Pregnancy after Transplantation of Cryopreserved Ovarian Tissue in a Patient with Ovarian Failure after Chemotherapy

TO THE EDITOR: Premenopausal women who undergo high-dose chemotherapy have a very high risk of ovarian failure. Cryopreservation of ovarian tissue with subsequent autotransplantation has effectively preserved fertility in an animal model, but its efficacy in humans has been uncertain. Eggs that were aspirated from cryopreserved ovarian tissue transplanted in heterotopic sites did not result in a pregnancy. A live birth was reported after transplantation of cryopreserved ovarian tissue in a woman who had undergone treatment for Hodgkin’s disease; however, since the woman had ovulated before transplantation, it is uncertain whether the egg came from the native ovary or the transplanted ovary. A recent report described a live birth after transplantation of fresh ovarian tissue from a fertile woman to her sterile monozygotic twin, but this approach does not involve preservation of fertility and hence is not applicable to women facing sterilizing chemotherapy.

We describe a live birth after in vitro fertilization following the transplantation of thawed cryopreserved ovarian cortical tissue into the ovaries of a 28-year-old woman who had ovarian failure after high-dose chemotherapy for non-Hodgkin’s lymphoma. Ovarian tissue (containing many primordial follicles) was harvested after administration of a second-line conventional chemotherapy regimen, before treatment with high-dose chemotherapy (Fig. 1A). The patient’s menses ceased after the high-dose chemotherapy. During the ensuing 24 months, the amenorrhea persisted, and laboratory testing consistently revealed high levels of follicle-stimulating hormone and luteinizing hormone (40 to 104 IU per liter) and undetectable levels of antimüllerian hormone and inhibin B — findings consistent with ovarian failure (Fig. 1B).

At 24 months, the patient remained free of disease and requested autotransplantation of the ovarian tissue in an attempt to restore fertility. After approval from the institutional review board and the patient’s written informed consent had been obtained, a laparotomy was performed; strips of thawed ovarian tissue were transplanted to the left ovary, and small fragments were injected into the right ovary (Fig. 2). Eight months after transplantation, the patient spontaneously menstruated. Basal levels of antimüllerian hormone (which previously was undetectable) were found to be high, a finding consistent with the presence of active, early-stage, growing follicles. This change was followed by a rise in inhibin B levels to the levels reported in ovulatory women (Fig. 1B). Ultrasonography revealed a preovulatory follicle in the left ovary. The time from transplantation to recovery was compatible with the time needed for the growth and maturation of primordial follicles.

Nine months after transplantation, the patient had a second spontaneous menstrual period. The level of follicle-stimulating hormone was 7.9 IU per liter, the level of luteinizing hormone 6.8 IU per liter, the level of estradiol 118 pg per milliliter, and the level of progesterone 0.5 ng per milliliter. A decision was made to perform in vitro fertilization. After a modified natural cycle, a single mature egg with a large cumulus was retrieved. The egg was fertilized in vitro with sperm from the patient’s husband, and two days later, a four-cell embryo was transferred to the uterus. Serum testing for human chorionic gonadotropin was positive 12 days after the embryo transfer. Repeated ultrasonography during the pregnancy showed normal fetal growth and development. At 38 weeks 5 days of gestation, a healthy-appearing female infant weighing 3000 g...
**Graph A**

- **Diagnosis**
- **Cryopreservation of ovarian tissue**
- **Transplantation**

- **First-line Chemotherapy**
- **Second-line Chemotherapy**
- **High-dose chemotherapy**
- **Pregnancy**

- **Months**

- **Ovarian failure at 24 mo**

**Graph B**

- **Follicle-Stimulating Hormone (IU/liter)**
- **Antimüllerian Hormone (ng/ml)**
- **Inhibin B (pg/ml)**

- **Estradiol (pg/ml)**
- **Progesterone (ng/ml)**

- **Days**

- **Months**

- **Eight Months after Transplantation**

- **Transplantation**
was delivered by cesarean section. The Apgar scores were 9 at one minute and 10 at five minutes.

Transplantation of ovarian tissue is associated with a theoretical risk of grafting malignant cells. Tissue was harvested in this patient after therapy, with no evidence of disease, and conventional histologic analyses showed no cancer cells.

Although we cannot rule out the possibility that the egg was derived from the native ovary, we consider this possibility very unlikely, given the consistent evidence of ovarian failure after high-dose chemotherapy and the timing of restoration of ovarian function after transplantation. The hormone levels provided strong evidence of the success of transplantation, despite its being performed after initial chemotherapy, rather than of the activity of a few residual follicles. Our results indicate that fertility preservation with cryopreservation and orthotopic transplantation of ovarian tissue can be successfully performed in humans.
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