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Infertile women with a history of fertility-sparing surgery for borderline ovarian tumors: IVF outcomes and the association between IVF and tumor recurrence

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Abstract

Background Borderline ovarian tumors (BOTs) are neoplasms of low malignant potential that predominantly affect women of reproductive age. Fertility preservation through fertility-sparing surgery is widely practiced; however, concerns remain regarding the risk of tumor recurrence and the reproductive outcomes following in vitro fertilization (IVF). This study aimed to evaluate IVF/ intracytoplasmic sperm injection (ICSI) outcomes in BOTs patients post-FSS and to assess the association between ovarian stimulation parameters and tumor recurrence.

Methods In this retrospective cohort study conducted at Sixth Hospital of Sun Yat-sen University from May 2010 to May 2023, 65 women with a history of FSS for BOTs who underwent IVF/ICSI were identified. After propensity score matching, 61 BOTs patients were compared with 181 control patients without ovarian tumors. Key outcomes evaluated included ovarian stimulation parameters, live birth rates, neonatal outcomes and risk factors for tumor recurrence.

Results The BOTs and control groups exhibited similar outcomes regarding the number of oocytes retrieved, the quality and number of embryos, and live birth rates from the first IVF/ICSI cycles. The cumulative live birth rate over 13 years and neonatal parameters (gestational age, birth weight, and body length) were also comparable between groups. Tumor recurrence was observed in 8.62% of BOTs patients, with no significant association identified between recurrence and ovarian stimulation parameters or peak estradiol levels.

Conclusions IVF/ICSI following fertility-sparing surgery for BOTs patients yields reproductive and neonatal outcomes comparable to those in patients without BOTs and does not increase the risk of tumor recurrence. These findings support the safety and efficacy of IVF as a fertility treatment option for BOTs patients after conservative surgery.

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Further prospective studies with larger cohorts are warranted to validate these results and refine ovarian stimulation strategies.

Clinical trial number Not applicable.

Keywords Ovarian borderline tumors, Fertility-sparing surgery, In vitro fertilization, Ovarian stimulation, IVF outcomes, Tumor recurrence

Background

Ovarian borderline tumors (BOTs) are unique neoplasms with biological behavior lying between benign and malignant ovarian tumors, characterized by low malignant potential. BOTs account for 15–20% of epithelial ovarian malignancies [1] and have an annual incidence of 1.8–5.5 per 100,000 women [2]. Around one-third of affected patients are under the age of 40 [3], with many diagnosed during their reproductive years. Fertility preservation is therefore a key consideration in managing BOTs, particularly for women who have not yet had children. Fertility-sparing surgical approaches, including cystectomy, unilateral oophorectomy, or unilateral salpingo-oophorectomy, are recommended to preserve the uterus and at least one ovary [3, 4]. However, postoperative complications such as pelvic adhesions and reduced ovarian reserve may impact natural conception [5], leading some BOTs patients to require in vitro fertilization (IVF).

Research on IVF outcomes in patients with BOTs after FSS is limited, primarily consisting of case reports [6–16], with a lack of comparative studies between BOTs and non-BOTs patients. Besides, a critical concern is the potential for residual tumor cells after conservative surgery [17], raising questions about the impact of ovarian stimulation on the recurrence of BOTs. The impact of IVF treatments on the risk of tumor recurrence remains crucial areas of investigation. This study aims to evaluate IVF outcomes in patients with BOTs after FSS, with a focus on fertility outcomes and recurrence risks, to aid in the counseling and treatment options for this unique patient population.

Methods

Study population

Between May 2010 and May 2023, 45,576 infertility patients who underwent IVF or intracytoplasmic sperm injection (ICSI) at Sun Yat-sen University Sixth Hospital were screened. Among them, 68 patients with a history of fertility-sparing surgery (FSS) for BOTs who underwent their first IVF/ICSI treatment were identified. Three patients who had chemotherapy were excluded, leaving 65 patients in the BOTs group. A control group of 36,733 patients without BOTs, other ovarian tumors or cancer history who underwent their first IVF/ICSI treatment cycles was matched 3:1 with the BOTs group based on age (± 1), body mass index (± 1), insemination method, date of first IVF/ICSI, ovarian stimulation protocols and antral follicle count. Ultimately, 181 control patients and 61 BOTs patients were successfully matched (Fig. 1). The study was approved by Sun Yat-sen University Sixth Hospital Medical Science Research Ethics Committee (2024ZSLYEC-397).

