Outcomes of Controlled Ovarian Hyperstimulation/In Vitro Fertilization for Infertile Patients with Borderline Ovarian Tumor after Conservative Treatment

To evaluate the outcomes of controlled ovarian hyperstimulation (COH)-in vitro fertilization (IVF) such as clinical pregnancy rate (CPR), implantation rate (IR) and live birth rate (LBR) for infertile patients with borderline ovarian tumor (BOT) after conservative treatment, 10 IVF cycles in five patients from January 1999 to July 2005 were analyzed. At the time of diagnosis with BOT, the mean age of patients was 30.0 yr (range, 22-40). For 8 cycles out of 10 attempted IVF cycles, except for 2 cancellation cycles, the mean number of oocytes retrieved was 5.6 (range, 2-16) with a mean fertilization rate of 74.4%. The CPR, IR, and LBR were 50.0% (4/8 cycles), 31.6% (6/19) and 50.0% (4/8 cycles) respectively. The mean follow-up period after COH-IVF initiation was 29.6 (range, 14-61) months. A gynecological oncologist followed all patients every 3 months during the first year and every 6 months thereafter. There was no recurrence during the follow-up period. Our results suggest that COH-IVF may be acceptable for infertile patients with BOT, especially in patients with early-stage BOT after conservative treatment.

Key Words : *In Vitro Fertilization; Borderline Ovarian Tumor; Conservative Treatment*

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INTRODUCTION

Ovarian tumors of borderline malignancy, borderline ovarian tumors (BOT), constitute about 10-15% of all epithelial ovarian malignancies (1). Radical surgery remains the standard treatment for BOT. However, conservative treatment might be considered in patients who want to preserve their fertility because of the excellent prognosis reported (2, 3). Although spontaneous conceptions have been reported after conservative surgery, some of these patients suffer from infertility and require infertility treatment. Some BOT infertile patients undergo assisted reproductive technologies (ART) to improve their chances of pregnancy.

The influence of infertility treatment on the development of ovarian malignancies is a controversial topic. In a case-control study, it has been reported that a history of infertility increases the overall risk of ovarian cancer (4). In addition, there are reports suggesting an association between fertility medication and BOT. However, the association between fertility medication and invasive ovarian cancer is not conclusive (5-7). It was suggested that high serum estradiol levels during ovarian hyperstimulation might promote tumor growth in BOT, especially in estrogen receptor expression-positive cases (8, 9). Therefore, the potential risk associated

with infertility and treatment must be considered for infertile patients after conservative treatment for BOT.

In early-stage BOT, it has been possible to consider ART after conservative treatment since a multicenter study that reported 16 BOT patients who had undergone in vitro fertilization (IVF) after conservative treatment (10). Fasouliotis et al. reported that the overall success rates of IVF were satisfactory for this group of patients, suggesting no known negative impact of prior BOT on pregnancy rates after IVF (11). However, for advanced-stage BOT the published reports are limited to case reports (12-14). Therefore, for patients with advanced BOT the safety of ART after conservative treatment remains anecdotal.

The purpose of this study was to evaluate the outcomes of COH-IVF in infertile patients after conservative treatment for BOT.

