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# The Role of Continuous Transvaginal Ultrasound Monitoring for Detection of Early Stage Ovarian Serous Carcinoma in Infertile Women: Three Cases with 5-Year Follow Up

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## Abstract

Epithelial Ovarian Carcinoma (EOC) is the most common type of ovarian cancer and the most lethal gynecologic malignancy, with a mortality rate of 70%. Serous Ovarian Carcinoma (SOC) is the commonest type of EOC. There is a high incidence of ovarian cancer in infertility. However, there are only a few case reports outlining how SOC was discovered in infertile women. Here, we detail three infertility cases, who were found with persistent ovarian cysts by using continuous ultrasound monitoring, and they were diagnosed as SOC in stage I by examination of surgical and pathology specimens. No recurrence of the cancers occurred. However, one of the women became pregnant after conservative surgery, resulting in the live birth of a healthy baby girl. These cases are rare and unusual and suggest that continuous transvaginal ultrasound monitoring is helpful in detecting SOC at an early stage.

**Keywords: Continuous transvaginal ultrasound; Infertility; Serous ovarian carcinoma stage I; Fertility preservation**

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## Introduction

Epithelial Ovarian Carcinoma (EOC) is the most common type of OC and the most lethal gynecologic malignancy, with a mortality rate of 70%. Among all types of OC, serous carcinoma is the most common. The most fatal serous carcinoma, which is characterized by a poor prognosis, accounts for more than 80% of all EOC. SOC is the most common epithelial ovarian malignancy. Several alternative treatments for SOC have been developed in recent years. Nevertheless, overall survival rates for patients with SOC have not improved, as well as the existence of unsolved problems in connection with the disease such as therapy resistance, disease recurrence and so on.

The pathogenesis of OC has yet to be clearly elucidated. The mechanisms which have been proposed include the incessant ovulation hypothesis [1,2], stimulation by hormonal exposures and inflammation mechanisms [3,4] and this partly explains why there is a high incidence of OC in infertility. The study by Rasmussen et al found a significantly increased risk of OC in women with infertility and the use of Hormone Replacement Therapy (HRT) [5]. As the disease has no characteristic symptoms in its early stages, most of the cases are diagnosed during more advanced stages leading to a low 5-year survival rate and the inability to preserve the fertility of individual patients.

Here we present three case reports after oophorectomy. The three cases, which were all diagnosed with OC stage I, were studied retrospectively to evaluate the efficiency of transvaginal ultrasonography in detecting the disease in its early stages. The three cases were all followed up for 5 years. None of the three women with OC in stage I experienced recurrence of the disease and one of them successfully became pregnant after conservative surgery, resulting in the live birth of a healthy baby girl. For reproductive specialists, detecting an abnormal ovarian cyst by continuous ultrasound monitoring in infertility is beneficial for the 5-year survival rate and the preservation of fertility in patients.

## Case Presentation

Informed consent was obtained from patients for these reports. The institutional review board


**Figure 1:** (A) During the third day of the menstrual cycle, the size of the right ovary increased to 71 mm × 50 mm with a cyst deformation being observed and the size of the left ovary reduced on October 9, 2008. (B) 3 days of menstrual cycle, the size of the right ovary and the cyst continued to increase on November 11, 2008. (C) The size of the right cyst increased to 35 mm × 27 mm on December 18, 2008.

of Maternal and Child Health Hospital in Guangxi, China indicated that a report of three cases did not require specific institutional review board review and allowed the study to take place.

## Case 1

A 35-year-old woman presented with menstrual disorder for more than nine years and with infertility for five years after marriage. This was diagnosed primary as infertility. The menstrual cycle varied from 37 days to 180 days, which was linked to a natural cycle ovulation on only rare occasions. Ovulation was stimulated in the patient by treatment with CC/HMG/HCG, but she failed to get pregnant. Polycystic changes were seen on the right ovary. Basic hormone measurements indicated that the levels of serum luteinizing hormone and testosterone were raised. After treatment with dyne-35 for 4 monthly cycles, the level of serum testosterone did not decrease, and this was accompanied with normal levels of 17-OH, 17-KS and cortisol. The results of repeated monitoring by transvaginal ultrasonography showed that the size of right ovary increased month by month, with a persistent corpus luteum cyst and normal levels of serum AFP and Ca125. In January 2009, the size of right ovary increased markedly. The cyst size grew from 26 mm ×18 mm to 53 mm × 32 mm, with abnormal hyperechoic areas being observed within it (Figure 1).