IVF/ICSI treatment

Ovarian stimulation was performed according to standardized protocols. Long-term GnRH agonist protocols were used for downregulation, followed by stimulation with gonadotropins. In the antagonist protocol, GnRH antagonists were administered once the follicles reached 12 mm. The mild stimulation protocol involved oral letrozole combined with low-dose gonadotropins. Progestin-primed ovarian stimulation protocols initiated progestin on the second day of the menstrual cycle to suppress the endogenous luteinizing hormone surge. The natural cycle protocol avoided ovarian stimulation, relying on spontaneous follicular development with timed oocyte retrieval guided by hormonal and ultrasound monitoring. Except for natural cycle protocol, oocyte retrieval was performed 36 h after human chorionic gonadotropin administration when three or more follicles reached ≥ 18 mm. Fertilization was assessed 16–18 h post-insemination, and embryo quality was assessed based on Istanbul Consensus Workshop on Embryo Assessment [18]. Fresh embryo transfer occurred on day 3 or 5 after retrieval and frozen embryo transfer was carried out on day 3 or 5 following endometrial luteinization.

Study outcomes

The primary outcome was live birth rate from first IVF/ICSI cycles, including both fresh and frozen embryo transfers. The second outcomes were ovarian stimulation parameters, pregnancy parameters, cumulative pregnancy rate, neonatal parameters and risk factors for tumor recurrence. Risk factors for tumor recurrence, including BOTs stage, pathological type, extent of ovarian surgery in FSS, interval from surgery to IVF, number of stimulation cycles and peak E_2 level in ovarian stimulation were analyzed. Pregnancy outcomes and tumor recurrence status were monitored through follow-up interviews.

