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Short-term Outcomes and Pregnancy Rate After Laparoscopic Fertility-Sparing Surgery for Borderline Ovarian Tumors

A Single-Institute Experience

Jianguo Zhao, MD, Caiyan Liu, MD, Jing Liu, MD, and Pengpeng Qu, MD, PhD

Objective: We investigated the short-term outcomes and pregnancy rate after a laparoscopic approach to fertility preservation in patients with borderline ovarian tumors (BOTs).

Methods: Clinic-pathologic variants of patients with BOTs who underwent conservative surgery at the Tianjin Central Hospital of Obstetrics and Gynecology between January 2009 and July 2015 were retrospectively analyzed.

Results: Among 211 patients with BOTs, 74 (35.1%) received conservative surgery (44 cases using a laparoscopic approach and 30 cases using a laparotomy approach). The mean age of the laparotomy group was significantly younger than that of the laparoscopic group ($P = 0.024$). The maximal longitude of the tumor in the laparotomy group was significantly longer than that in the laparoscopic group ($P < 0.001$). The number of incomplete surgery cases in the laparoscopic group was significantly greater than that in the laparotomy group ($P < 0.001$). The 2 groups showed no significant differences in gravidity and parity before surgery, abnormality of serum tumor makers, tumor lateralities, ascites, histology, duration of follow-up, pregnancy rate after surgery, or postoperative recurrence. Total recurrent rate was 6.7% (5/74). Two cases in laparotomy group and 3 cases in laparoscopic group relapsed respectively. There was no significant difference of recurrent rate between the 2 groups. The total pregnant rate was 33.8% (25/74). Nine patients (30%) in the laparotomy group and 16 patients (36.4%) in the laparoscopic group became pregnant during follow-up respectively. There were no significant differences in the postoperative durations of pregnancy, pregnancy type, age at pregnancy, tumor lateralities, ascites, or type of pathology between 2 groups. The pregnancy rate of incomplete surgery cases in laparoscopic group was significantly higher than that of laparotomy group ($P = 0.011$). No recurrence occurred among the pregnant cases.

Conclusions: A comprehensive laparoscopic surgery was not performed in incomplete surgery patients undergoing complete exploration. Good short-term outcomes and pregnancy were observed in patients receiving conservative laparoscopic surgery for BOTs, especially in patients receiving incomplete conservative laparoscopic surgery.

Key Words: Borderline ovarian tumors, Conservative surgery, Laparoscopy

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Department of Gynecological Oncology, Tianjin Central Hospital of Obstetrics and Gynecology, Tianjin, China.

Address correspondence and reprint requests to Pengpeng Qu, MD, PhD, Department of Gynecological Oncology Tianjin Central Hospital of Obstetrics and Gynecology, 156 3rd Rd, Nankai District, Tianjin 300100, China. E-mail: qu.pengpeng@hotmail.com.

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Borderline ovarian tumors (BOTs) accounted for 10% to 15% of ovarian tumors[1] and had a significantly better prognosis compared with epithelial ovarian cancer. The survival rate of patients with BOTs at 5, 10, 15, and 20 years had been reported to be 97%, 95%, 92%, and 89%, respectively.[2] Borderline ovarian tumors were more common in younger women, and most patients were diagnosed in the early stage, with nearly 50% to 80% diagnosed with the International Federation of Gynecology and Obstetrics (FIGO) stage I. Most BOTs were confirmed by analysis of frozen sections during the operation or postoperative pathology. Most patients relapsed after operation many years later with most recurrent tumors still being borderline tumors with a satisfactory prognosis.[3] Nearly one third of patients with BOTs were of childbearing age.[4] In addition, nearly two thirds of the patients with a strong desire for fertility-sparing surgery were less than 30 years old.[5] Thus, fertility-sparing surgery must be provided to patients with BOTs requesting fertility preservation. Over the past few years, the laparoscopic surgery had been widely used in gynecological oncology and laparoscopic fertility-sparing surgery had been performed in patients with BOTs.[4,5] Although the safety of laparoscopic fertility-sparing surgery has been recognized, its prognosis and pregnancy rate are still under investigation. At present, there are few reports that have evaluated pregnancy outcomes after laparoscopic fertility-sparing surgery in patients with BOTs. Thus, we performed a retrospective analysis of patients with BOTs who underwent fertility-sparing surgery at the Tianjin Central Hospital of Obstetrics and Gynecology from January 2009 to July 2015.

