

## Case Report

# Low-Oestrogen IVF Protocol Leading to Successful Pregnancy in Recurrent Microinvasive Seromucinous Borderline Ovarian Tumour

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## ABSTRACT

A 32-year-old woman with recurrent microinvasive seromucinous borderline ovarian tumour (SMBOT) and low ovarian reserve presented for fertility preservation prior to definitive surgery. After multidisciplinary evaluation, she underwent right adnexectomy and left ovarian cystectomy, with pathology confirming microinvasive SMBOT and no extraovarian spread. Controlled ovarian stimulation using a progestin-primed ovarian stimulation (PPOS) protocol with letrozole minimised oestrogen exposure was done and resulted in eight retrieved oocytes and four blastocysts. Following an initial failed frozen embryo transfer (FET), a second stimulation cycle produced two additional blastocysts. Hysteroscopy identified chronic endometritis, which was treated before a natural-cycle frozen transfer of a single 4AA blastocyst, resulting in an ongoing singleton intrauterine pregnancy. This case demonstrates that thoughtfully planned, low-oestrogen stimulation and coordinated oncologic surveillance may allow safe fertility preservation in selected patients with recurrent microinvasive SMBOT.

**Keywords:** Borderline ovarian tumour, Fertility preservation, Letrozole-based stimulation, Progestin-primed ovarian stimulation, Seromucinous tumour

## INTRODUCTION

Borderline ovarian tumours (BOTs) account for 10-20% of epithelial ovarian neoplasms and typically affect women in the reproductive age group.<sup>[1]</sup> Among these, seromucinous BOTs (SMBOTs) are rare, accounting for <5% of cases.<sup>[2]</sup> Although their prognosis is generally favourable, SMBOTs with microinvasion and recurrence present a greater risk profile, with malignant transformation to seromucinous or low-grade serous carcinoma reported in 2-4% of cases.<sup>[3]</sup> Management becomes complex in cases with bilaterality, microinvasion, or recurrence, where oncologic safety must be balanced against reproductive goals. Published evidence on reproductive outcomes in recurrent microinvasive SMBOT is limited, especially regarding controlled ovarian stimulation strategies intended to minimise oestrogen exposure. We report a young woman with recurrent microinvasive SMBOT who achieved a successful pregnancy following fertility-preserving surgery and *in-vitro* fertilisation using a tailored low-oestrogen stimulation strategy.

## CASE REPORT

A 32-year-old woman, married for 3 years and attempting conception for 1 year, presented for oncofertility consultation following recurrence of a BOT.

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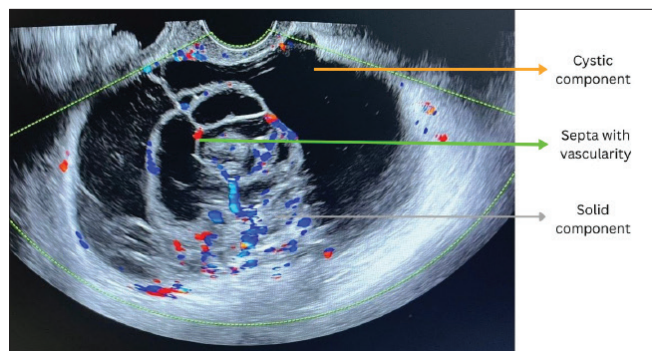
### Initial presentation and first surgery

At age 30, she was diagnosed with an  $11.2 \times 7.6 \times 8$  cm right ovarian complex cyst and a  $2.2 \times 1.2$  cm left endometriotic cyst. Laparoscopic right ovarian cystectomy revealed a SMBOT with microinvasion; peritoneal fluid cytology showed atypical cells. She was under periodic ultrasound follow-up.

### Recurrence and second surgery

Fifteen months later, MRI demonstrated a left ovarian complex cyst measuring  $9.5 \times 10.8 \times 15.2$  cm. Left cystectomy was performed, and histopathology revealed a microinvasive borderline seromucinous tumour with abnormal p53 expression (90%) and papillary projections with ER<sup>+</sup> status.

Within just a span of 3 months, she had a recurrence on the same side. She was referred to our unit for fertility preservation prior to a definitive surgery. She was found to have an  $11.3 \times 7.4 \times 7.4$  cm left ovarian complex cyst with two residual follicles [Figure 1]. The right ovary was not visualised. AMH was 0.6 ng/mL.



**Figure 1:** Left ovarian heteroechoic cystic solid mass with septations and vascularity. Cystic component (orange arrow), septa with vascularity (green arrow), solid component (grey arrow).

