Oncologic and reproductive outcomes of fertility-sparing surgery for borderline ovarian tumors: first presentation of 10-year experience from a Serbian referral center

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Abstract: The study aimed to assess the oncologic and reproductive outcome of fertility-sparing treatment of stage I borderline ovarian tumors (BOTs). A retrospective study of patients aged 18-40 years with stage I BOTs surgically treated during a 10-year period was conducted. In total, 52 patients (average age 32.7+/-5.9) were followed for 16 to 137 months after BOT diagnosis (mean 73.4 months). The overall survival rate was 100%. Recurrence was registered in 4 patients (7.7%). All patients underwent a unilateral salpingo-oophorectomy and all histologic findings corresponded with primary BOTs (3 serous; 1 endometrioid). Higher parity increased while the histological type and stage did not impact recurrence. Average recurrence-free survival was 36.2+/-23.6 months regardless of histological type and stage. Recurrence occurred during the first 3 postoperative years in 75% of cases. Out of 45 women treated with fertility-sparing surgery, 64.4% attempted pregnancy and the pregnancy success rate was 44.8%. Only one pregnancy was conceived by assisted reproduction, while all others were spontaneous. The fertility-sparing treatment in stage I borderline ovarian tumors can be a safe and successful option both in terms of oncologic and reproductive outcomes, regardless of patient and treatment characteristics. Pregnancies after BOT surgery can be achieved with satisfactory rates and adequate outcomes.

Keywords: borderline ovarian tumors; radical surgery; fertility-sparing surgery; oncologic outcome; reproductive outcome

INTRODUCTION

Borderline ovarian tumors (BOTs) are defined as epithelial tumors with increased cellular mitotic activity and nuclear atypia, but without infiltrative growth and stromal invasion, and they account for 10-20% of all ovarian tumors [1]. BOTs are usually diagnosed at an early stage (stage I 70-80%) and about 33% of patients are younger than 40 years [2,3]. These tumors have low malignant potential with a very good prognosis and survival in contrast to ovarian cancers. The 10-year survival rates range from 88 to 99% according to the disease stage (stages III and I, respectively) [4].

Complete tumor removal with surgical staging is the standard treatment for BOTs. Until recently this meant hysterectomy with bilateral salpingo-oophorectomy [1,5]. However, the indication for this treatment is challenging in patients who have not finished reproduction. At present, it is considered that a conservative treatment approach (defined as preserving at least part of 1 ovary and uterus) can be applied in younger patients even in higher stages in order to maintain ovarian function and fertility [5,6]. Fertility-sparing surgery (FSS) is regarded as safe and recommended for selected patients depending on the histological subtype and prognostic factors (early stage and some histology features) [6,7].

Recent literature data indicate that the oncologic outcome of BOT patients treated with FSS is comparable to those treated with standard (radical) surgical procedures. However, having in mind the possibility of late recurrence (after more than 10 years) and rare progression to ovarian cancer, the safety of this approach is still a concern [8,9].

Data on the reproductive outcome following FSS in BOT are still scarce. Literature data show that pregnancy rates range from 20 to above 50% [10,11]. Still, some studies indicate that infertility was present in a significant percentage of patients after surgical treatment of BOTs. The pregnancy rates appear to depend on the performed surgery as well as other factors that remain to be investigated [12].

The aim of the present study was to assess for the first time the oncologic and reproductive outcomes of patients with borderline ovarian stage I tumors according to the International Federation of Gynecology and Obstetrics (FIGO) treated in our referral tertiary University Clinic.

MATERIALS AND METHODS

Ethics Statement

The study was conducted in accordance with the principles embodied in the Declaration of Helsinki and local statutory requirements. The study was approved by the Ethical Review Board of the University Clinical Center of Serbia (No 622/3). All patients provided written consent for all procedures as well as for the study.