MATERIALS AND METHODS

Study Population

The full records of all patients with BOTs who were treated with fertility-sparing surgery from January 2009 to July 2015 at the Tianjin Central Hospital of Obstetrics and Gynecology were retrieved. There were 211 cases of BOTs during this period, with 137 cases (64.9%) receiving comprehensive surgery and 74 cases (35.1%) receiving conservative surgery, including 44 patients using a laparoscopic approach and 30 patients using a laparotomy approach.

Patients were included in the current study if they had the following: (1) previously untreated BOTs; (2) complete records; (3) pathological results that were reviewed by a pathologist; and (4) ethics committee approval and informed consent obtained. Exclusion criteria included the following: (1) nonepithelial BOTs; (2) incomplete records; (3) a borderline tumor that was diagnosed by intraoperative frozen section but was excluded by hematoxylin-eosin staining postoperatively; and (4) metastatic ovarian tumors.

Surgical Procedures

Peritoneal lavages or ascites were first extracted for cytological examination. Complete fertility-sparing surgery included unilateral salpingo-oophorectomy (USO), unilateral salpingo-oophorectomy plus contralateral cystectomy (USO + CC), bilateral cystectomy (BC), unilateral cystectomy (UC), and the previous procedures plus comprehensive abdominal exploration plus multiple peritoneal biopsy plus omentectomy below the transverse colon, as long as part of the ovary and uterus were retained. In addition, appendectomy was performed for mucinous BOTs. Incomplete fertility-sparing surgery was defined as surgical procedures not done as listed previously but for which part of the ovary and uterus were preserved too. Pelvic and para-aortic lymph node dissection was not included in the current study, in accordance with National Comprehensive Cancer Network ovarian cancer guidelines.[6] Surgical-pathologic staging was performed in accordance with the FIGO 2014 staging scheme.

Follow-up

Patients were examined every 3 months during the first 2 years, every 6 months during the following 3 years, and yearly thereafter. Contents of surveillance included physical examination, assessment of tumor markers, and pelvic ultrasound.[7] Recurrence was defined as an abnormality found during follow-up and was confirmed by pathologic analysis after a second cytoreductive surgery.

Analytical Methods and Statistics

Clinical-pathological characteristics and postsurgical pregnancy rate were retrospectively compared between laparoscopic and laparotomic group. Characteristics included age, preoperative serum markers, tumor size (maximal longitude), surgical approach, histology, complete surgery, recurrence, postoperative pregnancy, interval from surgery to pregnancy, ascites, etc. Recurrence-free interval was calculated as the number of months from the date of the initial surgery to the detection of recurrence/death or the date of censor. Recurrence rate and pregnancy were also analyzed. Descriptive statistics were calculated using SPSS 17.0 (SPSS Inc, Chicago, Ill). χ^2 and Fisher exact tests were used to evaluate the statistical significance for proportions. Both mean and median values were compared between the 2 groups using Student *t* tests. The cut-off value for statistical significance was set at $P < 0.05$.

RESULTS

From January 2009 to July 2015, 211 patients with full records were treated at our institute, with complete surgery performed in 137 cases and fertility-sparing surgery performed in 74 cases (74/211, 35.1%). Residual disease was not seen in cases with FIGO stage II or more after complete surgery or complete fertility-sparing surgery. Seventy-four cases underwent fertility-sparing surgery, which included 26 UC cases, 18 USO + CC cases, 12 BC cases, and 18 USO cases. Among conservative patients, 30 cases underwent laparotomic surgery including 8 UC cases, 3 BC cases, 10 USO cases, and 9 USO + CC cases, whereas 44 cases underwent laparoscopic surgery, including 18 UC cases, 9 BC cases, 8 USO cases, and 9 USO + CC cases. Thirty-six cases with elevated CA125 and 12 cases with elevated CA199 before surgery had been normalized postoperatively. Five cases (6.8%) had relapsed postoperatively, 1 case relapse in abdominal-pelvic cavity, and 4 cases in pelvic cavity. None of them died of disease after surgery. The interval to recurrence of 3 cases in laparoscopic group and 2 cases in laparotomy group was 23, 26, and 30 months, and 30 and 50 months respectively. These recurrent cases were treated

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by debulking/cytoreductive or fertility-sparing surgery with or without chemotherapy. The characteristics of the 74 patients who received fertility-sparing surgery are shown in Table 1. The mean age of the laparotomy group was significantly younger than that of the laparoscopic group ($P = 0.024$). In addition, the maximal longitude of the tumor in the laparotomy group was significantly longer than that in the laparoscopic group ($P < 0.0001$). The number of incomplete surgery cases in the laparoscopic group was significantly greater than that in the laparotomy group ($P < 0.001$). The 2 groups showed no significant differences in gravidity and parity before surgery, duration of follow-up, abnormality of serum tumor markers, tumor lateralities, ascites, histology, pregnancy rate after surgery, or postoperative recurrence.

