



Recurrence and Fertility Rate in Females with Borderline Ovarian Tumor

Azamsadat Mousavi,^{1*} Mahshid Shooshtari,¹ Setare Nassiri,¹ Abas Ali Aipour,¹ Setare Akhavan,¹ and Narges Zamani¹

¹Department Gynecology Oncology, Tehran University of Medical Sciences, Tehran, Iran

*Corresponding author: Azamsadat Mousavi, Department Gynecology Oncology, Tehran University of Medical Sciences, Tehran, IR Iran. Tel: +98-9121126544, Fax: +98-2161192363, E-mail: azamsadat_mousavi@gmail.com

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Abstract

Background: Currently, the prevalence of borderline ovarian tumors (BOT) is increasing, and given the higher diagnosis in the third and fourth decades of life, fertility sparing procedures are widely used. There are important consequences in females with borderline ovarian tumors and number of effective factors on recurrence and fertility rate.

Methods: In this cohort study, the required information was collected from a file of 43 patients with final pathologic diagnosis of borderline ovarian tumor, who had undertaken fertility sparing surgery at Imam Khomeini Hospital, Tehran University of Medical Sciences, and recurrence rate, fertility rate, and the effect of different variables were studied.

Results: There were significant correlations between oral contraceptive pill (OCP) consumption, serous pathology, micro invasion in pathology, advanced stages, and recurrence rate of BOT, while this relationship was not found between parity, surgical methods (laparotomy and laparoscopy), surgical techniques (cystectomy and USO), papillary projection, and recurrence rate.

Conclusions: Although the recurrence rate was higher in the current research when compared to other previous studies, yet only in one patient, the pattern of recurrence was invasive epithelial carcinoma, thus in the current study the overall survival did not seem to change. The results of this study on fertility rate are comparable to other studies on this issue. Therefore, these methods are recommended for young patients and emphasis should be place on follow-up.

Keywords: Borderline Ovarian Tumor, Fertility Preservation, Recurrence

1. Background

Borderline ovarian tumors (BOTs) often occur in the third or fourth decade of life, as such, most cases are limited to the ovary and have a very predictable biological and oncological behavior (1, 2) so that the ten-year survival rate in early stages and in late stages has been reported as 90% and 60%, respectively (3). Histologically, atypical nuclei are found at 10% or more of tumor volume yet in the entire tumor, there is no stromal invasion (4). Diagnostically, most of them are accidentally discovered through ultrasound with a papillary component inside the ovarian cyst. Obviously, the main diagnosis is based on a histological examination (5, 6). Surgical staging is recommended as treatment; complete para-aortic and pelvic lymphadenectomy is controversial because in some studies it does not play a role in increasing survival (7). Currently, the prevalence of these tumors are increasing, and given the higher diagnosis in the third and fourth decades of life, fertility sparing procedures are widely used (2). Various studies have been

performed on the safety of fertility sparing procedures, recurrence rate, fertility rate, and the effect of different variables on them and in most reports, the results have been acceptable. This research studied the rate of relapse and fertility and effective factors on each one, in a retrospective cohort of people.

2. Methods

The study sample of this retrospective cohort was the patients under 45 years of age, who had BOT, and had performed fertility sparing surgery at the gynecology oncology center of Imam Khomeini Hospital of Tehran, University of Medical Sciences, Tehran, Iran, during a period of 6 years from 2010 to 2016. The exclusion criteria were incomplete files. Data was extracted from the files and entered in the SPSS software, version 22 (IBM SPSS, Armonk, NY, USA). To describe qualitative variables, mean and standard deviation were used, and quantitative variables were expressed with numbers and percentages. T-test and Man-Whitney

test were used to analyze the quantitative variables, while Chi square test and Fisher exact test were used to analyze qualitative variables. The Kaplan-Meier survival analysis was used to estimate the relapse time and Long-Rank test to compare the recurrence time in the 2 groups. Cox regression analysis was used to study the simultaneous effect of variables on recurrence. Statistically significance was defined as lower than 0.05 and marginally significant was defined as 0.05 to 0.1.