MATERIALS AND METHODS

Patients

A retrospective review of IVF records from January 1999 to July 2005 revealed 10 attempted IVF cycles in five patients
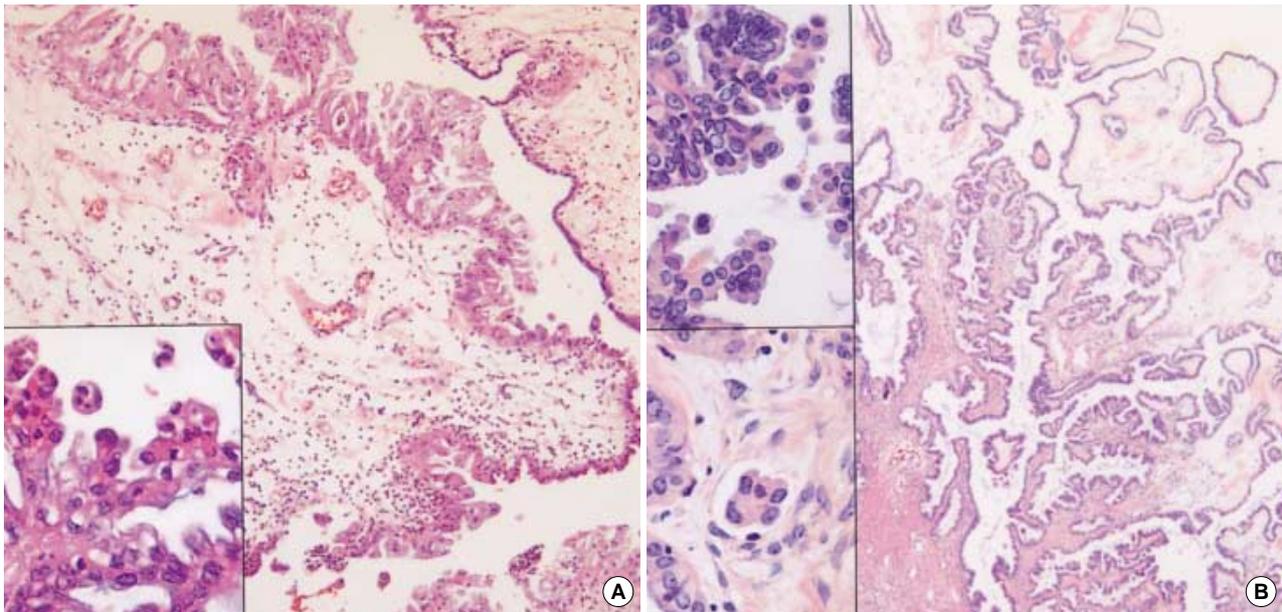
Fig. 1. (A) Mucinous borderline tumor, endocervix-like type. It is composed of broad papillae covered with proliferating mucinous eithelium. Proliferating tumor cells show tufting with mild to moderate cytologic atypia and neutrophils in their cytoplasm (inset). (B) Serous borderline tumor. This tumor is composed of numerous papillae that are covered with serous epithelium showing proliferation with tufting and cytologic atypia (left upper). This case reveals a few microinvasive foci (left lower) (H&E stain).

who had been previously diagnosed with BOT and had had conservative treatment to preserve fertility. BOT has the histological characteristics of ovarian tumors: 1) epithelial proliferation with the formation of a papillary configuration, 2) demonstration of atypical epithelial activity, 3) mild or moderate atypical nuclei, and 4) the absence of stromal invasion, which distinguishes it from invasive carcinoma (Fig. 1).

Conservative treatment is defined as preservation of the uterus and at least a portion of one ovary. In cases where the diagnosis of BOT was made intraoperatively, staging was made according to the International Federation of Gynecology and Obstetrics (FIGO) classification based on ipsilateral pelvic and paraaortic lymph node dissections, peritoneal cytology, omentectomy, and multiple peritoneal biopsies. After conservative surgery, a gynecological oncologist followed all patients every 3 months during the first year and thereafter every 6 months with a physical examination, serum CA-125 levels and transvaginal ultrasound. The main outcome measures were pregnancy outcomes such as clinical pregnancy rate (CPR), implantation rate (IR) and live birth rate (LBR) after COH-IVF, and the recurrence of BOT during the follow-up period. Approval from the institutional review board was not obtained because this study was a retrospective case observational study.