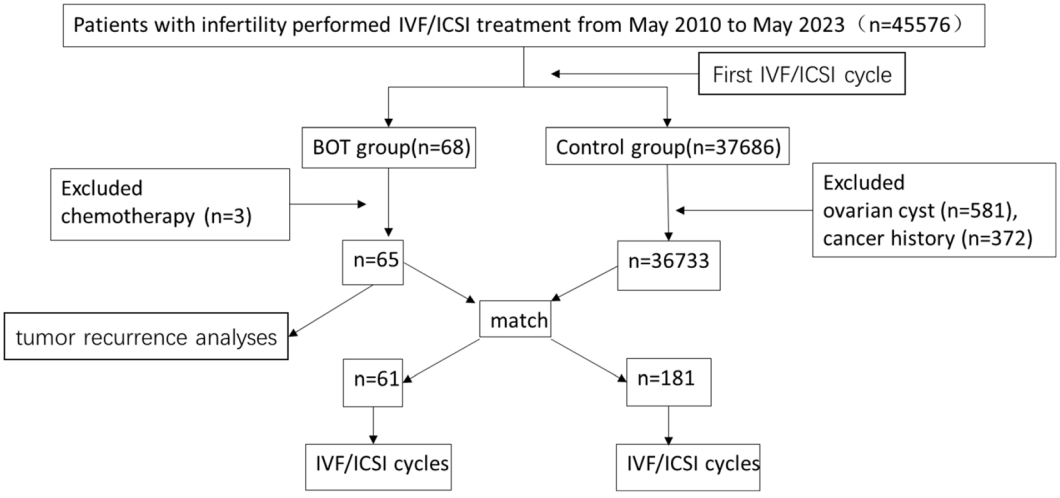

Fig. 1 Flow chart of study cohort selection

Table 1 Clinicopathological characteristics of bots patients

Characteristics	Results
Median age (years)	31(23–42)
Median interval between the initial surgery and IVF/ICSI (month)	14.5(2-180)
Median follow-up interval between first IVF/ICSI and 2023 May (month)	64.0(13–162)
Follow-up interval ≥ 24 months (%)	81.5(53/65)
FIGO stage	
IA (%)	43.1(28/65)
IB (%)	15.4(10/65)
IC (%)	26.2(17/65)
IIA (%)	1.5(1/65)
IIB (%)	6.2(4/65)
IIIA (%)	3.1(2/65)
IIIB (%)	4.6(3/65)
Histology	
Mucinous (%)	27.7(18/65)
Serous (%)	67.7(44/65)
Seromucinous (%)	3.1(2/65)
Endometrioid (%)	1.5(1/65)
Ovarian lesion site	
Unilateral (%)	53.8(35/65)
Bilateral (%)	46.2(30/65)
Ovarian surgery in FSS	
Unilateral oophorocystectomy (%)	24.6(16/65)
Bilateral oophorocystectomy (%)	13.8(9/65)
Unilateral oophorectomy (%)	29.2(19/65)
Unilateral oophorectomy + unilateral oophorocystectomy (%)	32.3(21/65)

Abbreviation: BOTs, borderline ovarian tumors; FSS, fertility sparing surgery

Statistical analysis

Continuous variables were expressed as means ± standard error or medians (interquartile range), depending on data distribution. Continuous variables were compared with the student's t-tests and categorical variables were compared using chi-square tests. Cumulative live birth probability was calculated using the Kaplan-Meier method and a log-rank test assessed statistical significance [19]. Logistic regression was used to analyze risk factors for tumor recurrence. A *P*-value of <0.05 was considered statistically significant. All analyses were performed using SPSS version 23.0 (SPSS, Inc., Chicago, Illinois).

Results

Clinicopathological characteristics of BOTs patients

The median age of BOTs patients was 31 years, with a median interval between surgery and IVF of 14.5 months (range 2–180 months). The median follow-up duration from first IVF/ICSI to May 2023 was 64 months, with 81% having follow-up periods exceeding 24 months. The most common histologic type was serous BOTs (67.7%), with 84.6% of patients presenting at stage I. Unilateral ovarian involvement was observed in 53.8% of cases, while 46.2% had bilateral involvement. Surgical procedures varied, with 24.6% of patients undergoing unilateral cystectomy, 13.8% bilateral cystectomy, and 29.2% unilateral oophorectomy (Table 1).

Demographics and baseline characteristics

There were no significant differences in age, BMI, antral follicle count, insemination method and initial ovarian stimulation protocol between the BOTs and control groups, as shown in Table 2.

Characteristics of the initial stimulation cycles

The characteristics of the initial stimulation cycles are summarized in Table 3. No significant differences were observed between the BOTs and control groups in terms of stimulation duration, total gonadotropin dose, number of retrieved oocytes, 2PN embryos, transferable embryos,

Table 2 Patient demographics and baseline characteristics in the study population with or without bots history

Characteristic	BOTs($n=61$)	Control($n=181$)	T(χ^2)	*P*
Age (years)	31.38 ± 0.513	31.21 ± 0.394	-0.258	0.797
BMI (kg/m2)	22.33 ± 0.465	22.01 ± 0.246	-0.641	0.522
AFC	6.52 ± 0.703	6.72 ± 0.397	0.250	0.803
Insemination method				
IVF (%)	51(83.6)	144(79.6)	0.478	0.489
ICSI (%)	10(16.4)	37(20.4)		
Initial stimulation protocol				
mini-stimulation (%)	22(36.1)	68(37.6)	0.322	0.988
PPOS (%)	11(18.0)	28(15.5)		
long-term stimulation (%)	9(14.8)	27(14.9)		
natural cycle (%)	3(4.9)	11(6.1)		
antagonist stimulation (%)	16(26.2)	47(26.0)		

Note: Continuous data are presented as mean ± standard error. Categorical data are presented as number (percentage)

Abbreviation: BMI, body mass index; AFC, antral follicle count; PPOS, progestin-primed ovarian stimulation

or good-quality embryos. Additionally, the percentage of 2PN embryos, transferable embryos, and good-quality embryos per oocyte retrieved did not differ significantly between the two groups. The live birth rate following the first IVF cycle was comparable between the BOTs and control groups, with no significant differences observed.