At Imam Khomeini Hospital, as a routine during admission, patients fill a consent form, in which the patient allows the use of her file for future research. In this study, patient's names were not mentioned at any stage of the work. This research obtained ethics approval from the ethics committee of the above-mentioned university.

3. Results

Overall, 43 BOT patients with an average age of 26 years (standard deviation: 4.31) were studied. For the outcomes of the relapse and fertility, 18 (45%) patients were null gravid and 25 (55%) had prior fertility; 16 (37%) patients had a history of infertility. Familial history of breast, ovary or endometrial cancer were found in 6 (14%) patients. Sixteen (37%) patients had prior history of OCP consumption. Eleven (25.58%) had bilateral BOT at diagnosis and 32 (74.3) had unilateral BOT. Eleven (25.6%) had undergone laparoscopic surgery and 32 (74.4) had performed laparotomy. Thirty-nine (90.6%) patients were in stage 1, and 4 (9.3%) in stage 3, and nobody was in stages 2 and 4. Serous BOT was found in 31 (72%) and mucinous type found in 11 (25.5%) patients, and the endometrioid subtype was only found in 1 patient. There were papillary projections in 28 (65%) and stromal micro invasion in 4 (9.3) of the BOT patients. Increasing serum level of CA 125 with cut off level of 35 miU/mL, was detected in 26 (60.4%) while 16 (39.5%) had normal range of CA125 (< 35 miU/mL). Recurrence of BOT was discovered in 27 (60%) patients (Table 1).

Patients were divided to 2 groups: Recurrent and non-recurrent. The recurrence rate was 60%, which was higher than other reports yet there were no statistical differences between the 2 groups in terms of the following variables, age, OCP, parity, history of infertility, unilateral or bilateral location of BOT, serum level of CA125, surgical methods (laparoscopy/laparotomy), surgical techniques (cystectomy/USO), and papillary projection.

There was a significant difference between the 2 groups in OCP consumption, ($P = 0.03$) and OCP was associated with lower recurrence rate. A marginally significant difference was found in stage ($P = 0.089$) thus recurrence rate was higher in stage 3 than stage 1. Serous subtypes of

Table 1. The Demographic Characteristics of the Patients

Demographic Characteristics			
Age	Average		28.63 (4.31)
	Age Interval		19 - 39
Marriage	Married		39 (90.7)
	Single		4 (9.3)
Pregnancy history	Gravid		25 (58.2)
	NG		18 (41.8)
Symptom	Symptomatic: 27 (63)	Pain	24 (88)
		Distension	2 (8)
		AUB	1 (4)
	Asymptomatic		16 (38)
Type of surgery	Laparoscopy		11 (25.6)
	Laparotomy		32 (74.4)
CA125 level	Positive (≥ 35)		26 (60.5)
	Negative (< 35)		17 (39.5)
Laterality	Unilateral		32 (74.4)
	Bilateral		11 (25.6)
Stage FIGO	1		39 (90.7)
	2		0 (0)
	3		4 (9.3)
	4		0 (0)
Pathology type	Serous		31 (72.69)
	Mucinous		11 (25.88)
	Endometrioid		1 (2.3)
Micro invasion	Positive		4 (9.3)
	Negative		39 (90.7)
Papillary projection	Positive		28 (65)
	Negative		15 (35)
Infertility before surgery	Positive: 16 (37.2)	Male factor	4 (9.3)
		Female factor	8 (18.6)
		Secondary	4 (9.3)
	Negative		27 (62.8)

BOT had more recurrence and it was also marginally significant. There was a significant difference between the 2 groups in micro invasion ($P = 0.05$) (Table 2).

There was a correlation between CA125 level and stage, so that in advanced stages, CA125 level was higher ($P = 0.002$).