Among the 74 cases that received fertility-sparing surgery, pregnancy was observed in 25 patients (33.8%) during follow-up (including 3 unplanned pregnant cases, 1 divorced, 2 unmarried), of which 9 (30%) were in the laparotomic group and 16 (36.4%) were in the laparoscopic group. The characteristics of 25 patients who achieved pregnancy are shown in Table 2. There was a significant higher pregnant rate in incomplete laparoscopic surgery cases than that in laparotomy surgery cases ($P = 0.011$). There were no significant differences in the postoperative duration of pregnancy, pregnancy type, age at pregnancy, tumor lateralities, ascites, or type of pathology between 2 groups. No recurrence occurred among the pregnant cases.

DISCUSSION

Patients with BOTs are generally younger than those with ovarian cancer, and most were early stage when detected. Therefore, patients with BOTs usually had a good prognosis.[8] Previous reports demonstrated that 70% of patients with serous BOTs and more than 90% of patients with mucinous BOTs were in stage I.[9] The 5-year survival rate of patients in the early stage had been reported to be 98%, and the 5-year survival rate of patients in the advanced stage was 86% to 92%.[10]

Given the high survival rate and late recurrence of patients with BOTs, it was reasonable for young patients with BOTs to request fertility preservation, even though most recurrences were borderline tumors too.[3] In view of the previous biological characteristics of BOTs and the application of laparoscopy in gynecologic oncology, more attention had been paid to laparoscopic fertility-sparing surgery for BOTs by gynecological oncologists. Therefore, in the current study, we evaluated the prognosis and pregnancy outcomes of young patients with BOTs after laparoscopic conservative surgery.

Boran et al[9] reported that the median age of patients with BOTs receiving conservative surgery was 25.7 years. Similarly, the median age in our study was 28.3 years. Uzan et al[11] demonstrated that age (with a cut-off of 30 years), the type of conservative treatment (cystectomy vs adnexectomy), and the presence of unilateral/bilateral tumor(s) predicted recurrence with univariate analysis. However, there was no

TABLE 1. Comparison of clinic-pathologic characteristics between 2 groups

Group	Total, n	Age, y	Duration of Follow-up, mo	Fertility		Staging Surgery	
				Parous	Nulliparous	Complete	Incomplete
Laparotomy	30	27 ± 6.5	20 ± 8.9	19	11	21	9
Laparoscopy	44	30 ± 5.0	23 ± 15.9	33	11	13	31
t or χ^2 value	—	2.42	0.868	1.162		11.75	
P	—	0.018	0.389	0.281		0.001	

Group	Total, n	Tumor Sizec, cm	CA125		CA199			Histology	
			Negative	Positive	Negative	Positive	Undetected	Serous	Nonserous
Laparotomy	30	12 ± 3.8	14	16	9	2	19	14	6
Laparoscopy	44	8 ± 1.6	24	20	19	10	15	22	22
t or χ^2 value	—	5.534	0.043			1.009		0.079	
P	—	0.000	0.506			0.315		0.778	

Group	Total, n	Laterality		Ascites		Pregnancy		Recurrence	
		Unilateral	Bilateral	Positive	Negative	Yes	No	Yes	No
Laparotomy	30	27	3	8	22	9	21	2	28
Laparoscopy	44	37	7	11	33	16	28	3	41
t or χ^2 value	—	0.533		0.026		0.323		0.001	
P	—	0.465		0.872		0.570		0.980	

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TABLE 2. Comparison of clinic-pathologic characteristics of pregnant patients between 2 groups