Afterwards, the patient was treated by laparoscopic surgery. Intra-operative findings showed that the appearance of the uterus and left ovary was normal; the right ovary was augmented (the size was 80 mm × 70 mm × 50 mm); some endometrium-like decaying tissue without a clear boundary was observed after the ovary was cut open after removal. When frozen sections were examined, a diagnosis of serous adenocarcinoma (III grade) was ascertained. After communication with the family members, an operation including total abdominal hysterectomy, greater omentum double attachment and appendectomy was performed. Post-operative diagnosis for the right ovary was serous adenocarcinoma (stage I). After surgery, 6 courses of chemotherapy with cis-platinum and cyclophosphamide were implemented. There was no post-operative recurrence during a follow-up of 5 years. Histological examination showed that it was endometrioid ovarian cancer during stage 1A.

## Case 2

A 32-year-old woman who was presented with infertility for 3 years after marriage and a pelvic mass two months ago and was intended to be treated with assisted IVF-ET reproduction for primary infertility. The level of serum CA125 was 207.1 U/mL and AFP was negative. Because of the high level of serum CA125, down-regulation

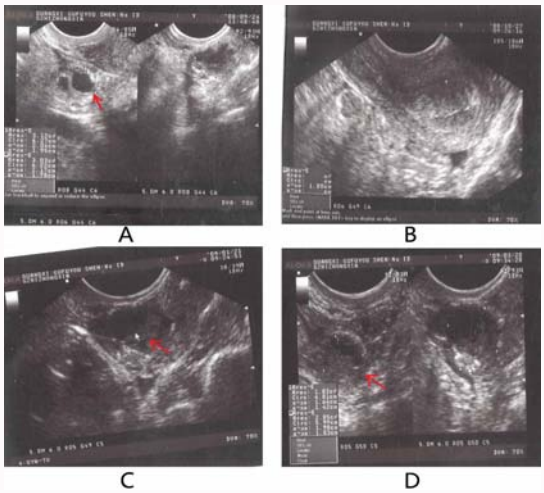


**Figure 2:** (A) A similar cyst of endometriosis in the right ovary on September 24, 2008. (B) Endometrial echo disorder before pituitary down-regulation on October 27, 2008. (C) Removal of approximately 3 mL of faint yellow liquid after puncture in the second pituitary down-regulation on January 21, 2009. (D) Removal of approximately 3 mL of dark brown liquid after puncture following the third pituitary down-regulation on March 20, 2009.

treatment was carried out 5 times from March to July in 2009, but failed. In January 2009, an ovarian cyst of 12 mm × 12 mm was found on the left side by ultrasound. It persisted and increased gradually and did not change during the menstrual cycle. In March 2009, the size of the ovarian cyst was measured at 37 mm × 18 mm × 18 mm, and it was observed to have two strong echoes and several dotted blood flow signals in it as well as an annular flow signal around it. This abnormal ovarian cyst was subjected to puncture treatment twice in January and March 2009. A bright yellow liquid was found during the first puncture and a dark brown liquid was found during the second procedure. Tumor cells were not found in either of these liquids. In addition, it was harder to puncture during the second procedure because the cyst had solidified. The patient had a regular menstrual cycle with occasional dysmenorrhea and no abnormal medical history (Figure 2).

