

Successful pregnancy achieved by in vitro fertilization after fertility-preserving treatments in an infertile woman with borderline ovarian tumor and endometrial complex atypical hyperplasia: a case report

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Summary

Both borderline ovarian tumors (BOTs) and complex atypical hyperplasia (CAH) are low malignant disease of the female reproductive system, which can be treated with fertility-preserving treatments for women of reproductive age. Assisted reproductive technology (ART) is used to achieve pregnancy in infertile women. Although treatments for the isolated disease have some guidelines, protocol making is not that simple when abnormalities coexist. Here, a case of patient with BOT, a history of CAH, and infertility is presented. After fertility-preserving surgery and in-vitro fertilization and embryo transfer (IVF-ET), the patient successfully achieved a twin pregnancy leading to term live birth. The treatment process towards the complex situation is available for future reference. *Consent:* We present the first case with abnormalities co-existence and the process of combined treatment is effective and available for future reference.

Key words: Borderline ovarian tumors; Complex atypical hyperplasia; Laparoscopy; Assisted reproductive technology.

Introduction

Accounting for 10-15% of epithelial ovarian tumors, borderline ovarian tumors (BOTs) are also termed as low malignant potential tumors. To this regard, since BOTs are more likely to affect younger women, and conservative surgery has become the recommended management for women who wish to retain their fertility [1]. Fertility-preserving surgery has proved to be effective and safe because the reported postoperative spontaneous pregnancies rate can reach 54%, while the lethal recurrence maintains less than 0.5% [2].

Since endometrial complex atypical hyperplasia (CAH) is a precursor to invasive disease with high risk of progression compared with simple hyperplasia, hysterectomy is regarded as the best treatment. However, for those fertile women with pregnancy demands, high-dose progestin therapy to allow for future fertility may be most appropriate as prior studies have documented high regression rates [3].

It was reported that 10-35% women with BOTs present a previous history of infertility [2], for whom assisted reproductive technology (ART), a technology that has been confirmed to result in a significantly higher live birth rate than spontaneous pregnancy in people with CAH [4], can be an option. However, it is still unclear whether the function of the ovary or endometrium in those patients will influence

the success rate of ART, and whether it will place those patients at the risk of disease recurrence.

Here the authors present a case of a successful application of in-vitro fertilization (IVF) in an infertile patient with BOT and a history of CAH, which caused problems when deciding on the treatment strategy in light of the rare concurrence of abnormalities in both the ovary and endometrium. After fertility-preserving surgery, a successful of pregnancy was achieved by IVF and the patient finally took home twin babies.

Case Report

A 30-year-old woman presented to this fertility Center for IVF with a history of five-year primary infertility. However, during the ovulation monitoring, transvaginal ultrasound assessment showed a left ovarian cyst measuring 30 mm in diameter, and the serum CA125 was measured at 95 U/ml. The IVF protocol was suspended and the patient was referred to the gynecology clinic for further diagnosis. During the four-month follow-up, the serum CA125 level did not increase but the mass did. In light of ovarian tumor being strongly suspected and the patient's demand for children, she was hospitalized for conservative surgery.

The woman had a history of endometrial CAH diagnosed five years prior in the local hospital. During the time when she successively received high-dose oral progestin and gonadotropin-releasing hormone agonist (GnRH-a) for fertility-sparing, serial

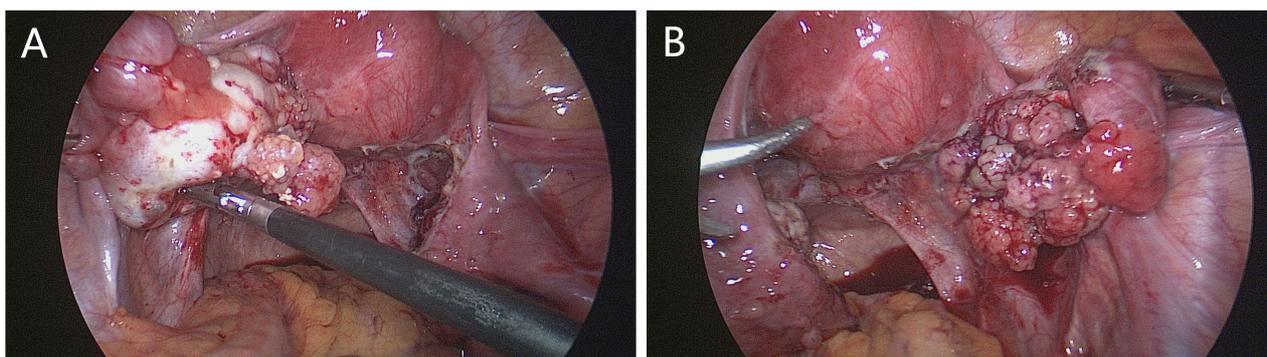


Figure 1. — Laparoscopic view of cauliflower-like neoplasms on the external surface of bilateral ovaries. A: Left ovary. B: Right ovary.

