A successful IVF–pregnancy in a patient who underwent conservative surgery followed by a regimen of cisplatin, vinblastine and peplomycin to treat an advanced ovarian mixed germ cell tumour: A Case Report

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Mixed germ cell tumours of the ovary, one type of malignant ovarian germ cell tumours (MOGCTs), are rare gynaecologic cancers usually affecting young women. We report the case of a patient with an advanced ovarian mixed germ cell tumour who underwent fertility-saving surgery followed by a chemotherapy regimen of cisplatin, vinblastine and peplomycin. The patient was disease-free 8 years after initial presentation. She conceived and gestated dichorionic twins after IVF–embryo transfer. To the best of our knowledge, the patient is the first to be treated successfully with the combination chemotherapy regimen and then conceive safely using assisted reproductive technology (ART).

Key words: assisted reproduction/pregnancy/chemotherapy/cancer/germ cell tumour

Introduction

Malignant ovarian germ cell tumours (MOGCTs) are rare gynaecologic cancers usually affecting young women. One type of MOGCT, the mixed germ cell tumour, is composed of more than one neoplastic germ cell element, for instance dysgerminoma combined with teratoma, yolk sac tumour, choriocarcinoma, embryonal carcinoma or polyembryoma, as well as any other possible combination of these tumour types (Kurman, 2002). Before the mid-1960s, virtually all patients with advanced non-dysgerminomatous disease died, and even those with exquisitely radiosensitive tumours were left with their fertility destroyed. But the introduction of effective combination chemotherapy has brought about dramatic improvements in the treatment of MOGCTs. For instance, the bleomycin, etoposide and cisplatin (BEP) regimen, which has been used since the 1980s, has resulted in a 5-year survival rate of up to 100% for dysgerminomas and 85% for non-dysgerminomatous MOGCTs (Low et al., 2000).

Here, we present the case of a patient with an advanced ovarian mixed germ cell cancer who was treated conservatively and delivered twin babies after an IVF–embryo transfer pregnancy. To our knowledge, this is the first case of a successful pregnancy with IVF–embryo transfer after fertility-preserving treatment of an advanced-stage ovarian mixed germ cell tumour.

Case report

A 19-year-old woman consulted our department in January 1993 because of abnormal genital bleeding. Ultrasonography and computerized tomography scans revealed a 9- to 10-cm solid, non-homogeneous tumour filling the pelvis and a remarkable quantity of ascites in the abdominal cavity. Serum levels of Ca125, CA19-9, carcinoembryonic antigen (CEA), α-fetoprotein and β-HCG were 89 U/ml, 13 U/ml, 1.4 ng/ml, 251 ng/ml and 8.7 ng/ml, respectively. A diagnosis of ovarian cancer was made, and a laparotomy was performed. After making a midline incision, samples were taken for peritoneal cytology, 3.5 l of ascites fluid was drawn from the abdomen, and a right ovarian mass 9–10 cm in diameter (560 g) with numerous foci of peritoneal seeding was observed. Instead of hysterectomy and bilateral salpingo-oophorectomy, right unilateral salpingo-oophorectomy was performed along with infracolic omentectomy and an appendectomy. Bilateral pelvic and para-aortic lymphadenectomies were not done, as there were no lymph nodes to palpate. The peritoneal cytology was positive for malignancy, and the omentum and appendix were positive for tumour. The components of the ovarian specimen were 90% immature teratoma, 5% choriocarcinoma and 5% yolk sac tumour, leading to a histological diagnosis of primary ovarian mixed germ cell tumour. The tumour was determined to be stage IIIb according to the International Federation of Gynecology and Obstetrics (FIGO) classification. After the surgery, the patient received six courses of chemotherapy regimen PVP (80 mg of cisplatin, 15 mg of vinblastine and 10 mg × 3 days of peplomycin).

Consistent with our clinic’s policy, a second look operation (SLO), including wedge resection of the left ovary, was carried...
out 7 months after the first operation. No gross tumour was found during the second surgery, and frozen sections of suspicious areas were negative for tumour. Likewise, paraffin-embedded biopsy samples from several parts of the peritoneum were found to contain only well-differentiated glia and villi. There was no evidence of disease. In addition, left ovarian specimens revealed a corpus luteal cyst, and the patient’s menstrual cycle continued throughout the treatment. Seven months after the SLO, however, the patient showed peritoneal fluid retention that was highly dependent on the stage of her menstrual cycle.