During the laparoscopic surgery, the appearance of the right ovary was found to be normal and there was a cauliflower-like mass on the surface of the left ovary. The size of the mass was approximately 80 mm × 70 mm × 50 mm and it was solid, edematous, pale and very brittle, with an irregular shape and without a capsule. No tumor cell was found in the ascites fluid associated with the mass. A pathological

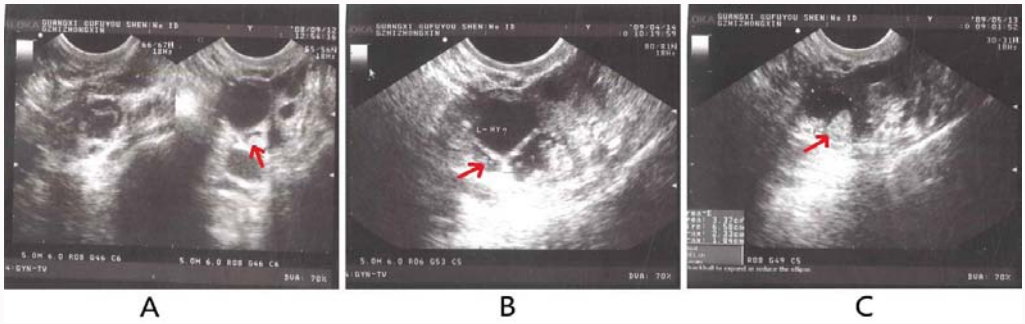


**Figure 3:** An abnormal left ovary cyst which existed persistently in the left ovary, 22 mm × 17 mm × 2.0 mm in size with strong echoes being observed within it.

examination revealed it to be an ovarian serous papillary carcinoma. Thus, an operation incorporating a total abdominal hysterectomy, including double attachment and appendectomy was performed. Routine post-operative pathological examination indicated that it was ovarian serous papillary adenocarcinoma with part ovarian cortex fibrosis and no tumor cell was found in the left fallopian tube. The result of post-operative diagnosis was left serous papillary adenocarcinoma (stage Ic). After surgery, 8 courses of chemotherapy with cis-platinum and cyclophosphamide were implemented. The level of serum CA125 was normal after the fourth week of surgery. The patient was followed-up for 5 years and did not experience any recurrence of the disease.

### Case 3

A 27-year-old woman was presented with infertility for one year after which a mass of tissue was observed on the ovary. The planned treatment for the patient was to implement IVF-ET for assisting reproduction. The base levels of sex hormones, serum CA125 and AFP were normal. Two ovarian cysts with sizes of 19 mm × 14 mm and 12 mm × 7 mm respectively, were found on the left side by ultrasound (Figure 3). There was 6 mL of yellow viscous liquid in one of the two cysts and 1.5 mL of brown liquid in the other which was observed after puncturing the two ovarian cysts, respectively. After puncturing, the two ovarian cysts did not shrink with strong echoes being seen within them. Cytological examination of the suction liquid indicated that they were infused with a conglobation of epithelial cells.

During the laparoscopic surgery, the appearance of uterus and the right ovary appeared normal; the left ovarian was in a crescent and the size was 50 mm × 40 mm × 40 mm with an irregular surface, and there was a 30 mm × 30 mm × 20 mm purple red tumor on the surface. There was no tumor cell in the ascites fluid. A pathological examination indicated that it was serous papillary adenocarcinoma, without obvious infiltration into the capsule. After communication with the families, we were urged to preserve reproductive ability of the patient. Thus, a laparoscopic operation was performed on the left ovarian tube and a right ovarian wedge resection was performed. A routine post-operative pathological examination indicated that there was ovarian serous papillary adenocarcinoma, without tumor cells being present in the right ovary. Post-operative diagnosis was established to be serous papillary adenocarcinoma (stage Ic), with extensive fibrosis in parts of the ovarian cortex. After surgery, 6 courses of chemotherapy were implemented. Three months after chemotherapy, this patient had a successful pregnancy resulting in the live birth of a healthy baby girl weighing 3.20 kg. She did not experience any recurrence post-operatively with a follow-up of 5 years. The data presented here would indicate that fertility-sparing surgery is an option for young, childless women who would like to preserve their fertility.

In these case reports, conservative surgery was chosen in case 3 for a young childless patient. We showed that a pregnancy following stage I ovarian cancer with conservative surgery was possible. Current data and our experience revealed that it is not possible to make a definite recommendation for the treatment of all young childless patients with stage I ovarian cancer. However, the use of continuous vaginal ultrasound monitoring in infertile patients with a stage I ovarian cancer appears to warrant recommendation in some cases.