The mean relapse time was 12 months; at higher stages it was shorter than lower stages, 6, CI (0 to 13.9) and 8, CI (0

Table 2. The Association Between Variables and Rate of Recurrence

	Recurrent (26)	Non recurrent (17)	P Value
Age	28.23	29.24	0.47
Cancer History	3 (11.5)	3 (17.6)	0.67
OCP	3 (11.5)	13 (76)	0.03
One side/both side	21 (80.8)	11 (64.7)	0.21
CA125	16 (61.5)	10 (58.8)	0.8
LUC	7 (26.9)	2 (11.8)	0.8
LBC	0 ()	2 (11.8)	
LAP-UC	9 (34.6)	5 (29.4)	
LAP-BC	2 (7.7)	2 (11.8)	
LAP-USO	5 (19.2)	4 (23.5)	
LAP-USO-C	3 (11.5)	2 (11.8)	
I/LAP	7 (26.9)	4 (23.5)	0.7
C/USO	18 (69.2)	11 (64.7)	0.5
Stage 1A	3 (50)	10 (64.7)	
Stage 1B	1 (3.8)	3 (17.6)	0.6
Stage 1C	8 (30.7)	4 (35.2)	
Stage 3/1	4 (15.4)	0	0.089
Serous	16 (61.5)	9 (52.9)	
S/M	22 (84.6)	10 (58.8)	0.06
Mucinous	1 (3.8)	1 (5.9)	
Papillary project	18 (69.2)	10 (58.8)	0.57
Micro invasion	4 (100)	0	0.05

Abbreviations: I/LAP, laparotomy/laparoscopy; LAP-BC, laparoscopic bilateral cystectomy; LAP-UC, laparoscopic unilateral cystectomy; LAP-USO-C, laparoscopic-unilateral salpingo-oophorectomy- cystectomy; LAP-USO, laparoscopic-unilateral salpingo-oophorectomy; LUC, laparotomic unilateral cystectomy; LBC, laparotomic bilateral cystectomy.

to 17.4) months, respectively. However, the difference was not statistically significant. Increasing CA125 was related to shorter time to relapse yet this was not significant; 5, CI (0 - 11.2) and 12, CI (0.33 - 23.11) months, respectively. Consumption of OCP extended the time for relapse although this was not statistically significant; 16.7, CI (6.3 to 17.73) and 5, CI (1.45 to 8.52) months, respectively. Only statistical significance was found in the surgical method so that the laparoscopic surgery was associated with extended recurrence time compared to laparotomy ($P = 0.04$) at 24 and 6 months, respectively.

In terms of fertility rate, in this study, 24 patients had a tendency to become pregnant; 14 (61%) were pregnant. Twenty-two patients had a good ovarian chemical reserve

(sufficient AMH). There was a significant correlation between age and fertility rate ($P = 0.04$) and for each year of age increase, pregnancy probability was reduced by 24%, CI (0.3 - 0.41). With increasing frequency of relapse, fertility rate decreased and it was marginally significant ($P = 0.09$).

There was no statistically significant relationship between fertility rates and surgical methods, surgical techniques, stage of the tumor, CA125 levels, bilateral or unilateral and type of pathology (Table 3).

4. Discussion

The primary treatment of BOT is surgery. In these types of tumors, due to low growth, the effect of chemotherapy is limited. Because most patients are young, the fertility sparing methods of surgery are widely used. In this study, all patients underwent fertility preservation methods, as follows: in unilateral tumors, surgical procedures were unilateral cystectomy or USO, and in bilateral cases, bilateral cystectomy or unilateral cystectomy plus contralateral salpingo-oophorectomy were performed. Recurrence rate after radical surgery was reported at about 5% while this rate was 10% to 36% after fertility preservation methods and recurrence pattern was often BOT, not invasive epithelial cancer (8). In the current study, recurrence rate was 61%, which was higher than previous studies and may have been due to the kind of surgical methods done by different surgeons (senior or junior) and/or some unknown factor. According to Riman's study, females with more than one parity are at a lower risk of BOT (9) yet in the current study number of parity had no effect on the rate of recurrence. Various results have been reported by numerous studies regarding the protective effect of OCP on recurrence rate. For example, in Rittman's study, OCP did not indicate a protective effect and in Danish's study, OCP was associated with lower relapse of BOT, probably due to suppression of gonadotropin hormones (9, 10). In the current study, consumption of OCP caused lower recurrence rate and longer interval between initial diagnosis and recurrence time. Although this second relationship was not statistically significant, it could be clinically significant and performing studies with a larger sample size should be considered in this regard.

