopic or open surgery), or hormonal therapy [4]. The efficacy of treatment varies depending on factors such as tumor type and stage, but overall, surgical removal is often curative with a low recurrence rate. Prognosis for BOTs is generally favorable, with most cases being benign and associated with a good long-term outcome post-treatment. However, close monitoring and follow-up are recommended due to the potential for recurrence or development of new tumors [5].

In 1973, the International Federation of Obstetricians and Gynecologists (FIGO) suggested that this group of ovarian tumors possess a low malignant potential. The World Health Organization (WHO) has since called

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these tumors as BOTs [2-6]. BOTs frequently occur in young females, diagnosed usually between 30 to 40 years [7]. Generally, BOTs have an excellent prognosis, and their ten-year survival is about 83 to 91% [8, 9]. The recurrence rate in these tumors is about 5%, and their fatality is even lower [10, 11]. The recurrence risk could be correlated with inappropriate cyst rupture, minimally invasive surgery and ovarian cystectomy [12]. Because of the good prognosis of these tumors and the younger age of patients, maintenance of fertility and endocrine function in these patients have paramount importance [13]. Among different treatment modalities, conservative surgery is curative in a significant number of patients and has shown fewer deleterious effects on fertility in comparison with radical surgery [2, 14-16]. Conservative surgery, such as unilateral or bilateral cystectomy or salpingo-oophorectomy, is indicated in BOTs primarily for younger patients who wish to preserve fertility. It is generally appropriate for Stage I disease confined to one or both ovaries, with low-risk histologic features and without invasive implants [14]. This approach aims to retain ovarian function while managing the tumor, with a focus on minimizing surgical morbidity [10]. Close follow-up is essential due to the risk of recurrence, especially in cases where cystectomy alone is performed [15].

In some cases, tumors may shrink or disappear in patients treated conservatively, particularly with certain types of BOTs. Conservative surgery, also known as fertility-sparing surgery, aims to remove the tumor while preserving the ovaries and uterus to maintain reproductive potential. This approach is often considered for younger patients desiring future fertility. Conservative surgery involves removing the tumor while sparing the healthy ovarian tissue as much as possible [8]. This can be achieved through various techniques such as cystectomy (removing only the tumor while preserving the ovary), unilateral salpingo-oophorectomy (removing one ovary and fallopian tube), or partial oophorectomy (removing a portion of the ovary containing the tumor). Criteria for evaluating relapse after conservative surgery typically include regular follow-up visits with physical examination, imaging studies (such as ultrasound or MRI), and monitoring of tumor markers (if applicable) [9]. Signs of relapse may

include the recurrence of symptoms such as abdominal pain or bloating, or the detection of new masses on imaging studies. Early detection of relapse allows for timely intervention and management [10].

Given the significance of fertility-sparing surgeries in Borderline Ovarian Tumors (BOTs) and the scarcity of data regarding their outcomes in Iran, our objective was to assess the recurrence rate and fertility outcomes among BOT patients who underwent conservative surgery.

Materials and methods

Study design

This was a retrospective cohort study. All patients with BOT who referred to gynecology clinics of Isfahan University of Medical Sciences and underwent a conservative surgery between 2015 and 2019 in Isfahan, Iran were evaluated to enter the study. Due to rarity of condition, a census sampling method was considered. The Ethics Committee of Isfahan University of Medical Sciences approved the study protocol with the code IR.MUI.MED.REC.1398.460.

Inclusion and exclusion criteria

Inclusion criteria were all patients with BOTs who underwent fertility-sparing surgical approaches (e.g., unilateral or bilateral cystectomy, salpingo-oophorectomy, and salpingo-oophorectomy with cystectomy), a definite diagnosis of BOT based on pathology study (Al-Zahra and Shahid Beheshti hospitals, Isfahan, Iran), age between 18 and 45 years, availability for follow-up and a written informed consent. Exclusion criteria were not providing an informed consent, a need for radical surgeries, missing/inaccessible patients' clinical/paraclinical findings, and establishment of other diagnoses before/during the study period.