### Multidisciplinary discussion and surgical plan

A tumour board including reproductive medicine, gynaecologic oncology, and oncopathology specialists reviewed the case. Given recurrence and microinvasion, staging surgery (bilateral salpingo-oophorectomy with uterine preservation and omentectomy) was advised. However, the couple was keen to use autologous oocytes despite poor ovarian reserve. A two-step plan was agreed upon:

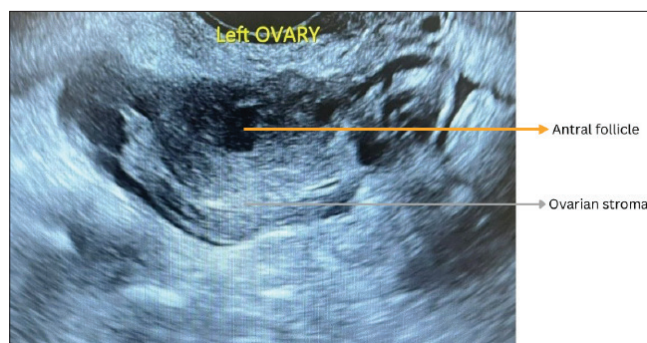
1. Left cystectomy to enable follicular access and disease control.
2. Controlled ovarian stimulation and oocyte retrieval for fertility preservation prior to eventual completion of staging surgery.

The patient underwent right adnexectomy involving right salpingectomy, left cystectomy, infra-colic omentectomy, and peritoneal biopsies. The right ovary was absent. Histopathology

confirmed borderline seromucinous tumour with microinvasion; all peritoneal and omental biopsies and endometrial curetting were negative for malignancy.

### Controlled ovarian stimulation and embryo development

Post-surgery, she presented on cycle day 2 with six antral follicles in the left ovary [Figure 2]. Controlled ovarian stimulation (PPOS) protocol with a progestin-primed ovarian stimulation (PPOS) protocol using a total daily gonadotropin dosage of 300 IU comprising (rFSH)225 IU (Gonal-f, Merck) and (HMG)75 IU (Menopur, Ferring Pharmaceuticals) + Medroxyprogesterone acetate 10 mg/day. Letrozole 5 mg/day (Letroval, Sun pharma) was given throughout stimulation to limit oestradiol elevation. The cumulative gonadotropin dosage was 2100 IU of rFSH and 900 IU of HMG.



**Figure 2:** Post left ovarian cystectomy showing residual ovarian tissue with 6 antral follicles. Antral follicle (orange arrow), ovarian stroma (grey arrow).

After 10 days of stimulation, agonist trigger (Inj Leupride 2 mg s/c) was given, and eight oocytes were retrieved. Five were mature, and four blastocysts were obtained (2-4AA,1-4BB,1-4BC).

### First frozen embryo transfer (FET)

A mild stimulation FET cycle was started using tamoxifen 40 mg/day for 5 days. On day 10 of the cycle, a dominant follicle of 18 mm was noted on the left ovary with endometrial thickness (ET) of 8.5 mm, triple line pattern, and optimal blood flows. Trigger was given with recombinant human chorionic gonadotropin (rHCG), and luteal priming was initiated 36 h later with micronised vaginal progesterone 400 mg (C.Susten) twice daily. 1-4 AA blastocyst was transferred, but did not yield a pregnancy.

### Second IVF cycle (Pooling)

A second cycle of embryo pooling was planned in view of the high risk of recurrence of disease, with the aim of having supernumerary embryos. Controlled ovarian stimulation (COS) with PPOS protocol was initiated from day 2 of the cycle along with letrozole 5 mg (Letroval, Sun Pharma). The total daily dosage

was 300 IU. Total cumulative dosage across 9 days of stimulation was 900 IU of r-FSH (Inj Gonal-f, Merck) + 1800 IU of HMG (Inj Menopur, Ferring). Four oocytes were retrieved, and two blastocysts were formed (4AB,3BB).

### Endometrial evaluation

Hysteroscopy was done, which revealed focal hyperaemia; MUM-1 (Multiple myeloma oncogene -1) immunostaining identified 11 plasma cells/high power field, consistent with chronic endometritis, based on a diagnostic threshold of  $\geq 5$  plasma cells. She received an extended course of broad-spectrum antibiotics with Doxycycline 100 mg + Metronidazole 400 mg twice daily for 2 weeks, followed by oral probiotics.

### Second FET and pregnancy outcome

A natural cycle FET was chosen to minimise hormonal exposure. A 19 mm follicle with 9.5 mm trilaminar endometrium with good Doppler parameters was noted on day 15. A single 4AA blastocyst was transferred on day 20 [Figure 3]. Serum Beta hCG (human chorionic gonadotropin) on day 14 post-transfer was 3089 mIU/mL. A transvaginal ultrasound at 7 weeks confirmed a single live intrauterine pregnancy. Pregnancy is ongoing with regular oncologic surveillance [Figure 4].



**Figure 3:** One 4 AA grade blastocyst that was transferred. Inner cell mass (orange arrow), trophoctoderm (black arrow).