The patient was 27 years old when first seen in our infertility section, with irregular ovulatory cycles. Her serum hormone levels at day 3 of the cycle were as follows: FSH, 13.53 mIU/ml (follicular phase normal range: 5.2–14.4 mIU/ml); LH, 4.36 mIU/ml (follicular phase normal range: 1.8–7.6 mIU/ml); prolactin, 12.45 ng/ml (normal range: 3.20–26.2 ng/ml); and estradiol, 38.03 pg/ml (follicular phase normal range: 19–255 pg/ml). All tumour markers, including Ca125, CA19-9, CEA, α-fetoprotein and ß-hCG, were within the normal range. The patient underwent hysterosalpingography, and left tubal passage was confirmed. Her partner’s sperm was normal.

We first thought that the patient might be able to become pregnant as a matter of natural course, without the use of assisted reproduction technology (ART). However, the adnexa in this patient were floating in a substantial amount of peritoneal fluid, which we surmised was making it difficult for the fimbria to retrieve the oocyte.

In an effort to achieve pregnancy, the patient underwent a short regimen of GnRH agonist. Initially, 300 IU of human menopausal gonadotrophin (Nikken Chemicals, Tokyo, Japan) was administered from day 3 to day 8 of her menstrual cycle. The number of developed follicles was four. She then received hCG on day 9, and four oocytes were retrieved 34 h later, after the retained peritoneal fluid (300 ml) was removed by vaginal puncture. After the specimen was cytocentrifuged, an air-dried slide was stained with Papanicolaou stain and periodic acid/Schiff (PAS) alcian blue stain. We analysed cancer cells and found no evidence for cancer. All of the oocytes were successfully fertilized and reached the 3- to 5-cell stage on day 2 after fertilization. The patient elected to have three embryos transferred on that day. The remaining embryo was cryopreserved.

The patient conceived and gestated dichorionic twins but suffered from abdominal tenderness due to accumulation of peritoneal fluid as a result of the embryo transfer. On five occasions during the period extending from day 10 after embryo transfer to the 11th week of gestation, this fluid (3.5 l in total) was removed from the Douglas pouch by puncture. No peritoneal fluid was obtained with the last puncture. After 29 weeks of gestation, the patient presented with preterm labour and was administered a tocolytic agent, ritodrine. The tocolysis was successful, and a healthy female infant weighing 2380 g and a male infant weighing 2198 g were delivered by selective Caesarean section after 36 weeks of gestation. At that time, there was no evidence of residual tumour, but a filmy adhesion between the peritoneum and uterus was observed, suggesting the earlier peritoneal fluid retention was due to a pseudocyst.

Both babies did well through the neonatal period. Following the Caesarean section, there was no longer accumulation of peritoneal fluid during menstrual cycles.

Discussion

The combination chemotherapy regimen that has dramatically improved the previously dismal prognosis for MOGCTs has been evolving since 1970s. The vincristine, actinomycin D and cyclophosphamide (VAC) regimen was popular in 1970s, but the introduction of cisplatin into clinical trials in the late 1970s made platinum-based combination chemotherapy popular. Currently, the bleomycin, etoposide and cisplatin (BEP) regimen is standard for MOGCTs. In our case, the patient was treated during a period of transition, and we selected the PVP regimen.

Conservative surgery with adjuvant chemotherapy has made preservation of fertility in young patients possible, even in patients with advanced disease, such as the one described here (Gershenson, 1993). In that regard, there have been several reports of successful pregnancy after treatment with combination chemotherapy (Schwartz and Vidone, 1981; Yoshinaka et al., 2000; Zanetta et al., 2001; Tangir et al., 2003). For instance, Schwartz and Vidone (1981) were the first to describe a pregnancy following combination chemotherapy for a mixed germ cell tumour of the ovary; that case was a stage I tumour treated using the VAC regimen. In addition, Tangir et al. (2003) described three successfully treated cases of advanced mixed germ cell tumour, after which two patients conceived successfully. The treatment regimen they used is unclear, however. Our case differs from those in that ART was employed to achieve a successful IVF–embryo transfer pregnancy following combination chemotherapy.