Study population

We retrospectively identified patients with borderline ovarian stage I tumors surgically treated in the Clinic for Gynecology and Obstetrics, University Clinical Center of Serbia, over a 10-year period (2010-2019). Our Clinic is the regional referral center for fertility preservation of gynecologic oncology patients. In the Clinic, a Council for Cancer and Human Reproduction (gynecologists, oncologists, perinatologists, pathologists, endocrinologists, psychologists and other practitioners) annually manages about 50 women with oncological and fertility issues. All BOTs were histologically confirmed and staged upon initial surgical treatment. The staging was retrospectively reviewed and adjusted to the International Federation of Gynecology and Obstetrics (FIGO) 2014 criteria [13]. The study inclusion criteria were as follows: less than 40 years of age, FIGO stage I BOT that was adequately surgically staged and regularly followed up after surgery according to current protocols for at least 12 months. The exclusion criteria were having comorbidities that might impact fertility such as polycystic ovary syndrome (PCOS), myoma, aggressive histological tumor type (clear cell, aplastic, etc.) or other concurrent malignancy

Study data

Patient demographic and clinical characteristics were retrieved from medical records (at the time of initial diagnosis and treatment and from all check-ups) and completed by a structured telephone interview to obtain data regarding overall health status and reproductive outcome. Study sampling is presented in Supplementary Fig. S1. The number and date of each surgical procedure per patient were recorded. Patients were stratified according to surgical treatment type (radical or fertility-sparing), indications (1st or 2nd step staging and/or full treatment), and approach (laparotomy or laparoscopy). Radical surgery (RS) was defined as hysterectomy with bilateral salpingo-oophorectomy. Fertility-sparing surgery (FSS) was defined as any surgery that preserved the uterus and at least part of one ovary (unilateral cystectomy – UCE; unilateral oophorectomy – UOE; unilateral salpingo-oophorectomy – USOE; bilateral cystectomy – BCE).

Follow-up was done according to current standard protocols with regular clinical and ultrasound examination and laboratory testing [5,6]. Follow-up duration was noted for each patient (for a minimum of 12 months). In case of recurrence, localization and time of recurrence, as well as subsequent treatment were documented. Recurrence-free survival and overall survival were calculated. Recurrence-free survival was defined as the time from initial surgical resection to the date of recurrence. Overall survival was defined as the time from surgical resection to death from any cause. Among patients who underwent FSS and wanted to remain fertile, we assessed the reproductive outcomes in terms of attempting and achieving pregnancy, the method of conception (spontaneous or assisted), time to conception, number of miscarriages, preterm and term deliveries, and delivery mode (vaginal or cesarean section – CS).

Table 1. Borderline ovarian tumor patient characteristics, follow-up and outcome overview.

Parameters	Minimum	Maximum	Median	Mean	Standard deviation
Patients age (years)	18.00	40.00	37.00	32.75	5.97
Follow-up (months)	16.00	137.00	68.50	73.42	35.29
Recurrence (months)	20.00	70.00	27.50	36.25	23.58
Pregnancy (months)	12.00	77.00	36.00	38.23	19.46

Statistical analysis

Collected data were analyzed using SPSS software (version 20.0, SPSS, Inc., Chicago, IL, USA). Differences in the characteristics of patients and treatments were assessed using the Kruskal Wallis χ^2 test. Associations of investigated parameters were examined by Pearson's correlation (ρ). Survival analysis (overall survival – OS and recurrence-free survival) was performed using the Kaplan-Meier method with a log-rank test for time-to-event outcome comparisons. The Kaplan-Meier method was also used to investigate the time to pregnancy after BOT diagnosis and treatment. The cut-off for statistical significance was set at $P<0.05$.

RESULTS

General patient data

During the study period, we identified 52 patients with stage I BOT who were radically (7 patients) or conservatively (45 patients) treated. The mean age of this group was 32.6+/-5.9 years (Table 1). Radically treated patients were significantly older (37.4 vs 32.0 years; P=0.022) and had all already reproduced before BOT diagnosis. Most of the patients were nulliparous (63.5%).