**Figure 4:** Ongoing pregnancy of 13 weeks of gestation.

## DISCUSSION

SMBOTs with microinvasion are uncommon, and published reports describing fertility-preserving approaches in recurrent disease are limited. In most previous reports, fertility preservation was performed either after primary excision or in non-recurrent disease, whereas our case involved recurrence within a short interval and persistent microinvasion, making the reproductive decision-making more complex.

Similar to studies by Babaier *et al.*<sup>[3]</sup> and Della Corte *et al.*,<sup>[4]</sup> recurrence risk in this case was associated with microinvasion and incomplete staging. Similar to the case reported by Choi *et al.*<sup>[5]</sup>, where oocyte vitrification before bilateral surgery for BOT led to a live birth via IVF/ICSI, our case confirms that assisted reproduction can yield favourable outcomes after fertility-sparing management. Li *et al.*<sup>[6]</sup> reported live births in 8/17 women undergoing IVF after fertility sparing surgery for BOT, with a recurrence rate around 24%, supporting the feasibility of ART in this setting.

However, most published cases involve serous BOT and conventional antagonist protocols; our case is distinct in involving recurrent microinvasive seromucinous BOT and the use of letrozole-supplemented PPOS to limit estradiol exposure. Few publications describe this approach in recurrent microinvasive SMBOT, and successful pregnancy outcomes after such low-estrogen stimulation remain rare. This case describes the feasibility of fertility preservation in select situations, provided there is multidisciplinary planning and meticulous oncologic monitoring.

### Oncologic consideration

Seromucinous BOTs are a distinct subtype combining serous and endocervical-type mucinous epithelium, representing <5% of all BOTs.<sup>[2]</sup> They are frequently associated with endometriosis (30-70%)<sup>[7]</sup> and show ER/PR positivity in most cases, indicating possible hormonal responsiveness. They present in the early stage and have 10-year survival rates of >90% and 1-3% risk of malignant transformation. However, late recurrence can occur up to 10 years post-treatment.<sup>[8]</sup> Recurrence risks rise with incomplete staging, bilaterality, and microinvasion.<sup>[4]</sup> Definitive management involves total hysterectomy with bilateral salpingo-oophorectomy and staging, which is curative in >95% of patients.<sup>[9]</sup> In young women desiring fertility, conservative management may be offered if there is complete cytoreduction and histologic confirmation of non-invasion.

### Differential diagnosis

Given the rapid recurrence and p53 overexpression, low-grade serous carcinoma, recurrent endometriotic cyst with atypia, and mucinous borderline tumour were considered. However,

histopathology confirmed SMBOT with microinvasion and no invasive implants.

### Fertility preservation with poor reserve

While natural fertility in women after conservative surgery can be favourable, recurrence risk and time constraints often justify assisted reproduction. Ovarian stimulation in BOT patients poses concern due to oestrogen sensitivity. However, studies show no significant increase in recurrence with ART when stimulation is carefully controlled.<sup>[10]</sup> In our case, letrozole-supplemented PPOS minimised oestradiol peaks (<1000 pg/mL), theoretically reducing hormonal stimulation of residual disease. Dosing has to be individualised to maximise retrieval, as achieving adequate oocyte yield is challenging with low AMH.

### Chronic endometritis and implantation

The incidental finding of MUM1-positive chronic endometritis after failed embryo transfer highlights the importance of endometrial evaluation. Treatment with oral antibiotics (Doxycycline 100 mg + Metronidazole 400 mg twice daily) for 2 weeks, followed by oral probiotics and the subsequent natural cycle FET, resulted in successful implantation, emphasising that fertility optimisation extends beyond ovarian management.

### Prognosis and prevention

Evidence shows excellent long-term survival in early-stage SMBOT, although recurrence may occur up to 10 years. Prevention primarily involves complete staging surgery and surveillance rather than hormonal suppression. In our case, embryo cryopreservation prior to definitive surgery preserves reproductive potential without delaying oncologic management.

### Ethical and emotional considerations

Patient autonomy and informed choice were central. The couple's desire for genetic parenthood required sensitive counselling about recurrence risk and fertility prognosis.

### Outcome, prognosis, and clinical relevance

This case illustrates that fertility preservation is achievable even in select cases of recurrent, microinvasive BOTs when guided by stringent histologic verification, low-oestrogen stimulation, endometrial evaluation, and vigilant multidisciplinary oncological surveillance. She remains under oncologic follow-up.

## CONCLUSION

Fertility preservation in recurrent BOTs with microinvasion requires individualised, multidisciplinary planning. Letrozole-supplemented ovarian stimulation for ER<sup>+</sup> BOTs and vigilant oncologic follow-up can yield favourable reproductive outcomes without compromising safety. This case illustrates that even in

complex oncologic scenarios, autologous conception is possible through coordinated oncofertility care.

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