Data gathering

According to these criteria, 101 patients were enrolled. Patients' characteristics including age, marital status, history of cancer, family history for cancer, infertility, trying for pregnancy, gravidity, parity and abortion, side of tumor, serum CA125 (higher than 45 U/mL was considered positive), LH (luteinizing hormone), FSH (follicle-stimulating hormone) and AMH (Anti-

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Mullerian Hormone) levels, FIGO stage of the tumor, surgical method, histopathology type and the rate of tumor recurrence were recorded.

Follow-up and recurrence

Also, patients were followed during the study period either by telephone contact or during the follow-up visits. Recurrence was defined as regrowth of the tumor after surgery, either confirmed by further pathology studies or required another surgery [6]. A recurrence was detected when patients were monitored for their sign/symptoms, clinical and paraclinical data (contacted actively), or during the follow-up examinations, with or without clinical symptoms (passive). Also, The tumor stage was defined based on the FIGO staging system for tumors [6].

Statistical analysis

Data was analyzed using SPSS v.20 (SPSS Inc. Chicago, IL, The USA). Quantitative data was presented as mean and standard deviation, and qualitative data as numbers and percentages. Quantitative data was analyzed using an independent t-test, and qualitative data using chi-square test. *P*-values less than 0.05 were considered as statistically significant.

Result

Study population

In this study, 101 patients with BOT were evaluated. **Table 1** represents baseline characteristics of the participants. Most patients (85.1%) were married, and the frequency of infertility was 9 (26.7%) in all patients.

Demographic data

The frequency of gravidity, parity, and abortion are shown in **Table 1**. Nine (8.9%) patients had a positive history of cancer, and 18 (17.8%) had a family history of cancers. The frequency of positive CA125 finding was 36.6%. The tumor involved the left ovaries mostly, as found in 44.6% patients. The frequency of the FIGO stage, surgical method, OCP and tumor histopathology type were demonstrated in **Table 1**. Also, the borderline ovarian tumor was recurrent in 45 (44.6%) patients. The mean age of patients was 31.02 ± 5.06 years and patients

were followed up for 3.04 ± 0.75 years (patients were followed up between 1.5 to 5 years). The mean duration to detect recurrence was 1.59 ± 0.28 years. FSH, LH and AMH levels are summarized in **Table 2**.

Recurrence

Based on the recurrence rate, patients were categorized into recurrent and non-recurrent BOT groups. The mean age of patients with recurrent BOT was notably higher than that of those without recurrence ($P=0.001$). Furthermore, the incidence of infertility and abortion among patients with recurrent BOT was significantly elevated compared to those without recurrence ($P<0.05$). However, no significant associations were observed between recurrence rate and marital status, positive family history of cancer, personal cancer history, tumor side, oral contraceptive pill (OCP) use, anti-Müllerian hormone (AMH) levels, positive CA125 levels, or follow-up duration ($P>0.05$). Patients with recurrent BOT displayed significantly higher mean levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) compared to those without recurrence ($P<0.05$). Additionally, notable differences were noted between the two groups concerning FIGO stage, surgical type, and histopathology type ($P<0.05$) (**Table 3**). Moreover, there was no significant distinction between surgical methods concerning infertility ($P=0.54$).

Discussion

A surgical approach is the primary choice in BOTs. In these tumors, the effect of chemotherapy is limited due to the tumor low growth rate. Also, investigations have not revealed a remarkable impact of adjuvant therapy in BOT patients [17]. Fertility preservation in BOT patients should be considered seriously due to the high fertility expectancy in young age spectrum [18, 19].

In our study, 17 patients (16.8%) experienced infertility, all of whom had a recurrent BOT. The abortion rate was higher in the recurrent BOT group than in those without it. Patients with recurrent BOT had a lower gravidity rate than those without it, and most patients with recurrent BOT and all patients without recurrent BOT had no fertility complications.