Oncologic outcomes – surgical details

The surgical staging was performed as a first-step procedure in more than half of the patients (55.8%), and laparotomy was the preferred approach (71.2%). Second-step surgery was performed in 25 patients mostly for staging (64%) and via laparoscopy in 6 cases. During staging surgery, the omentum was assessed in 94.2% of patients and the contralateral ovary in 59.6%, while lymph nodes and the appendix were examined in 10 and 3 cases, respectively. Cytological examination of the peritoneal wash was performed in all patients (Table 2).

Table 2. Histopathological and surgical details of borderline ovarian tumors

Characteristic		Frequency	Percent
BOT histology	serous	27	51.9
	mucinous	22	42.3
	endometrioid	3	5.8
BOT stage	IA	23	44.2
	IB	2	3.8
	IC1	19	36.5
	IC2	2	3.8
	IC3	6	11.5
Surgical staging	1 step	29	55.8
	2 step	23	44.2
First operation surgical approach	laparotomy	37	71.2
	laparoscopy	15	28.8
Second operation surgical approach	laparotomy	17	73.9
	laparoscopy	6	26.1
Type of adnexal operation	UCE	9	20.0
	UOE	2	4.4
	USOE	26	57.8
	USOE+UCE	5	11.1
	BCE	3	6.7
Fertility sparing surgery	yes	45	86.5
	no	7	13.5

BOT – borderline ovarian tumor; UCE – unilateral cystectomy; UOE – unilateral oophorectomy; USOE – unilateral salpingo-oophorectomy; BCE – bilateral cystectomy

Upon staging, the decision for radical surgery was taken for 7 (13.5%) patients, while the others had FSS. In the RS group, 6 out of 7 patients underwent a second-step procedure and all were performed via laparotomy. In the FSS group, the initial approach was laparoscopy in 13 and laparotomy in 32 cases. USOE (57.8%) was the most common primary surgery. Removal of involved adnexa was performed in 73% (33/45) of cases, while the involved adnexa was spared in 27% (12/45) of cases. In 6 patients, initial cystectomy was followed by the removal of the involved ovary during the second-step procedure. No residual atypical or malignant ovarian tissue was found during second-step surgery (Table 2).

Oncologic outcomes – histology and stage of disease

The most common histological type was serous BOT, which was diagnosed in 27 (52%) patients, followed by mucinous histology in 22 (42%) and endometrioid BOT in 3 patients. More than 2/3 of tumors were in stages IA and IC1. In 1 patient with serous histology, noninvasive implants were noted (Table 2).

Oncologic outcomes – recurrence

There were no recurrences in radically treated patients while 4 recurrences (7.7%) were noted in the FSS group. All patients with recurrence underwent USOE with biopsy of the contralateral ovary via laparotomy. We diagnosed 3 ovarian and 1 peritoneal (in the region of the removed ovary) recurrences. Recurrent disease was of the same serous BOT histology in 3 cases, and in 1 patient endometrioid cancer was diagnosed. There was no malignant transformation at recurrence.

The characteristics of patients with recurrent disease are presented in Table 3. Patient 1, initially diagnosed with endometrioid BOT, was radicalized due to FIGO stage IA endometrioid cancer of the preserved ovary. Patients 2 and 3 developed recurrent disease on the preserved ovary. Patient 2 opted for radicalization, while in patient 3, initially diagnosed with serous BOT staged IC3 with noninvasive peritoneal implants, cystectomy of recurrent serous BOT was performed during the cesarean section. Patient 3 was radicalized 3 years after the diagnosis of recurrence because of suspicion of malignancy. Patient 4 developed peritoneal recurrence in the fossa of the removed ovary and underwent subsequent FSS.

Although 3 out of 4 patients with recurrence had serous BOT, the histological type (P=0.619), stage (P=0.186) and age (p=0.424) at diagnosis were not associated with recurrence. Only higher parity positively correlated with BOT recurrence (P=0.025).

Oncologic outcomes – follow-up and survival

The median follow-up time was 68.5 months (range: 16-137 months; mean: 73.4 months), and 27 out of 52 patients were followed for more than 60 months. All patients were alive at the end of the follow-up period, giving an overall survival (OS) rate of 100%. There were no observed differences in OS regarding any patient or treatment characteristics.