Group	Total, n	Age, y	Interval From Surgery to Pregnancy, mo	Pregnant Age*		Staging Surgery		Pregnant Method*		Laterality*		Ascites*		Histology*	
				<35 y	≥35 y	Yes	No	Spontaneous	IVF	Unilateral	Bilateral	Yes	No	Serous	Nonserous
Laparotomy	9	24 ± 5.8	16 ± 3.1	8	1	6	3	8	1	8	1	2	7	3	6
Laparoscopy	16	27 ± 3.8	20 ± 8.2	14	2	5	11	13	3	14	2	2	14	9	7
t or χ^2 value	—	1.549	1.685	—		4.163		—		—		—		—	
P	—	0.135	0.105	1		0.041		1		1		1		0.411	

*Fisher exact test.

significant difference in the prognosis based on FIGO stage (Ia, Ib, Ic), microinvasion, micropapillary patterns, or peritoneal cytology.[11] Only age of patients was an independent prognostic factor for recurrence with multivariate analysis.[11] In this previous study, the median follow-up duration was 45 months (range, 12–120 months) and the recurrence rate was 32%. Despite being high the recurrence rate, the overall survival and prognosis were not influenced.[11] In another study with a median 57-month follow-up duration, 56% of the patients showed recurrence within 48 months, with 5-year and 10-year survival rates of 100% and 92%, respectively.[5]

Furthermore, the 5-year and 10-year recurrence-free rates were 36% and 22%, respectively, with no significant differences between conservative and complete surgeries. In patients with advanced serous BOTs, there was no significant difference in the recurrence rate between laparotomy and laparoscopic surgeries.[5] The current study showed that the recurrence rate for sparing-fertility surgery was only 6.8%, significantly lower than that of the studies mentioned above. This may be due to the relatively short follow-up time of the current study (median follow-up time only 21.4 months) and the fact that only 6 cases' FIGO stage were more than stage II.

It had been previously reported that overall survival of incomplete surgery patients with stage I BOTs did not decrease more than that of complete surgery patients (laparoscopic surgery accounted for 60% of cases in this previous study).[12] Tinelli et al[8] suggested that, after a simple laparoscopic cystectomy for a supposed benign cyst with no presurgical suspicion of malignancy in the initial surgery, no further complete surgery was needed if the following standards were met: (1) a complete exploration on abdominopelvic cavity was performed; (2) no spillage occurred during the operation; (3) the borderline lesion was on the inner side of the cyst; (4) there was no vegetation on the outer side of the cyst; (5) there was enough healthy margin; and (6) sufficient follow-up was carried out. The advantages of this approach include mild disturbance to abdominopelvic organs, reduced adhesions in the abdominopelvic cavity, improved chance of pregnancy, and a faster recovery. We adopted these criteria when performing laparoscopic fertility-sparing surgery for patients with BOTs. In the current study, incomplete patients accounted for 54.1% (40/74) of the cases. The recurrence rate for patients receiving incomplete laparoscopic fertility-sparing surgery was 9.7% (3/31), which we considered an exciting short-term outcome. The long-term prognosis remains to be studied with further follow-up.

In the current study, patients who underwent fertility-sparing surgery were divided into laparotomy and laparoscopy groups. The age of the laparotomic group was found to be younger than that of the laparoscopic group, with 4 patients under 20 years old in the laparotomic group, including 1 who was only 11 years old. In addition, the average tumor size of the laparotomy group was significantly larger than that of the laparoscopic group, owing to a larger proportion of big mucinous BOTs in the laparotomy group. The median tumor size in the laparoscopic group was only 8.2 cm, which may have led to a low recurrence rate. We suggested that the choice of surgical approach should be based on the size of the tumor and that the laparoscopic procedure should be closely evaluated before the operation.

Although blood loss, operation time, and hospital stay of the laparoscopic surgery group were significantly less and shorter than those of the open surgery group (data not given), some disadvantages of laparoscopic surgery exist. The risks include cyst rupture, intraabdominal spillage, and contamination of the abdominal wall, which may cause implantation at trocar sites. These risks can be reduced to an acceptable level using a lap-sac and abundant peritoneal washing.[8] The recurrence rate in the current study was 6.8% (5/74), and no implantation of trocar sites occurred.

Therefore, we believed that laparoscopic fertility-sparing surgery could be performed in patients with BOTs. Cysts were fed into a lap-sac, and cyst fluid was absorbed to reduce intraoperative contamination of the abdominopelvic cavity. If there was intraoperative rupture of a cyst during laparoscopy, copious washing of the pelvis and abdomen should be performed to prevent implantation in the abdomen and trocar sites. The postoperative 2-year recurrence rate did not increase, and there was no significant difference in postoperative pregnancy rates between the laparotomy and laparoscopy groups (30% vs 36.4%). We believed that the surgical approach had no influence on pregnancy. However, because of several recurrent cases, we could not compare the recurrence rates in pregnant patients between laparotomy and laparoscopy groups.