hysteroscopy with biopsies showed the persistence of endometrial complex hyperplasia for three years but a significant regression a year ago. She also presented with a history of two repeat IVF failures with a negative screening protocol for recurrent miscarriage, including hydrotubation, cytogenetic analyses of both partners, maternal thyroid stimulating hormone and thyroxine, homocysteine, antiphospholipid antibodies, and lupus anticoagulant (LA). She has regular menstrual cycles and there was nothing remarkable in her family history.

The gynecological examination revealed a painless left-sided adnexal mass on palpation. The preoperative examination confirmed the presence of the cystic mass located on the left adnexal area with no signal of blood flow by transvaginal ultrasound, the diameter of which had reached 33 mm, while the serum CA125 level was 107.6 U/ml.

Two days after admission, laparoscopic surgery was performed after obtaining the informed consent of the patient and her family. Intraoperatively, after separating the adhesion between the adnexa and nearby organs including rectum, posterior uterine, and pelvic wall, the left ovary was found enlarged to 5 cm in diameter with cystic component and multiple cauliflower-like neoplasms could be found on the external surface of bilateral ovaries while bilateral fallopian tubes appeared normal (Figure 1). Finally, laparoscopic bilateral ovarian cystectomy, omentectomy, and adhesiolysis were performed under general anesthesia. A Stage Ic serous borderline BOT (according to the FIGO staging classification) was diagnosed by both the intraoperative pathological examination and the final pathological assessment. In consideration of the history of endometrial CAH, hysteroscopy plus fractional dilatation and curettage (D&G), and hydrotubation were performed simultaneously with the laparoscopy. The postoperative pathological analysis showed the proliferative stage of the endometrium and focal irregular hyperplasia with sporadic superficial squamous epithelium. Fourteen days after the operation, the serum CA125 levels decreased to 11.18 U/ml. Because of the recurrence risk and the patient's strong desire to procreate, rapid achievement of pregnancy was required.

Four months after the operation, through two cycles of unsuccessful efforts to conceive naturally, the patient was referred to the present Fertility Center again for IVF. Initial evaluation on cycle day 2 revealed five antral follicles in right ovary and one in left with normal hormonal levels: estradiol (E2) 20 pg/ml, follicle stimulating hormone (FSH) 8.95U/L, and luteinizing hormone (LH) 4.88U/L. The antagonist protocol was used for controlled ovarian hyperstimulation (COH) which was conducted from day 2 to 10 using recombinant-FSH (rFSH) and hMG with 2,700 U in total. GnRH antagonist (GnRH-ant) was administered from day 7 to 10, during which letrozole was administered at 5 mg daily additionally. Follicular growth was monitored by transvag-

inal ultrasonography and serum E2 levels. In the presence of two leading follicles with a mean diameter of 19 mm and 11 follicles of at least 10 mm, while serum E2 level was 1,142 pg/ml, oocyte maturation was triggered by administering 6,500U of recombinant hCG (rhCG) on day 10. Transvaginal retrieval of oocytes was performed 36 hours later and a total of five oocytes was picked up. After a conventional IVF protocol, two embryos (8/ II) were transferred on day 3 while two embryos were cryopreserved. In view of the history of 'unexplained' repeat IVF failure, the women received low dose aspirin 80 mg daily and subcutaneous heparin 5,000 IU daily empirically, as well as progesterone sustained-release vaginal gel 90 mg daily and oral dydrogesterone 20 mg daily for luteal support, beginning from the day of embryo transfer (ET) and continuing until ten weeks of gestation.

At four weeks from ET, a twin pregnancy was detected with ultrasound. After an uneventful course of pregnancy with no evidence of recurrence, a cesarean section was performed at 37 weeks and 1 day of gestation. The woman delivered a male child weighing 2,320 grams and a female child weighing 1,570 grams, both of whom showed no specific abnormalities.

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from the participant included in the study.

