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FERTILITY PRESERVATION

Legal termination of a pregnancy resulting from transplanted cryopreserved ovarian tissue due to cancer recurrence

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Abstract
Purpose To report on a woman who conceived naturally and had a normal intrauterine pregnancy following transplantation of frozen/thawed ovarian tissue but decided to have an early abortion due to recurrence of breast cancer.
Methods The patient was diagnosed breast cancer and received antineoplastic treatment that forced her into premature ovarian insufficiency and infertility. Ovarian tissue cryopreserved prior to chemotherapy was transplanted following cancer treatment restoring fertility and regular menstrual cycles.
Results The patient conceived 6 month after transplantation. However, she experienced recurrence of breast cancer and decided on legal termination of the pregnancy in the first trimester.
Discussion The obtained pregnancy only 6 month following transplantation underlines the ability of the procedure. The recurrence occurred near the original site of the tumor and was most unlikely related to the transplantation. The activity of the transplanted tissue is likely to be destroyed by the renewed antineoplastic treatment she will receive. However, she still has the majority of one ovary cryostored and may later want to undergo additional transplantation to regain fertility or to have menstrual cycles back.

Keywords Transplantation · Fertility preservation · Cancer · Ovarian cryopreservation · Premature ovarian insufficiency

Capsule A woman achieves pregnancy following autotransplantion of cryopreserved ovarian tissue but undergoes legal abortion due to cancer recurrence.

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Introduction

Due to the development of new and aggressive treatment regimens many girls and women facing a cancer disease now face a good chance of becoming long time survivors [1]. As a side effect, these new hard-line antineoplastic treatments may render the patient sterile due to elimination of the pool of ovarian follicles. As a quality of life aspect many young female cancer patients express a great wish to maintain fertility upon treatment [2].

Cryostorage of ovarian tissue for fertility preservation is a new option in which the tissue is removed prior to cancer treatment and replaced after treatment in case the woman becomes menopausal. This technique has shown promising results in both women and children [3–5] and is the only fertility preserving opportunity available for patients who cannot delay the start of chemotherapy and for young prepubertal girls [6]. Currently a total of more than 20 healthy children have been born following transplantation of frozen/thawed ovarian tissue, without one single case of cancer relapse due to the transplantation of ovarian tissue [7, 8].

Recurrence of the primary malignancy is always of concern in these patients. For each individual patient there is a risk of spontaneous recurrence and in connection with transplanting ovarian tissue this risk may be augmented since the tissue was collected when an active cancer was present. Ideally, transplantation should only be considered when the risk of recurrence is minimal or absent. The patients' wishes to obtain pregnancy or avoid post-menopausal symptoms should be taken into consideration when assessing pros and cons connected with ovarian auto transplantation and risk of recurrent cancer. Once the tissue is transplanted it cannot easily be recovered again and it is likely to become inactive in connection with a renewed cancer treatment.

In this case report a woman is described who became pregnant following transplantation of frozen/thawed ovarian tissue but decided to undergo legal abortion due to recurrence of her mammary cancer.

Case report

The 33-year-old patient was operated with breast conservation, sentinel node biopsy and axillary lymph node dissection for a 12 mm invasive ductal carcinoma. Pathology showed 95 % estrogen receptor positive, 90 % progesterone receptor positive, malignancy grade I, HER2 positive by gene amplification, and with micro-metastasis in 2 of 3 sentinel nodes. A total of 11 lymph nodes were removed. The microscopically resection margin was 10 mm. The operation was in accordance with the guidelines of the Danish Breast Cancer Cooperative Group (DBCG). She also received adjuvant therapy according to the DBCG. Thus, she was treated with 7 cycles of CEF (Cyclophosphamide 600 mg/m^2, Epirubicine 60 mg/m^2, 5-Flourouracil 600 mg/m^2) in 3-weekly intervals. Two weeks after chemotherapy the patient started tamoxifen 20 mg daily with a planned duration of 5 years. Three weeks after last chemotherapy treatment she started adjuvant trastuzumab (loading dose 8 mg/kg, thereafter 6 mg/kg) given every 3 weeks 17 times, thus lasting for 1 year. Also 3 weeks after chemotherapy she received whole breast irradiation with a dose of 48 Gy/24 fractions followed by a tumour bed boost of 10 Gy/5 fractions. The follow-up was performed according to the DBCG guidelines where the patient was seen in the Department of Oncology every 6 months for clinical examination. Every 12 months a clinical mammography was performed in accordance with the DBCG guidelines.