COH-IVF and embryo transfer

COH was performed with gonadotropin-releasing hormone agonist (GnRH-a) long protocol or flare-up protocol using human menopausal gonadotropin (Menogon®, Fer-

ring, Germany) or recombinant follicle-stimulating hormone (Puregon®, Organon, Netherland). For the long protocol, patients underwent pituitary desensitization with GnRH-a (Suprefact®, Hoechst, Germany) from the previous menstrual mid-luteal phase, and gonadotropins were administered after pituitary down regulation and continued up to hCG (Pregnyl®, Organon, Netherland) administration. For the flare-up protocol, GnRH-a was administered from the second day of the menstrual cycle and gonadotropins were administered from the third day of the menstrual cycle until hCG administration. Oocyte retrieval was performed via the transvaginal approach with sonographic guidance 36 hr after 10,000 IU of hCG administration. After oocyte retrieval, oocyte maturation was evaluated under an inverted microscope at $\times 400$. The oocytes were incubated in human tubal fluid (Irvine Scientific, Irvine, CA., U.S.A.) medium supplemented with 10% synthetic serum supplement (SSS; Irvine Scientific) at $37°C$, 5% CO_2 in air.

Embryos were transferred into the uterine cavity the third day after oocyte retrieval. Pregnancy was determined by serum β-hCG levels above 5 mIU/mL 12 days after the oocyte retrieval. Clinical pregnancy was defined as the presence of a gestational sac on transvaginal ultrasound.

RESULTS

Ten IVF cycles were performed in five infertile patients after conservative treatment for BOT. Two cycles out of 10 attempted IVF cycles were cancelled due to poor ovarian res-

ponse during COH.

Table 1 shows the demographics for the five patients and the surgical findings. At the time of diagnosis with BOT, the mean age of patients was 30.0 yr (range, 24-40), and four out of five patients were nulliparous. In three patients (Patient No. 2, 4, and 5) the diagnosis was made intraoperatively and staged as Ia, Ia, and IIIc, respectively. In the remaining two patients (Patients No. 1 and 3) the diagnosis was made postoperatively without complete surgical staging. The microscopic findings in three patients showed the mucinous type, and the remaining two patients had the serous type. Patient No. 5 had a few foci showing microinvasion (Fig. 1B).

Patient No. 2 underwent a right salpingoophorectomy; disease recurrence occurred in the remaining ovary 9 yr after the initial diagnosis and the recurrence showed a histology and stage identical to the primary disease. The patient was conservatively treated by cystectomy on the remaining ovary. Patient No. 5 had right-side pelvic and paraaortic lymph node dissections, peritoneal cytology, omentectomy, and mul-

tiple peritoneal biopsies; she was diagnosed with stage IIIc disease. For the stromal microinvasion, the patient was treated with six cycles of taxol and cisplatin-based chemotherapy.

At the time of the first IVF cycle the period of infertility after conservative treatment ranged from 17 to 45 months with a mean duration of 32.4 months. The indications for IVF included severe endometriosis, male factor and unexplained infertility. Table 2 shows ART and pregnancy outcomes. In patient No. 1, one cycle out of 2 attempted IVF cycles was cancelled due to poor ovarian response. Because pregnancy was not achieved with her own IVF cycles, oocyte donation (OD) was performed due to the decreased ovarian reserve. The patient was pregnant on the second OD cycle and delivered a healthy infant. Patient No. 3 had one cycle out of 4 attempted IVF cycles cancelled due to poor ovarian response. Patient No. 4 had two pregnancies and delivered twice; the first was after fresh embryo transfer and the second was after frozen-thawed embryo transfer.

In 10 attempted IVF cycles, two cycles were cancelled with a 20.0% cycle cancellation rate. For eight IVF cycles, except the cancelled cycles, the mean serum estradiol level on hCG administration was 1,032.6 pg/mL (range, 200-2,380 pg/mL). The mean number of retrieved oocytes was 5.6 (range, 2-16), and the mean fertilization rate was 74.4% (range, 50.0-100.0%). The mean number of transferred embryos was 2.4 (range, 1-4). The CPR, IR, and LBR were 50.0% (4/8 cycles), 31.6% (6/19), and 50.0% (4/8 cycles), respectively.