In total, survival without recurrence was noted in 91% of examined patients at the end of the follow-up period. The average recurrence-free survival was 36.3+/-23.6 months (Table 1). Recurrence occurred more often (75%) in the first 3 years after primary surgery and significantly less after this period (5-year recurrence 30% and no significant differences in 5- and 10-year recurrence rates) (Supplementary Fig. S2). Recurrence-free survival was similar regardless of BOT histological type (P=0.157) and stage (P=0.308) or any other patient characteristic (P>0.05).

Reproductive outcomes

Out of 45 women treated with FSS, 29 (64.4%) tried to conceive and 13 women succeeded (pregnancy rate 44.8%). Only 1 pregnancy was achieved by assisted reproduction, while the others conceived spontaneously (Table 4). Moreover, 3 patients achieved 2 successful pregnancies each. There was no correlation between the type of adnexal surgery (cystectomy or removal of involved ovary) and becoming pregnant while achieving pregnancy negatively correlated with patients' age (ρ=-0.478; P=0.009).

Patients became pregnant in the interval of 1 to 7 years after BOT diagnosis (mean 38.2+/-19.5 months) (Table 1 and Supplementary Fig. S3). Younger women conceived in a shorter time (P=0.012). The histological BOT type (P=0.067), stage at diagnosis (P=0.554)

Table 3. Characteristics of patients with recurrence of borderline ovarian tumors

Patient	Age	Histology	Stage	Adnexal staging	Other ovary biopsy	HT	PFS	Recurrence localization	Histology	Pregnancy achieved
1	39	endom	IC1	USOE	yes	no	70	other ovary	endom CA	no
2	39	serous	IC2	USOE	yes	yes	20	other ovary	serous BOT	no
3	27	serous	IC3	USOE	yes	no	20	other ovary	serous BOT	yes
4	35	serous	IA	USOE	yes	no	35	peritoneum	serous BOT	yes

USOE – unilateral salpingo-oophorectomy; HT – chemotherapy; endom – endometrioid; Ca – carcinoma

Table 4. Obstetrical characteristics of investigated borderline ovarian tumor patients.

Parameters		Frequency	Percent
Women attempted pregnancy	yes	29	64.4
	no	16	35.6
Pregnancy achieved	yes	13	44.8
	no	16	55.2
Pregnancy type*	spontaneous	15	93.7
	assisted reproduction	1	6.3
Delivery type	vaginal	6	37.5
	caesarean section	10	62.5

Caption: * 3 patients had 2 pregnancies each – in total 6 singleton pregnancies

Table 5. Characteristics of investigated patients with BOT who achieved pregnancy.

Patients	Age	Histology	Stage	Adnexal staging	HT
1	29	mucinous	IB	BCE	yes
2*	29	mucinous	IA	USOE	no
3*	24	serous	IC3	UOE	yes
4*	20	serous	IC3	USOE	yes
5	25	serous	IC1	USOE	yes
6	27	serous	IC3	USOE	no
7	29	serous	IA	USOE	no
8	27	mucinous	IA	USOE	no
9	38	mucinous	IA	BCE	no
10	31	mucinous	IC1	UCE	no
11	26	serous	IC1	UCE	no
12	35	serous	IA	USOE	no
13	33	mucinous	IA	USOE+UCE	no

Caption: UCE – unilateral cystectomy; UOE – unilateral oophorectomy; USOE – unilateral salpingo- oophorectomy; BCE – bilateral cystectomy; USOE+UCE – unilateral salpingo-oophorectomy and unilateral (contralateral) cystectomy; * – 2 pregnancies

and adnexal surgery type (P=0.730) did not significantly influence the time to pregnancy. Out of 4 women with BOT recurrence, 3 attempted and 2 (50%) spontaneously became pregnant before recurrence. No miscarriages were registered. All 16 children were live-born, term singletons and in good condition at birth (Tables 4 and 5).