Du Bois's study showed that laparoscopic surgery was associated with higher recurrence rate, (11) yet in 2 other studies, no laparotomy and laparoscopic discrepancies were observed in the rate of relapse (12, 13). In the current study, there was no significant difference between laparotomy and laparoscopy in recurrence rate of BOT thus laparoscopy could be used in young patients, who desire to preserve fertility because of the less chance of adhe-

Table 3. The Clinicopathological Characteristics of Patients with BOTs and Pregnancy Outcome

		Totality	Pregnancy	P Value
Surgery type	Laparoscopy	8	4 (50)	0.6
	Laparotomy	16	10 (62.5)	
Pathology type	Serous	20	9 (45)	0.6
	Mucinous	4	1 (25)	
FIGO stage	1	23	14 (60.9)	0.4
	2	1	0 (0)	
Laterality	Unilateral	19	11 (78.6)	0.67
	Bilateral	5	3 (21.4)	
Recurrence	0	8	6 (75)	0.09
	1	14	8 (57.1)	
	2	2	0 (0)	

sion and other morbidity that are important in fertility outcomes.

Faluyi showed that there was no difference in recurrence rate between cystectomy and USO (14). Chen found the same result from his research (15). The current results were also in line with the mentioned studies. Therefore, more conservative surgery could be used in younger patients to achieve better fertility results.

Uzan found that histological items, such as type of pathology (serous or mucinous), papillary projection, and micro invasion, were not associated with recurrence rate of BOT (16). However, in another study, it was shown that the mucinous type caused higher recurrence rate and shorter interval between diagnosis and relapse (17). In the current study, there was no significant difference in the amount of papillary projection between the recurrence group and another group. Serous type and the existence of stromal micro invasion were significantly associated with higher recurrence rate.

Unilateral or bilateral location of the tumor did not affect the rate of relapse in Seong study, (18); the current results were similar.

In a study on the risk factors for recurrence in BOT, it was shown that higher serum levels of CA125 and advanced stages of BOT were associated with higher recurrence rate (19). In the current study, there was a marginal significant difference in the stage of disease, between the 2 groups. The mean interval between initial diagnosis and recurrence time was shorter in advanced stages, although this was not significant yet showed that at higher stages, relapse accrues in a shorter time. In the current study, the researchers could not find a significant difference between the 2 groups in serum level of CA125, yet observed a signif-

icantly higher level of CA125 in advanced stages. At higher levels of CA125, recurrence occurs during a shorter time. Therefore, it could be concluded that at higher preoperational levels of CA125, it is more likely to encounter more advanced stages during surgery.

In terms of fertility, the results of previous studies are similar. Fertility rate has been reported at about 50% in 2 studies and 74% in another study (18, 20, 21). Fertility rate was 58% in the current research, and there were no significant difference between the 2 groups in the method of surgery, pathologic type, stage of BOT, bilateral or unilateral location of tumor and cystectomy or USO; on the other hand, these factors had no effect on fertility. However, there was a significant difference in patient's age between the 2 groups and for each year of age increase, fertility rate was reduced by 24%. It was also found that increasing the frequency of relapses, could reduce fertility rate although levels of AMH was not different after recurrence. Due to recurrence of disease and repeat conservative surgery, in addition to reducing ovarian reserve, pelvic anatomical change and adhesion formation were also important in reducing fertility.

In summary, the current study showed that there was a significant correlation between OCP consumption, serous pathology, micro invasion, advanced stages, and recurrence rate of BOT, while this relationship was not found between parity, surgical methods (laparotomy and laparoscopy), surgical techniques (cystectomy, USO), papillary projection and recurrence rate. Although recurrence rate was higher in the current research, only in one patient, the pattern of recurrence was invasive epithelial carcinoma thus in this study overall survival did not seem to change; of course the results of overall survival need a

longer follow-up. The results of this study on fertility rate, were comparable to other studies in this field.

Today, due to the progress in the accuracy of pathologic diagnostic methods and changes in risk factors associated with BOT, the prevalence of this tumors is increasing, and given the higher diagnosis in the third and fourth decades of life, fertility sparing procedures are widely used. This study also recommends these methods in young patients and emphasizes on exact follow-up.

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