The treatment we used was standard fertility-saving surgery (unilateral salpingo-oophorectomy) and adjuvant chemotherapy. The PVP regimen used might be considered old-fashioned, but the patient has survived disease-free for over 10 years and has conceived two babies. Still, the operation and chemotherapy might have caused the adhesion seen in the peritoneal cavity. Our patient required ART because adhesions and peritoneal fluid resulted in infertility by causing mechanical blockade to the Fallopian tubes thus preventing oocyte retrieval (Cheong et al., 2001). We selected the flare-up protocol because the day 3 FSH level was somewhat high (13.53 mIU/ml), and the patient was thought to be a poor responder (Toth et al., 1996; Gurgan et al., 1997). Tewari et al. (1998) reported the case of a germ cell ovarian cancer arising in the setting of fertility-drug therapy. But the safety issue in using fertility drugs is still controversial. Mahdavi et al. (2006) reviewed the literature about induction of ovulation and ovarian cancer. The findings on ovarian cancer risk associated with fertility-drug treatment were reassuring but not definitive. Most of these patients who have received combination chemotherapy resume normal ovarian function and can expect a normal fertility rate and healthy offspring. The congenital malformation rate of ovarian cancer patients is slightly higher than that of the normal population, but no significant difference has been observed between patients who received or did not receive chemotherapy.
Low et al. (2000) reported on 74 patients with malignant germ cell tumours of the ovary who underwent conservative surgery, 47 of whom (64%) received adjuvant chemotherapy. Of these, 20 attempted conception and 19 were successful (95%). A total of 16 live births were documented, 14 of which were from chemotherapy group. There were no documented congenital defects in any of the 16 infants. It was not clear how many of these 20 patients had advanced-stage tumours.

Zanetta et al. (2001) reported on 81 patients who were treated conservatively and received adjuvant chemotherapy. Twenty patients attempted to conceive, and 16 were successful (80%), compared with 12 of 12 in the group not treated with chemotherapy. There were six patients with advanced disease in this series.

Kanazawa et al. (2000) reported on 20 patients who underwent conservative surgery for fertility preservation. Eight of 20 patients delivered a total of 9 normal babies with no congenital abnormalities; 7 of 9 babies were from women treated with chemotherapy. One case, who received no chemotherapy, conceived two times. One of these eight patients had stage IIIc disease.

Gershenson (1988) reported a series of 40 patients with MOGCTs, 16 of whom had attempted to conceive. Nine conceived naturally, and three more did after infertility treatment (75%). Of the 12 patients, 11 patients delivered 22 healthy infants, none of whom had major birth defect. Ten patients in this series had stage III disease. It was not stated how many of these 10 advanced-stage patients attempted or were able to conceive.

Brewer et al. (1999) reported a series of 16 patients with dysgerminoma who underwent conservative treatment. Three of the 16 who attempted to conceive were successful. Five pregnancies have occurred in this group of patients after chemotherapy. There was no evidence of birth defects.

Zanagnolo et al. (2004) reported eleven pregnancies occurred in 36 women treated with fertility-sparing surgery who were of childbearing age. Ten women delivered 11 healthy babies; there were no miscarriages. None of these patients had difficulty conceiving, and there was no evidence of birth defects or other disabilities in any of the offspring.

Tangir et al. (2003) reported on 29 patients who conceived a total of 47 pregnancies. There were 38 children born (including three sets of twins), 10 elective terminations and 2 spontaneous abortions. Eleven patients had one child, eight had two children, two had three children, and one had five children. Follow-up was available for 16 of these children. One child has ‘speech problem’. Another child, whose mother was treated with chemotherapy during the third trimester of pregnancy, had juvenile arthritis. This, however, is a prevalent disease in this family. One of a patient’s twins has problems processing high-order thinking and is currently undergoing future workup. The other 13 children were reported as completely normal at the time of follow-up. The noble aspect of the study is the finding that 8 of 10 women with stage III disease successfully treated with fertility-preserving surgery were able to conceive.

Although spontaneously occurring pregnancies in patients treated in this manner have been reported as above, our case report can be considered to be of sufficient interest because the pregnancy was the first generated through ART. This case may open a way of proceeding for couples presented with the combined problem of MOGCT and severe male infertility where spontaneous conception may not be possible at all.

References


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