DISCUSSION

The study results indicate that fertility-sparing treatment in stage I borderline ovarian tumor can be a safe and successful option in terms of both oncological and reproductive outcomes. Given the average follow-up period of 73.4 months (with an interval of 16-137 months, i.e. 1.3-11.4 years), the observed oncologic outcomes are relevant despite the relatively modest number of analyzed cases. The major novelty of our investigation was the finding that in our population the first 3 postoperative years present the critical time for recurrence, especially in multiparous women with serous BOTs treated by USOE.

In our sample, the serous subtype was predominant (more than 50%). According to literature data, serous subtypes are frequently encountered, although mucinous BOT is considered as the most common BOT subtype [10,14,15]. All examined patients underwent radical surgical treatment with adequate staging or FSS treatment with adequate staging to preserve fertility depending on the disease features and patient's resolve. In cases of FSS, unilateral salpingo-oophorectomy was the most common procedure. Special consideration is always given to unilateral cystectomy (with proper staging) as a definitive treatment due to potentially higher recurrence risk, ranging from 24 to 33% [16]. This procedure was performed in 20% of cases while others report similar or lower (10-15%) frequencies [11,16,17]. A possible explanation for the higher UCE rate in our study may be due to the higher rate of emergency procedures without the possibility of frozen section assessment. Despite this, the overall survival in our study was 100% and no recurrences were noted in patients treated with UCE.

We registered 4 recurrences in the 45 patients treated with FSS while there were no recurrences in the radically treated group of patients. The recurrence rate of 7.7% is comparable to the commonly reported recurrence rate following radical surgical treatment of stage I BOT, which is 5% [6]. Moreover, it was somewhat lower than the recurrence rate after FSS described in other investigations (13.4%) [18]. All examined patients with subsequent recurrences primarily underwent USOE. Patients who had UCE did not have recurrences, which proved the safety of such a procedure for BOT treatment. The disease stage did not impact the frequency of recurrence. Recurrences were mostly localized on the contralateral ovary. All patients with recurrence had a normal result of contralateral ovarian biopsy during the first staging operation (performed in accordance with the guidelines and recommendations relevant at the time).

In our study, the mean recurrence-free survival was 36.2 months, which is consistent with data from the literature [17]. Recurrences mostly occurred during the first 3 postoperative years (20-35 months) with a low rate after the 5-year period. One recurrence was noted 6 years after initial surgery. All patients were followed-up from 10-25 months after being treated for recurrences and none of them presented evidence of the disease. Nevertheless, we must point out the need for prolonged yearly follow-up due to the possibility of recurrence 10 and more years after surgery [8,9].

All recurrences that were diagnosed had the same histology as the primary BOTs (3 serous and 1 endometrioid adenocarcinoma). This finding is somewhat different from other studies that indicate that mucinous BOTs are more likely to have recurrences. The incidence of cancer after the serous BOT is about 3% while after mucinous BOT it is around 15% [19-21]. Recurrence in the form of endometrioid adenocarcinoma is found to occur more often after previous treatment of serous BOT, but so far there are only some cases of endometrioid adenocarcinoma after the treatment of endometrioid BOT [22]. The total number of recurrent cases was insufficient for an in-depth analysis of the association with the histological BOT subtypes, which should be performed in future on larger samples.

In the fertility-sparing group, 64.4% tried to conceive, which resulted in a pregnancy success rate of 44% (13 patients), while 3 patients had 2 pregnancies each (a total of 16 pregnancies). The observed findings correspond with literature reports (the pregnancy-rate range of 20-80%). Some larger studies even report lower pregnancy rates [10,16,23,24]. Assisted reproduction is widely accepted for achieving pregnancy after BOT treatment.