IVF/ICSI cycle characteristics and pregnancy results

With first live birth as the primary study endpoint, comparable numbers of ovarian stimulation cycles, oocyte retrieval procedures, and embryo transfer attempts were observed between the two cohorts. The groups demonstrated comparable live birth rates when analyzed per initiated stimulation cycle, per completed oocyte retrieval, and per embryo transfer procedure. Importantly, the cumulative live birth rate analysis revealed no significant difference in reproductive outcomes between the BOTs group and the control population (Table 4).

Table 4 Cycle characteristics and pregnancy results from 2010 to 2023 of IVF/ICSI treatment for bots and control groups till a live birth occur or all embryos were transferred

	BOTs ($N=61$)	Control ($N=181$)	T (χ^2)	*P*
Stimulation cycles	2.18 ± 0.208	2.18 ± 0.135	-0.013	0.989
Oocyte retrieval cycles	1.95 ± 0.177	1.70 ± 0.096	-1.283	0.201
Embryo transfer cycles	1.34 ± 0.155	1.25 ± 0.073	-0.585	0.559
CLBR	0.841 ± 0.131	0.789 ± 0.079	1.291	0.256
LBR per started stimulation (%)	18.0 (24/133)	22.8 (90/394)	1.350	0.245
LBR per oocyte retrieval (%)	20.2 (24/119)	29.2 (90/308)	3.594	0.058
LBR per embryo transfer (%)	29.3 (24/82)	39.6 (90/227)	2.787	0.095

Note: Continuous data are presented as mean standard error. Categorical data are presented as number (percentage)

Abbreviation: LBR, live birth rate; CLBR, cumulative live birth rate

Neonatal parameters

No statistically significant differences were observed in gestational age at delivery, neonatal birth weight, or body length between the BOTs group and control group, irrespective of singleton or twin gestation (Table 5).

Analysis of risk factors for tumor recurrence in patients after FSS

During follow-up, seven patients in the BOTs group declined to disclose their disease recurrence status post-IVF/ICSI. Recurrence was observed in five cases in the BOTs group (5/58, 8.62%) (Table 6).

Logistic regression analysis showed no significant association between tumor recurrence and factors including BOTs stage, pathological type, lesion site, surgical methods (unilateral cystectomy, bilateral cystectomy, unilateral oophorectomy with contralateral cystectomy,

Table 3 Ovarian stimulation characteristics in first cycles

	BOTs ($n=61$)	Control ($n=181$)	T (χ^2)	*P*
Duration of stimulation (day)	6.66 ± 0.499	6.75 ± 0.304	0.150	0.881
Total dose of injected gonadotropins (IU)	1281.35 ± 129.082	1207.76 ± 66.469	-0.538	0.591
Number of retrieved oocytes	6.31 ± 0.740	6.50 ± 0.534	0.183	0.855
Number of 2PN embryos	5.89 ± 0.719	6.06 ± 0.510	0.180	0.857
Number of transferable embryos	3.70 ± 0.534	3.99 ± 0.362	0.416	0.678
Number of good quality embryos	3.05 ± 0.429	3.27 ± 0.318	0.359	0.720
Percentage of 2PN embryos per oocyte retrieved (%)	52.650 ± 4.107	60.60 ± 2.587	1.599	0.111
Percentage of transferable embryos per oocyte retrieved (%)	44.111 ± 3.631	48.620 ± 2.563	0.939	0.349
Percentage of good quality embryos per oocyte retrieved (%)	33.787 ± 3.641	39.686 ± 2.624	1.317	0.190
Live birth rate of first started cycle (%)	17/61(27.869)	69/181(38.122)	2.094	0.148

Note: Continuous data are presented as mean standard error. Categorical data are presented as number (percentage)

