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Ovarian tissue cryopreservation and transplantation in a young patient with cervical cancer: the first successful case in Korea

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Summary

Cytotoxic treatment, such as chemotherapy and/or radiotherapy, can cause severe gonadal damage, resulting in premature ovarian failure and infertility. Fertility preservation plays an important role in the care of young reproductive women with cancer who desire future fertility. Ovarian tissue cryopreservation and transplantation is an effective option to preserve patient fertility and to restore gonadal endocrine function. To the best of the authors' knowledge, this is the first case of a successful ovarian tissue transplantation after cryopreservation, and recovery of endocrine function for a cervical cancer patient in Korea. In order to provide better treatments for preserving fertility in cancer patients, physicians should recognize and consider many options for fertility preservation and provide timely information and appropriate counseling.

Key words: Cervical cancer; Ovary; Tissue; Cryopreservation; Transplantation.

Introduction

Cytotoxic treatment, such as chemotherapy and/or radiotherapy, can cause severe gonadal damage, resulting in premature ovarian failure and infertility [1]. Fertility preservation plays an important role in the care of young reproductive women with cancer who desire future fertility [2]. Ovarian tissue cryopreservation and transplantation is an effective option to preserve patient fertility and to restore gonadal endocrine function [3]. Here, the authors report the first case of successful ovarian tissue transplantation after cryopreservation in Korea.

Case Report

A 23-year-old young woman presented with postcoital bleeding. She underwent cervical cancer screening with Pap smear and HPV DNA test at a private hospital. The results showed a low-grade squamous intraepithelial lesion and a HPV 16-positive status. Colposcopic biopsy was performed at a tertiary academic hospital and a squamous cell, non-keratinizing carcinoma was reported by a gynecology pathologist. The involvement of the parametrium was determined by rectal examination. Pelvic MRI showed a 4-cm mass lesion at the uterine cervix with invasion of parametrium. A PET-CT was performed for metastatic cancer evaluation and it revealed the intense hypermetabolic lesion at the posterior uterine cervix with max SUV 11.8. Finally, she was diagnosed with cervical cancer with parametrial invasion (squamous cell carcinoma, Stage IIB) in 2011 (Figure 1).

Pelviscopic of both ovaries' partial resection for ovarian tissue cryopreservation and ovarian transposition was performed to preserve patient's ovarian function. Ovarian tissue cryopreservation (2×3×1 mm or 3×3×1 mm in size, about 150 pieces) was performed using vitrification prior to concurrent chemoradiation therapy (CCRT) with cisplatin plus pelvic radiation therapy. Vitrification solution consisted of 38% ethylene glycol and 0.5 M trehalose in basic solution with 6% HSA in MEM-GlutaMAX at 10% [three minutes at room temperature (RT)], 50% (one minute at RT), and 100% (one minute at RT). All tissues were placed on an electron microscope grid and divided into 34 cryo-tubes (about 4-5 samples in each cryotube). After vitrification, they were plunged into the liquid nitrogen. Institutional Review Board approval was obtained before ovarian tissue cryopreservation from Korea University Anam Hospital.

During the CCRT, however, sequential measured hormone levels indicated that patient developed chemo-radiotherapy-induced premature ovarian failure after cancer treatment. Hormone replacement treatment was administrated before ovarian tissue transplantation. During the follow-up, no tumor recurrence was detected for five years after cancer treatment. The patient and family requested ovarian tissue transplantation and it has been performed with sufficient information regarding frozen ovarian tissue transplantation. Some tissues were thawed to evaluate the ovarian follicles and tissue damage before transplantation. All tissues were thawed in the operating room and patient was prepared to receive the tissue samples under general anesthesia. Thawing solution consisted of 0.5 M sucrose in basic solution (five minutes at RT), 0.25 M sucrose in basic solution (five minutes at RT), 0.125 M sucrose in basic solution (five minutes at RT), and basic solution (five minutes at RT, three times).

With the patient in the supine position, the abdomen was surgically prepared and Pfannenstiel incision was performed. After cutting the subcutaneous tissue and fascia, the peritoneum was opened. Both lateral pelvic walls were opened and three pockets were prepared in each pelvic wall to place the ovarian tissue. After all tissue samples were placed in the retroperioneum, pelvic lateral wall was closed by continuous interlocking sutures with vicryl 3-0. The patient received successful ovarian tissue trans-