Ovarian stimulation with oocyte retrieval in BOT patients was found to be relatively safe and feasible before or during surgery, depending on the size of the tumor. Still, the possibility of spontaneous conception after BOT treatment is a significant advantage of FSS [25]. This is especially important as some studies indicate that assisted reproductive technology (ART) might cause BOT development although no dose-response relationship was observed and it is still under investigation which ART parameters could increase the risk [26,27]. Nevertheless, other investigations proved that

ovarian stimulation is safe in BOT patients and did not find a significant increase in BOT recurrence in patients treated with FSS [28,29]. In our study, almost all pregnancies were achieved spontaneously without any fertility issues, and only 1 was achieved by intrauterine insemination. This is a better rate of spontaneous pregnancy (6.25% use of ART) than in other investigations where ART was applied in 9-16% of cases to achieve pregnancy after BOT [10]. Of the remaining 16 patients who failed to conceive, 3 had unsuccessful IVF procedures. Patients who underwent assisted reproduction were thoroughly informed and fully aware of all potential risks. Pregnancies were achieved after 38.2+/-19.4 months (about 3 years), which does not significantly differ from the literature data (ranging from 13 to 37.5 months) [21,24].

Some previous studies indicated that the extent of the procedure on the ovary (cystectomy vs unilateral salpingo-oophorectomy) is important for later pregnancy success [30,31]. Our data showed that the surgical treatment was not significantly associated with the rate of pregnancies, with 61.5% (8/13) achieved in patients who had USOE. Other patients who gave birth afterward had unilateral cystectomy (2), unilateral ovariectomy (1), bilateral cystectomy (1) and a combination of unilateral salpingo-oophorectomy with contralateral cystectomy (1 patient). Considering the total number of patients who attempted pregnancy following treatment, the sub-stage and histological subtype of the disease was not statistically significantly associated with pregnancy.

There were 2 patients who conceived and had a recurrence of the disease. There are no large studies dealing with this issue and previous case studies do not link pregnancy with greater recurrence risk [32]. This issue should be analyzed further.

One of the study limitations is the small sample, which impacts the generalizability of our findings. However, borderline ovarian tumors account for less than 20% of all ovarian tumors [1]. Therefore, our sample is comparable with other single-centered investigations. Although our study was performed in only one institution, it is the tertiary referral center for gynecologic oncology. Moreover, a 10-year period was covered to optimize the reliability of the data. Another limitation might be the follow-up period of a

minimum of 12 months, which could have prevented diagnosing recurrence in some patients. Nevertheless, according to the literature, the recurrence of BOTs is generally infrequent and rarely occurs long (on average 2 years) after primary treatment [15]. This was proven in our study in which the median follow-up time was 5.7 years. Certainly, multicentric studies with a longer follow-up are recommended for obtaining additional evidence regarding BOT patients.

CONCLUSIONS

The study objective was to assess for the first time the oncologic and reproductive outcomes of patients with stage I BOT treated by FSS in our referral tertiary university hospital. The overall survival rate in our study of examined Serbian BOT patients treated and followed-up according to current protocols was 100%, while the recurrence rate was 7.7%. The overall survival was not influenced by any patient or treatment characteristic. Recurrence was rare and mostly occurred during the first 3 years after primary surgery; the recurrence rate was especially low after this period. Recurrence was more often in multiparous patients who were treated with unilateral salpingo-oophorectomy and who had serous BOT histology. Based on our 10-year experience, in comparison with radical surgical treatment, fertility sparing treatment in stage I borderline ovarian tumors has proved to be a safe option both in terms of oncological and reproductive outcome. The pregnancy rate after BOT surgery was somewhat low (44.8%); however, only 1 pregnancy was achieved by assisted reproduction and all children were on term and in good condition at birth.

Conflict of interest disclosure: The authors declare no conflict of interest.

Data availability: All data underlying the reported findings have been provided as part of the submitted article and are available at: https://www.serbiosoc.org.rs/NewUploads/Uploads/Likic%20 Ladjevic%20et%20al_7928_Data%20Report.pdf

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Supplementary Data

The Supplementary Material is available at: https://www.serbiosoc.org.rs/NewUploads/Uploads/Likic%20Ladjevic%20et%20al_7928_Supplementary%20Material.pdf