There was one case of disease recurrence after conservative treatment; this recurrence developed before IVF treatment. However, no recurrence was identified since the first IVF cycle (Table 3). The follow-up period from initial diagnosis to the first IVF cycle ranged from 5 to 127 months with a mean duration of 33.0 months. Since the first IVF cycle, the follow-up period ranged from 14 to 61 months with a mean duration of 29.6 months. Patient No.2 had disease recur-

Table 1. Clinical and pathological characteristics of BOT at diagnosis

Patient	Age (yr)	Parity	Dx.	Stage	Histology	Treatment
1	40	G1P1	Postop	-	Mucinous	Cystectomy
2	24	G0P0	Intraop	Ia	Papillary serous	RSO
	33	G0P0	Intraop	Ia	Papillary serous	Cystectomy
3	26	G0P0	Postop	-	Mucinous	LSO+WR
4	29	G0P0	Intraop	Ia	Mucinous	RSO*
5	31	G0P0	Intraop	IIIc	Papillary serous microinvasion	RSO+WR†

*, Combined with infracolic omentectomy and multiple biopsies; †, Combined with infracolic omentectomy, Rt. pelvic & para-aortic lymph node dissection and chemotherapy.
BOT, borderline ovarian tumor; RSO, Rt. Salpingo-oophorectomy; LSO, Lt. Salpingo-oophorectomy; WR, Wedge resection.

Table 2. ART and clinical pregnancy outcomes

Patient	Infertility duration (mo)	Indication	IVF cycle No.	Age (yr)	Basal FSH (mIU/mL)	E2 on hCG (pg/mL)	No. of retrieved oocytes	No.of mature oocytes	No. of transferred embryos	Clinical pregnancy
1	38	Endometriosis IV	1	41	12	936	4	2	2	Non
			2	41	20	260	OPU fail	-	-	Cancel
			3*	42					4	Non
			4*	43					3	Single
2	17	Unexplained	1	33	3.5	653	4	4	2	Non
			2	33	8.9	1,267	3	3	3	Single
3	18	Male factor	1	27	13	560	3	2	2	Non
			2	27	10	320	2	1	1	Non
			3	29	18	-	-	-	-	Cancel
			4	29	8.2	200	2	1	1	Single
4	45	Tubal factor	1	30	1.7	1,945	16	10	4	Single
			2†	32	-	-	-	-	2	Single
5	44	Unexplained	1	33	4.5	2,380	11	7	4	Twin

*Oocyte donation cycles; †Frozen thawed embryo transfer. ART, assisted reproductive technologies; IVF, in vitro fertilization.

Table 3. Recurrence of BOT after conservative treatment

Patient	Time from surgery to 1st IVF (mo)	IVF cycles	Follow-up periods from 1st IVF (mo)	Recurrence
1	7	2	27	No
2	108*	-	-	Yes
	19†	2	15	No
3	5	4	61	No
4	5	2	31	No
5	21	1	14	No

*Elapsed time from initial BOT to recurrence; †Elapsed time from recurrence to the 1st IVF cycle.
BOT, borderline ovarian tumor; IVF, in vitro fertilization.

rence 108 months after the initial diagnosis and 19 months elapsed from the recurrence to the first IVF cycle. Patient No.5 with stage IIIc disease had no recurrence identified by exploration during cesarean section and continues to be followed up by a gynecological oncologist.

DISCUSSION

Since the prognosis for BOT is excellent, patients of childbearing age can be treated with conservative surgery to preserve fertility (2, 3). Unilateral adnexectomy is the optimal treatment in patients whose diagnosis of BOT was made intraoperatively; cystectomy can be considered in cases of recurrence in the remaining ovary. Some patients are infertile after conservative treatment and request ART in spite of the potential risk associated with infertility treatment. A history of infertility and the prior use of fertility medications have been associated with the development of ovarian tumors. Recent case control studies showed that infertility per se elevates the overall risk of ovarian cancer (5). Rossing et al. reported an increased risk of ovarian tumors, both invasive and borderline, after the prolonged use (>12 cycles) of clomiphene citrate (15). Shushan et al. reported increased incidence of epithelial ovarian tumors in patients with previous human menopausal gonadotropin (hMG) treatment compared to healthy controls (6).