Abbreviation: PN, pronuclear

Table 5 Neonatal outcomes

	Single birth				Twin birth			
	BOTs(*N* = 21)	Control(*N* = 75)	T(χ2)	*P*	BOTs(*N* = 5)	Control(*N* = 15)	T(χ2)	*P*
Gestational age at delivery (days)	265.7 ± 2.49	268.43 ± 1.57	0.850	0.397	254.2 ± 5.67	253.0 ± 2.27	-0.236	0.815
Birth weight (g)	3085.2 ± 130.57	2880.2 ± 75.78	-1.289	0.201	2434.0 ± 113.74	2261.7 ± 83.03	-1.087	0.284
Birth length (cm)	48.38 ± 0.48	48.27 ± 0.37	-0.155	0.877	46.7 ± 0.70	45.7 ± 0.52	-0.975	0.336

Table 6 Analysis of risk factors for recurrence in bots patients underwent FSS

	Recurrence (%)							*P*
FIGO stage	I		II		III			0.729
	9.6(5/52)		0(0/1)		0(0/5)			
Histology	Mucinous		Serous		Seromucinous			0.749
	5.6(1/18)		10.5(4/38)		0(0/2)			
Lesion site	Unilateral		Bilateral					0.175
	5.1(2/39)		15.8(3/19)					
Extent of ovarian surgery in FSS	Unilateral oophorocystectomy		Bilateral oophorocystectomy		Unilateral oophorectomy		Unilateral oophorectomy + contralateral oophorocystectomy	0.901
	7.7(1/13)		12.5(1/8)		5.3(1/19)		11.1(2/18)	
Interval from surgery to IVF (years)	≤ 1		>1,≤2		>2			0.982
	8.0(2/25)		10.0(1/10)		8.7(2/23)			
Number of stimulation cycles	1	2	3	4	5	6	7	0.239
	10.3(3/29)	0(0/11)	0(0/6)	0(0/5)	25.0(1/4)	0(0/1)	50(1/2)	
Peak E2 level in ovarian stimulation(pg/ml)	≤ 500	>500, ≤1000	>1000, ≤1500	>1500, ≤2000	>2000, ≤2500	>2500		0.578
	13.6(3/22)	7.1(1/14)	0(0/6)	0(0/3)	25.0(1/4)	0(0/9)		

Note: Categorical data are presented as number (percentage)

Abbreviation: FSS, fertility sparing surgery; FIGO, International Federation of Gynecology and Obstetrics

unilateral oophorectomy), the interval from surgery to IVF, the number of stimulation cycles and the highest estradiol level during ovarian stimulation (Table 6).

Discussion

To our knowledge, this study is the largest to date evaluating fertility outcomes following IVF/ICSI in women with BOTs after FSS. It is also the first cohort study focused specifically on this patient population. Our results indicate that IVF and pregnancy outcomes in BOTs patients are comparable to those in non-BOTs patients.

Some researchers have suggested that mild ovarian stimulation protocols should be the primary approach during controlled ovarian stimulation for BOTs patients following FSS [20], as these protocols may theoretically reduce the risk of malignant transformation or the proliferation of residual tumor cells by limiting estrogen elevations beyond physiological norms [17, 21]. However, in our study, we did not find significant associations between the type of stimulation protocol, the number of stimulation cycles, or estrogen levels and tumor recurrence. It should be noted that, due to the retrospective design and limited sample size of our study, the recurrence risk may be underestimated, and these results should be interpreted with caution. Moreover, although mild stimulation protocols might theoretically reduce estrogen exposure, they are associated with a lower number of retrieved oocytes, which could decrease cumulative pregnancy rates [22]. For instance, in a case series by Song et al. [6], which included 17 BOTs patients over 29 stimulation cycles, 51.7% (15/29) of the cycles employed mild stimulation protocols; however, some patients still failed to obtain transferable embryos after two mild stimulation cycles. Based on the current evidence, the applicability of mild stimulation protocols for BOTs patients requires further investigation. Considering both reproductive benefits and potential oncologic safety, the choice of stimulation protocol should be individualized rather than based on a one-size-fits-all recommendation. Future large-scale prospective studies are needed to further evaluate the long-term impact of different ovarian stimulation strategies on recurrence risk and reproductive outcomes in BOTs patients.