## Discussion

Ovarian cancer is usually a fatal disease because it is difficult to detect during its early stage. Ovarian serous carcinomas are the most common EOC. Recent research described the role of sex steroid hormones in the etiology of EOC arising in the ovaries [6], and the incidence of ovarian serous carcinomas becomes more frequent in women during their reproductive years. The International Ovarian Tumor Analysis (IOTA) group is a multicenter collaboration whose aim is to design tools for the preoperative diagnosis of ovarian cancer that can be used by non-expert ultrasound operators. By using standardized terms and definitions to describe morphological features of ovarian tumors, the 'simple-rules' model of observed ultrasound features was designed. There no features are seen in the three case reports, which were unclassified or indeterminate. So for high-risk groups, continuous transvaginal ultrasound monitoring for detection of early stage ovarian serous carcinoma is significant. The data suggest that the incidence in women who were younger than 50 years of age was about 45% [7]. Thus, early detection of ovarian cancer may not only reduce the mortality of the disease, but also may have positive significance on fertility preservation. However, reports regarding the detection of early ovarian cancer by transvaginal ultrasonography are limited [8-10].

In these three case reports outlined here, we found three individuals with stage I ovarian serous carcinomas linked to infertility and these patients were followed-up for 5 years. None of the three patients experienced recurrence of the disease, and one of them conceived naturally which led to a live birth. The association between the long-term usage of infertility drugs and development of ovarian serous adenocarcinoma has previously been noticed. It was noticed that patients with ovarian serous adenocarcinoma may be prone to clinical problems after induction of ovulation or IVF procedures. Infertility alone and nulliparous women with refractory infertility may particularly harbor a high risk of ovarian cancer [11]. It is normal that childless women would like to preserve their fertility. These cases

showed the benefits of transvaginal Doppler in detecting ovarian cancer during its early stages in asymptomatic women. These results could highlight the importance of diagnosing ovarian carcinoma as early as stage I in order to improve the patients' chances of survival and wellbeing.

To date, similar cases have been reported rarely. David et al. [12] reported an abnormal ovarian lesion which was subjected to ultrasound-guided needle aspiration during IVF. The patient underwent laparotomy after the IVF cycle. Two years later, the patient underwent a successful pregnancy with a donor oocyte. To the best of our knowledge, there is no report in which a clinical reproductive doctor detected an ovarian cancer by continuous ultrasound monitoring. During the process of IVF for assisted reproduction, continuous ultrasound monitoring, which provide the necessary condition to discover an abnormal cyst, is necessary, especially in the case of young women who wish to protect their fertility with conservative surgery. In one report [12], the authors concluded that conservative surgery could be considered for young patients with EOC at stage IA and grade 1 in order to preserve their fertility potential, and in another report it was concluded that refreezing of transplanted ovarian tissue is beneficial to the patients with low risk of malignant cell recurrence [13]. Conservative management of EOC at the very early stages and low grade is an option for those young childless women who would like to preserve their fertility. However, induction of ovulation remains classically contraindicated in EOC and the treatment must be undertaken very cautiously and requires rigorous surveillance.

As is well known, the ability to detect early ovarian cancer is difficult. In these three cases, it would seem that continuous ultrasound monitoring is an ideal screening procedure which could detect early stage ovarian cancer in asymptomatic women.

## Ethics

Verbal consent was obtained from the patients when they were followed up. The patients' identification has been protected and any information which could potentially be used to reveal the identity of any of the patient has been removed.

## Conclusion

We report here on three cases of infertilities who were found with persistent ovarian cysts, which were diagnosed as stage I SOC by obtaining surgical and pathology specimens. Because of the early detection, the three patients were all treated in time. As a result, no recurrence of the cancers occurred and one of the women became pregnant after conservative surgery, resulting in the live birth of a healthy baby girl. The report shows that such cases is rare and unusual and warrant further investigation. The report also shows that continuous transvaginal ultrasound monitoring is helpful in detecting SOC at an early stage. This report suggests that continuous transvaginal ultrasound monitoring can be a viable option for patients in order to detect early stage SOC.

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