Prior to the above-described cancer treatment and follow-up the patient had her left ovary excised by laparoscopy. After a 5 h transport on ice in culture medium the ovary was dissected into 29 pieces of cortex and cryopreserved as previously described [4]. In brief, the cortical tissue was cut into 1–2 mm thickness and a size of approximately 5× 5 mm. The tissue was cryo-stored in a mixture of cryoprotectants containing ethyleneglycerol, sucrose and human serum albumin [4, 9]. There was performed no histological assessment of the tissue prior to cryopreservation, nor was it transplanted to immunedeficient mice.

Already at the time of cancer diagnosis the patient had a pregnancy wish. The oncologists advised her to wait at least 2 1/2 year in order to complete the majority of the systemic therapy and to receive tamoxifen as long as possible. Two and a half years after diagnosis the patient discussed her pregnancy wish with the oncologists. Her risk of relapse was evaluated based on estimates from Adjuvant! Online (www.adjuvantonline.com), where the age of the patient, tumour characteristics, and therapy based on first generation chemotherapy, were entered. Her 10-year relapse risk was then estimated to be 10.8 %, and since she was alive without relapse 2 1/2 year after diagnosis, her risk was estimated lower and in the range of 5–7 %. Adjuvant! Online cannot estimate the effects from trastuzumab. However, the positive HER2 status doubles the risk of relapse, and trastuzumab halves this risk [10]. According to DBCG guidelines, patients are advised to stop tamoxifen 6 months before they start trying to become pregnant. The patient was informed about these concerns and estimates. She then decided to stop tamoxifen in order to pursue her pregnancy wish.

Six month later, when consulted by the gynaecologists, she was having regular menstruations and the husbands' semen parameters were found within normal reference values. The couple was referred for Intra Uterine Insemination (IUI) treatment. However, the woman did not become pregnant following three treatment cycles, of which the two latter were stimulated with clomiphene citrate 100 mg/day from day 3–7 in the cycle. The patient was offered IVF treatment, but declined due to the amount of required exogenous hormone administration associated with the treatment. An additional 2 years of attempts to become pregnant spontaneously was also unsuccessful.

The couple returned for transplantation of the cryopreserved ovarian tissue to augment the pool of follicles and chances of obtaining a pregnancy. Hormone parameters just prior to transplantation were; AMH below 3 pmol/L, a FSH of 39 IU/L, a LH of 18.8 IU/L and an estradiol of 0.19 nmol/L and in accordance with this, menstruations were now irregular with long intervals of amenorrhea. The oncologists did not consider transplantation of ovarian tissue to augment the risk of relapse in this patient in any way. Further, the regional ethical board approved the protocol followed in the transplantation procedure.

The patients' cryopreserved tissue was thawed and transplanted as previously described [4]. In brief, the in situ ovary was extracted from the peritoneal cavity using laparoscopy. Two small pockets were prepared just below the cortex on either side of her right ovary. Four pieces of

cortex were positioned in the pockets and secured by sutures. Thereafter the ovary was returned to the peritoneal cavity. Additionally eight pieces of cortical strips were transplanted to a subperitoneal pocket as previously described [4].

At follow-up 4 month later the patients' hormone profile was AMH<3.0, FSH 7.0 IU/l, LH 3.7 IU/l.

Six month after transplantation the patient conceived naturally. Vaginal ultrasound showed a single embryo with heart beat and normal appearances.