Fauvet et al[6] reported that the median interval from surgery to pregnancy was 28.6 ± 24.6 months (ranging from 4 to 89 months), and the recurrence rate was 23.8%, which is significantly higher than that in our study owing to the short duration of the follow-up. In general, no relationship is thought to exist between BOTs and pregnancy.[10] Borderline ovarian tumors had been reported to recur after in vitro fertilization (IVF) in previous studies.[10] At present, most researchers believed that IVF should only be conducted in stage I patients with limited ovulation.[10] Infertile patients with BOTs should be informed of the possible risks of recurrence before IVF. In addition, the patients with BOTs should be closely monitored postovulation.[8] In our study, there were only 4 patients who underwent IVF and none suffered recurrence. The effect of IVF on the recurrence of the tumor should be observed continuously. Moreover, the influence of age on pregnancy cannot be ignored, because previous studies had shown that the pregnancy rate was 42% in patients under 35 years of age, which was significantly higher (by 20%) than that for patients aged 35 to 40 years.[6] However, it had been reported to show no influence on pathological type, mode of operation, operative approach, or FIGO stage.[6] In our study, the patients were relatively young, with only 3 cases over 35 years of age; thus, the influence of age on pregnancy could be assessed closely. In general, positive treatment should be used for fertility-sparing patients over 35 years of age to help the patients become pregnant as early as possible.

In summary, fertility-sparing surgery is feasible for patients with BOTs who have fertility requirements. Given the distinct advantage and rapid development of laparoscopy, laparoscopic fertility-sparing surgery could be performed in some patients with BOTs who have strong fertility requirements. During the operation, technique and equipment prevented tumor rupture and implantation at trocar sites should be adopted. After the operation, patients should be closely followed based on individual conditions. Pregnancy guidance should be given to help patients become pregnant as early as possible.

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REFERENCES

1. Gershenson DM. Clinical management potential tumours of low malignancy. *Best Pract Res Clin Obstet Gynaecol*. 2002;16:513–527.
2. Leake JF, Rader JS, Woodruff JD, et al. Retroperitoneal lymphatic involvement with epithelial ovarian tumors of low malignant potential. *Gynecol Oncol*. 1991;42:124–130.
3. Sobiczewski P, Kupryjanczyk J, Michalski W, et al. The evaluation of risk factors associated with relapse and recurrence of borderline ovarian tumors with long-term follow-up. *Int J Gynecol Cancer*. 2016;26:1053–1061.
4. Lazarou A, Fotopoulou C, Coumbos A, et al. Long-term follow-up of borderline ovarian tumors clinical outcome and prognostic factors. *Anticancer Res*. 2014;34:6725–6730.
5. Uzan C, Kane A, Rey A, et al. Outcomes after conservative treatment of advanced-stage serous borderline tumors of the ovary. *Ann Oncol*. 2010;21:55–60.
6. Fauvet R, Poncelet C, Boccara J, et al. Fertility after conservative treatment for borderline ovarian tumors: a French Multicenter study. *Fertil Steril*. 2005;83:284–290.
7. Song T, Lee YY, Choi CH, et al. Prognosis in patients with serous and mucinous stage I borderline ovarian tumors. *Int J Gynecol Cancer*. 2012;22:770–777.
8. Tinelli R, Tinelli A, Tinelli FG, et al. Conservative surgery for borderline ovarian tumors: a review. *Gynecol Oncol*. 2006;100:185–191.
9. Boran N, Cil AP, Tulunay G, et al. Fertility and recurrence results of conservative surgery for borderline ovarian tumors. *Gynecol Oncol*. 2005;97:845–851.
10. Cadron I, Leunen K, Van Gorp T, et al. Management of borderline ovarian neoplasms. *J Clin Oncol*. 2007;25:2928–2937.
11. Uzan C, Muller E, Kane A, et al. Prognostic factors for recurrence after conservative treatment in a series of 119 patients with stage I serous borderline tumors of the ovary. *Ann Oncol*. 2014;25:166–171.
12. Rao GG, Skinner E, Gehrig PA, et al. Surgical staging of ovarian low malignant potential tumors. *Obstet Gynecol*. 2004;104:261–266.

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