Discussion

As a distinct diagnostic category of epithelial ovarian tumors with low indolent behavior, over 80% of BOTs are diagnosed as Stage I (FIGO staging classification), indicating longer patient survival and later recurrence [5, 6]. Although BOTs may develop at any age, the highest frequency occurs in 15-29 year-old women of reproductive age, for whom fertility-preserving surgery has been widely performed. As to the specific surgical approach, consensus has been reached that minimally invasive surgery like laparoscopy is both safe and effective for BOTs [7], and unilateral salpingo-oophorectomy (USO) was recommended in the case of mucinous BOT, while bilateral cystectomy (BC) seemed more beneficial to bilateral BOT which is always serous [1].

ART, especially IVF-ET, is suggested for those women with primary infertility or BOT-associated infertility caused by conservative surgery, but the application of it is still controversial. On the one hand, supporting data on successful application of IVF-ET in women with BOTs undergoing conservative treatments indicated that the ovarian function of those women may not influence the success rate, which confirmed the feasibility and efficacy of IVF-ET. On the other hand, although IVF-ET seemed to have no significant associations with ovarian cancer in infertile women [8], in a whole-population cohort study of 21,639 women, Stewart *et al.* [9] found that infertile women undergoing IVF-ET had an increased rate of BOTs (HR 2.46; 95% CI 1.20-5.04). Their finding cannot be explained by infertility since infertility itself had not yet been confirmed to be associated with BOTs [10]. As to patients with BOTs, cell experiment toward the effects of fertility drugs showed that there was no stimulatory effect of FSH or E2 on cultured BOT cells [11], while clinical studies had opposite findings. Prior review by Darai *et al.* [2] found that the recurrence rate after IVF was approximately 23%, higher than the overall recurrence rate following conservative surgery for BOTs, which was only 13%. In conclusion, because of the lack of high-quality data and existing conflicting reports, it is still inconclusive whether IVF-ET can be safely offered to infertile women with BOTs. In the present case, the patient was diagnosed with serous BOT with micro-papillary patterns that was regarded as a high-risk pathological pattern with a significantly high recurrence rate of 24.4% [12], which cause problems when deciding on the treatment strategy. However, according to prior studies that isolated ovarian recurrences can be cured by secondary surgery which was both well-tolerated and effective [13]. The present authors finally chose the laparoscopic fertility-preserving surgery BC as recommended, and IVF-ET for subsequent pregnancy by taking the patient's fertility desire into consideration. The cycle of ovulation-promoting was begun four months after the surgery since the recommended time to try to conceive was three to six months [13]. In order to minimize the effect of COH on ovaries after ovarian cystectomy, with advantages of shorter duration of analog treatment and lower risk of developing ovarian hyperstimulation syndrome (OHSS) [14], GnRH-ant protocol was selected as the drug protocol for ovulation induction.

Endometrial hyperplasias are classified as complex and atypical based on the presence of architectural abnormalities with cytologic atypia. Although prior studies had shown a markedly high complete response rate of endometrial hyperplasia (65.8%) by progestin therapy [3], for fertile patients with CAH, characterized as precancerous condition, it is not that simple to make a decision to administer conservative treatments because of the reproducibility [3] and the inconsistency of diagnosis. It is

difficult to make an accurate diagnosis of CAH before hysterectomy because of the high risk of concurrent subclinical invasive malignancy [15]. In the present case, the patient had a history of CAH which was diagnosed by D&G, therefore the possibility of concurrent endometrial carcinoma cannot be ignored. The patient is thus at relatively high risk of recurrence and should be under regular follow-up despite achieving complete remission pre-admission.

The subsequent ART is regarded as feasible because the successful prior clinical applications prompted that the endometrial situation of patients with CAH that had reached disease regression makes no difference in the approach of IVF-ET [16, 17]. Since there is no evidence that the IVF-ET is associated with elevated endometrial cancer risk, let alone with CAH, which indicates that the IVF-ET is relatively safe. However, because of the estrogen dependency of hyperplasia, mild stimulation approach may be suitable for an acceptable recurrence rate. During the gonadotropin-stimulated cycle, letrozole, a kind of aromatase inhibitor, was administered additionally to limit the exposure to elevated E2 concentrations resulted from exogenous gonadotropin stimulation. As a result, the E2 level on the day of hCG administration was controlled to 1,142 pg/ml, and twin pregnancy was achieved in the first attempt without any disease recurrence.

In conclusion, for women with low malignant potential diseases of the ovary and/or endometrium who wish to preserve fertility, conservative treatments are allowed after thorough disease assessment by experienced gynecological oncologists. Subsequent pregnancy should be attempted in short-term and IVF-ET with mild stimulation protocol is recommended for patients with infertility. The risk of disease recurrence should not be ignored and long-term follow-up is necessary. If isolated recurrence is detected, secondary surgery is both well-tolerated and effective because of the low indolent behavior of those kinds of disease.

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