However, during the first trimester of pregnancy the patient was diagnosed with a new left sided breast cancer in the same quadrant as the breast cancer 8 years earlier. She was mastectomized and diagnosed with 3 tumours with the same histological pattern: 9 mm invasive ductal carcinoma with ductal carcinoma in situ (DCIS) around the tumours, estrogen receptor positive, and HER2 negative. It was decided to regard the tumours as new primaries based on presence of DCIS in the specimen, and the 8-year interval between the tumours.

The patient decided, after informed consent, to have an abortion in the 8th week of pregnancy.

Discussion

This report demonstrates that a woman with compromised ovarian function and difficulties conceiving may enhance her chances of becoming pregnant by having frozen/thawed ovarian tissue transplanted. Several studies have shown that a period of 4–5 months is required for frozen/thawed ovarian tissue to regain activity and provide pre-ovulatory follicles [4, 6]. This patient conceived 6 months after transplantation suggesting that indeed the transplanted tissue enhanced fertility of this woman. Whether or not the oocyte that resulted in the pregnancy originated in the transplanted tissue or in the in situ ovary, which was not completely without function, remains unknown. However, the chances of pregnancy do increase with a larger pool of follicles leading to a better follicle selection with more viable oocytes.

To our knowledge, this study is the first to describe a woman who had a viable intrauterine pregnancy following transplantation of frozen/thawed ovarian tissue but where termination was inevitable due to recurrence of cancer and renewed cancer treatment. The follicles of the transplanted tissue is likely to suffer from the chemotherapy the woman will experience and she is likely to be menopausal again after having completed cancer treatment.

However, the woman still has the majority of her tissue from one ovary cryostored. In theory, she may want to return for transplantation once more when she has recovered from her second chemotherapy, perhaps just for having normal menstrual cycles. The risk of cancer recurrence having the tissue transplanted should not be increased. The overall prognosis and medical history of the patient needs to be taken into consideration before a decision regarding a second auto transplantation can be taken. If the patient should return with a pregnancy wish, the treating doctors will provide every information and advice accessible so that the patient, in the end, can make an informed decision.

Around 40 % of one ovary was transplanted to this patient, which constitutes more tissue than we usually previously have grafted per transplantation [4]. This was performed in order to increase the pool of ovarian follicles and thereby provide a more suitable environment for having an oocyte developed with a pregnancy potential. This case indicates that a relatively large pool of ovarian follicles do favour conditions for a successful pregnancy. In contrast women who prefer to avoid menopausal symptoms without becoming fertile may only require a smaller amount of tissue, which potentially may last for a longer period. Our clinical experiences have lead us to believe that women having larger amounts of ovarian tissue transplanted have larger fecundity than women having smaller amounts transplanted. This could be due to successful follicle selection with more viable oocytes. Further observations are, however, required to substantiate this policy.

Recurrence of cancer happened in her left breast at the site of the original cancer and according to the treating oncologists it is unlikely that the transplanted tissue had any effect on this. We can only speculate whether the return of natural ovarian function had an impact on the course of her cancer development. However, the patient had natural ovarian activity with menstruation, although very irregular, and she was exposed to circulating levels of estradiol prior to transplanting of ovarian tissue. Transplantation appears only to have augmented her pool of ovarian follicles rather than increasing the levels of estradiol present. Following the ASCO guidelines there has been a number of studies showing that breast cancer, especially in the early stages, very rarely metastasises to the ovaries. We, and others, now have considerable experience with transplantation of ovarian tissue from former breast cancer patients and have not observed any relapse due to the ovarian transplant.

In conclusion, the present study further enforces the ability of frozen/thawed ovarian tissue to restore fertility in women recovered from a cancer disease. Further, replacement of a relatively large amount of tissue from one ovary may facilitate an environment favouring pregnancy. Excising one whole ovary for freezing may be advantageous when an unforeseen situation occurs in which recurrence of the cancer happens simultaneously with the patient becoming pregnant and where the transplanted tissue is unlikely to survive renewed cancer treatment. This patient's remaining cryostored ovarian tissue provides her with the possibility for yet another transplantation.

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Conflict of interest None declared

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