However, the risk from ovarian hyperstimulation in patients treated for early stage BOT is low. Madelenat et al. reported five pregnancies in 16 patients who subsequently underwent IVF after conservative treatment for BOT and found no case of relapse during the follow-up period, 46 months on average (10). Beiner et al. suggested that ART might be considered after the diagnosis of BOT. Recurrence occurred in 4 patients out of 7 who underwent IVF, two patients before and two patients after IVF treatment. All of the recurrences had histology identical to the initial diagnosis, borderline malignancy (16). Fasouliotis et al. reported 17 IVF cycles in five patients after conservative BOT treatment. A mean of 7.9 oocytes were retrieved with a 57.1%

fertilization rate, and a mean of 3.1 embryos were transferred. The pregnancy rate per embryo transfer was 42.9% (17). To date, there is no evidence in the literature to restrict the use of ART in patients with early stage BOT after conservative treatment. In our present study, the CPR and LBR for 7 IVF cycles in patients with early stage BOT was 42.9% (3/7 cycles) and 42.9% (3/7 cycle), respectively. The achieved pregnancy outcomes suggest that prior BOT, diagnosis and treatment, have no perceptible negative impact on pregnancy outcomes in COH-IVF. Therefore, COH-IVF can be safely offered to the patients with early stage BOT.

However, there are few reports on the safety of COH-IVF in cases of advanced stage BOT after conservative treatment. Seidman and Kurman suggested that the existence of invasion in a peritoneal implant is a poor prognostic factor in patients with BOT with peritoneal implants; 16% had recurrence with a noninvasive implant, whereas 64% had recurrence with an invasive implant (18). Considering the poor prognosis of BOT with invasive peritoneal implants, it seems logical to propose conservative treatment only in patients with BOT who do not have invasive implants. At present there is no evidence that pregnancy affects the course of BOT. However, it is not yet possible to provide guidelines for COH-IVF in patients with advanced stage BOT despite successful pregnancy outcomes (11-13, 19). In our study one patient with stage IIIc disease, without invasive peritoneal implant, had conservative treatment and underwent COH-IVF subsequently that resulted in a successful pregnancy and delivery. There is no evidence of recurrence during the follow-up period. It seems that the number of COH-IVF cycles should be limited in patients with advanced stage BOT because rapid progression to invasive ovarian cancer, after a successful delivery with the first IVF cycle has been reported (20). Although the pathogenic mechanisms for tumor progression remain unknown, it may be related to hormonal influences (9). Estrogen receptor expression was recently demonstrated in BOT, and high serum E2 levels during COH-IVF may have a role in tumor promotion (10).

After conservative treatment of BOT the recurrence rate is estimated to be 0-20% (21). All recurrences can be detected with close follow-up. There is no significant difference in survival rates between conservative and radical treatment (22, 23). Beiner et al. reported a 29% recurrence rate in an IVF treatment group that was not significantly different from the 19% recurrence in the non-IVF group (16). Fasouliotis et al. reported a 20% recurrence rate after IVF treatment. All recurrences had a histology identical to the primary diagnosis; they were conservatively treated without evidence of recurrence at the last follow-up (11). In our study, no recurrence of BOT was detected after COH-IVF; this is a lower recurrence rate than reported in patients who underwent conservative treatment without subsequent fertility treatment. Although the perod of 29.6 (14-61) months is not a long follow-up period, our results suggest that COH-IVF may

not affect recurrence of BOT, and that pregnancy per se has no effect on the course of BOT.

In conclusion, the current study suggests that IVF may be considered for infertile patients after conservative treatment for early stage BOT. For patients with advanced stage BOT, larger clinical trials with longer follow-up are necessary to evaluate the safety and efficacy of COH-IVF. All patients should be informed of the potential risks associated with ovarian hyperstimulation, and close follow-up is necessary after COH-IVF.

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