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Table 1. Baseline characteristics of the participants

Variables		Frequency	Percentage (%)
Marital status	Single	15	14.9
	Married	86	85.1
Family history	Yes	18	17.8
	No	83	82.2
Infertility	Yes	17	16.8
	No	84	83.2
Gravity	0	20	19.8
	1	27	26.7
	≤2	54	53.5
Parity	0	24	23.8
	1	23	22.8
	≤2	54	53.4
Abortion	No	83	82.2
	Yes	18	17.8
OCP	Yes	49	48.5
	No	52	51.5
Cancer history	No	92	91.1
	Yes	9	8.9
Side	Right	38	37.6
	Left	45	44.6
	Both	18	17.8
CA125	Positive	37	36.6
	Negative	64	63.4
Try for pregnancy	Yes	23	22.8
	No	78	77.2
FIGO stage	Stage 1A	42	42.4
	Stage 1B	35	35.4
	Stage 1C	12	12.1
	Stage 3/1	10	10.1
Surgery Method	Unilateral cystectomy	30	29.7
	Bilateral cystectomy	35	34.7
	Salpingo-Oophorectomy	29	28.7
	Salpingo-Oophorectomy and cystectomy	7	6.9
Histopathology Type	Serous	68	67.3
	Mucus	33	32.7
Recurrence Rate	Yes	45	44.6
	No	56	55.4

Table 2. Laboratory findings, recurrence time and follow-up duration in the study participants

Variables	Mean ± SD
Age (Year)	31.02±5.06
FSH (IU/L)	17.80±7.25
LH (IU/L)	18.19±7.89
AMH (IU/L)	3.35±0.87
Recurrence Time (Year)	1.59±0.28
Follow up time (Year)	3.04±0.75

In many BOT patients, fertility-sparing approaches are mostly preferred over radical ones. Low mean age in most BOT patients and subsequent high fertility expectations, desirable safety of conservative surgeries, and the possibility of preserving the uterus and some functional ovarian tissues are some advantages of fertility-sparing surgeries [17, 20, 21]. On the other hand, various studies have shown that salpingo-oophorectomy might effectively reduce the recurrence rate in BOT patients.

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Table 3. Comparing baseline characteristics between the two groups

Variables		recurrent (n=45)	Non-recurrent (n=56)	P Value
Age		32.86±5.01	29.55±4.63	0.001*
Marital status	Single	6 (13.3%)	9 (16.1%)	0.46**
	Married	39 (86.7%)	47 (83.9%)	
Positive Family history for cancer		6 (13.3%)	12 (21.4%)	0.21**
Positive Infertility		16 (35.6%)	1 (1.8%)	>0.001**
Positive cancer history		5 (11.1%)	4 (7.1%)	0.36**
Using OCP		23 (51.1%)	26 (46.4%)	0.39**
Side	Right	19 (42.2%)	19 (33.9%)	0.50**
	Left	20 (44.4%)	25 (44.6%)	
	Both	6 (13.3%)	12 (21.4%)	
Positive CA125		13 (28.9%)	24 (42.9%)	0.10**
FSH		22.97±7.14	13.64±3.90	>0.001*
LH		20.57±6.59	16.28±8.37	0.006*
AMH		3.48±1.07	3.25±0.66	0.17*
Follow Up Time		3.20±0.74	2.91±0.74	0.56*
Gravity		1.57±1.17	1.67±1.26	0.68*
Parity		1.40±1.17	1.66±1.17	0.27*
Abortion	No	32 (71.1%)	51 (91.1%)	0.009**
	Yes	13 (28.9%)	5 (8.9%)	
FIGO stage	1A	9 (21.1%)	33 (58.9%)	<0.001**
	1B	12 (31.6%)	23 (41.1%)	
	1C	12 (26.3%)	0	
	3/1	10 (21.1%)	0	
Surgical methods	Unilateral cystectomy	20 (44.4%)	10 (17.9%)	<0.001**
	Bilateral cystectomy	19 (42.2%)	16 (28.6%)	
	Salpingo-Oophorectomy	6 (13.3%)	23 (41.1%)	
	Salpingo-Oophorectomy and cystectomy	0	7 (12.5%)	
Histopathology type	Serous	39 (86.7%)	29 (51.8%)	<0.001**
	Mucous	6 (13.3%)	27 (48.2%)	

*Independent T test, **Chi Square.