Regarding the impact of IVF/ICSI on BOTs recurrence, particularly the potential increase in recurrence due to elevated estrogen levels, there is currently no consensus. Residual tumor cells or lesions may persist in the remaining ovary after FSS [17], and overexpression of estrogen receptors is a common characteristic of ovarian tumors. Theoretically, the elevated estrogen levels induced by ovarian stimulation could have an adverse effect on BOTs. Basille et al. [23] evaluated the response of BOTs

cells to follicle-stimulating hormone and estradiol in vitro. Although primary cultured cells expressed FSH and estradiol receptors, neither FSH nor estradiol treatment induced proliferation in primary cultures of serous BOTs cells, suggesting that FSH and estradiol may be used in treating infertility in BOTs patients after surgery.

In a multicenter retrospective study from France, 30 patients with non-invasive implant BOTs underwent ART after surgery. Of these, three patients used clomiphene for ovarian stimulation, while 27 patients underwent IVF and embryo transfer. The median time from surgery to ART was 36 months (1–160 months), and the median follow-up after ART was 42 months (12–156 months). The tumor recurrence rate was 16% (4/25), and the clinical pregnancy rate was 40%. Notably, three recurrences occurred in patients who had undergone cystectomy, suggesting that recurrence may be more closely associated with cystectomy than with ART, indicating that ART is feasible for BOTs patients with infertility after surgery [24]. A meta-analysis by Darai et al. [5] of 22 studies involving 126 BOTs patients showed a cumulative pregnancy rate of 80% (95% CI = 68–92%, I2 = 57%) and a recurrence rate of 23% (95% CI = 6–39%, I2 = 85%) following IVF-ET. Song et al. [25]. collected data from 17 BOTs patients with postoperative infertility, reporting a pregnancy rate of 58.8% (10/17) and a recurrence rate of 23.5% (4/23) after a median follow-up of 29 months post IVF-ET.

Our study demonstrated a tumor recurrence rate of 8.62% in BOTs patients following IVF/ICSI, with no statistically significant associations observed between recurrence and either estrogen levels or the number of ovarian stimulation cycles. However, these findings must be interpreted with caution. Given the retrospective design and limited sample size, the recurrence risk may be underestimated, and potential risks related to the hormonal responsiveness of residual BOTs cells cannot be entirely excluded. Although our recurrence rate is lower than that reported in some previous studies, further prospective studies with larger cohorts are necessary to confirm these findings and to more comprehensively assess the safety of controlled ovarian stimulation in this patient population.

A key strength of this study is its large sample size, which includes 65 BOTs patients and is the largest cohort to date assessing fertility outcomes following IVF/ICSI in this population. Furthermore, the matched cohort design allows for a more robust comparison of outcomes between BOTs patients and controls. However, this study is retrospective in nature, which limits its ability to establish causality.

Conclusion

This study represents the largest cohort to date investigating fertility outcomes in patients with BOTs undergoing IVF/ICSI following FSS. Our study demonstrates that IVF/ICSI following FSS for borderline ovarian tumors yields reproductive outcomes comparable to those observed in non-BOTs patients, with a tumor recurrence rate of 8.62%. These findings suggest that IVF/ICSI treatment can be considered a viable option and controlled ovarian stimulation does not significantly increase the risk of tumor recurrence in this population. However, given the retrospective design and limited sample size, these results should be interpreted with caution. Further prospective studies with larger cohorts are warranted to validate the long-term safety and efficacy of IVF/ICSI in BOTs patients and to optimize individualized ovarian stimulation strategies.

Abbreviations

BOTs	Borderline ovarian tumors
FSS	Fertility sparing surgery
IVF	In vitro fertilization
ICSI	Intracytoplasmic sperm injection

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Not applicable.

Author contributions

YL, WZH and PCH contributed equally to the study design, data collection, and manuscript preparation. WZ and YX conducted the statistical analysis and contributed to data interpretation.JP supervised the clinical study, provided critical revision, and ensured the ethical conduct of the research. JL provided oversight for the research project, contributed to the literature review, and assisted in manuscript drafting. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The retrospective study was approved by Sun Yat-sen University Sixth Hospital Medical Science Research Ethics Committee (2024ZSLYEC-397) and was conducted in accordance with the Declaration of Helsinki. All participants in the study provided written informed consent prior to their inclusion in the research.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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