However, survival and oncologic outcomes after fertility-sparing approaches are differently reported (especially when comparing different fertility-sparing surgery methods).

The probability of pregnancy following unilateral salpingo-oophorectomy is less (due to reduced ovarian reserves) compared to cystectomy, however, there are not consistent evidence-based results in different studies [19]. Evaluating the consequences of conservative surgeries in BOT in a meta-analysis by Vasconcelos and de Sousa Mendes demonstrated that the pregnancy rate in BOT patients was 55%, and there was no statistically significant difference between cystectomy and unilateral salpingo-oophorectomy regarding the pregnan-

cy rate [17]. Also, the findings of a meta-analysis by Wang and Fang revealed that tumor relapse was significantly more frequent in patients treated with unilateral and bilateral cystectomy [19]. Our study also revealed that most patients with recurrent BOT had undergone unilateral and bilateral cystectomy. In contrast, the most frequent surgical methods in patients without BOT were salpingo-oophorectomy and salpingo-oophorectomy with cystectomy. Therefore, the findings of our study are consistent with the results of previous investigations.

The mean age of patients with recurrent BOT was higher than those without it. Age and higher FIGO stage or serous tumor types seem to be

remarkable recurrence risk factors [22]. Although we did not evaluate the recurrence rate in patients older than 45 years, some similar studies have demonstrated that age was associated with a higher incidence of recurrent BOT [9].

Trillsch et al. revealed that the most frequent tumor histopathology type in BOT patients was serous type, and higher tumor stages (FIGO stage \geq II) were more frequently found in those younger than 40 years. In their study, patients older than 40 experienced recurrent BOT three times more than those below 40 years [23]. Du Bois et al. also found that BOT was diagnosed in most patients at stage FIGO I, and the most frequent type of tumor histopathology was serous type. Their study also found that higher stages were linked with a higher risk of recurrent BOT [3]. Based on the results of a study by Zanetta et al., the most common type of tumor histopathology was serous. Most patients were diagnosed with FIGO stage I tumor, and the most common surgeries performed were unilateral salpingo-oophorectomy and cystectomy, respectively. In their study, 42 of 339 subjects experienced a recurrence, of whom 35 underwent fertility-sparing surgeries. In our study, patients without recurrence of BOT were found to have stages 1A and 1B more than other stages, while those with recurrent BOT presented with more different stages [24]. Furthermore, our analysis identified serous tumors as the most prevalent histopathology among BOT patients. This multi-centric investigation represents one of the few studies to evaluate the recurrence and fertility rates of BOT patients in Iran. Our approach of comparing BOT-related variables in two groups of patients with and without recurrence adds a novel perspective to previous studies. However, significant limitations hinder the generalizability of our results. Limited access to patient information prevented the examination of other potential influencing variables, such as smoking or alcohol consumption. Additionally, the study's design and modest sample size prevented the determination of long-term patient survival. Given the enrollment of patients below 45 years in this research, it is advisable to interpret the findings with caution. Thus, further extensive studies with larger sample sizes in the future may yield more accurate and comprehensive findings.

Conclusion

In patients with recurrent BOT, the mean age, frequency of infertility and abortion, as well as the mean levels of hormones (FSH, LH, and AMH), and FIGO stage were significantly higher compared to those without recurrence. Moreover, most patients with recurrent BOT had undergone unilateral or bilateral cystectomy. However, no significant relationship was found between recurrence rate and marital status, positive family history of cancer, personal cancer history, tumor side, positive CA125 levels, or follow-up duration.

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Disclosure of conflict of interest

None.

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