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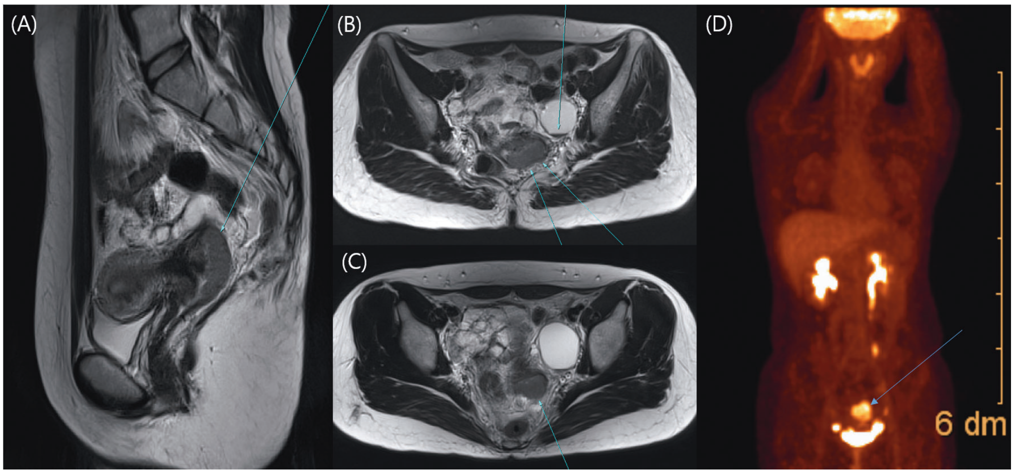

Figure 1. — (A-C) A Pelvic MRI shows a 4-cm mass lesion at the uterine cervix with invasion of parametrium (slightly T2 high signal intensity). (D) A PET-CT is performed for metastatic cancer evaluation and it reveals an intense hypermetabolic lesion at the uterine posterior cervix.

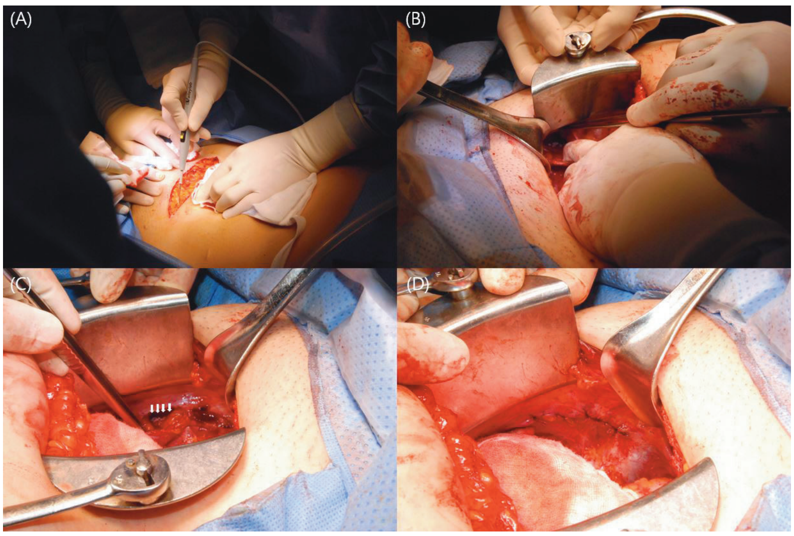

Figure 2. — (A-B) Both lateral pelvic walls are opened and three pockets are prepared for each pelvic wall to place ovarian tissue. The patient received successful ovarian tissue transplantation in pelvic lateral wall. (C) White arrows show position of transplanted ovarian tissue in the pelvic lateral wall. (D) After placement of all tissue in the retroperitoneal space, pelvic lateral wall is closed by continuous interlocking sutures with vicryl 3-0.

plantation in pelvic lateral wall (Figure 2). Hormone levels were assessed every month after transplantation. Finally, a rise in estradiol level and a decrease in FSH level were detected five months after transplantation (Figure 3).

Discussion

Transplantation of cryopreserved ovarian tissue has shown to be a potential method for recovery of ovarian endocrine function in young women after cancer treatment. Advantages of ovarian tissue transplantation are not only fertility preservation, but also restoration of endocrine function in young women after cancer treatment [4]. To the best of the authors' knowledge, this is the first case of successful ovarian tissue transplantation and recovery of endocrine function after cryopreservation in Korea.

Ovarian tissue cryopreservation and transplantation are the main option to preserve fertility in patients with cancer who require cancer treatments without delay or do not want to undergo ovarian stimulation. For prepubertal girls with cancer, ovarian tissue freezing is the only option for fertility preservation. The first case of human ovarian tissue cryopreservation and auto-transplantation was reported in 2000 [5]. Human ovarian tissue transplantation is still considered as an investigational method. However, to date, a total of 86 live births and nine ongoing pregnancies were reported after transplantation of frozen-thawed ovarian tissues in the world [6].

Two methods are used for ovarian tissue cryopreservation, namely slow freezing and vitrification [7]. Slow freezing demonstrated complete stability in many studies, and is the method to freeze the tissues slowly by controlling liquid nitrogen or methanol temperature. Vitrification is the method to freeze tissues rapidly to place them into liquid nitrogen after removing the water from cells using a cryoprotectant. Although slow freezing has demonstrated stability, its disadvantages are expensive equipment and long-term procedure. Vitrification does not require expensive equipment and a complicated process. Vitrification showed better outcomes than slow freezing for embryo or oocyte, but little information is available for tissues cryo-

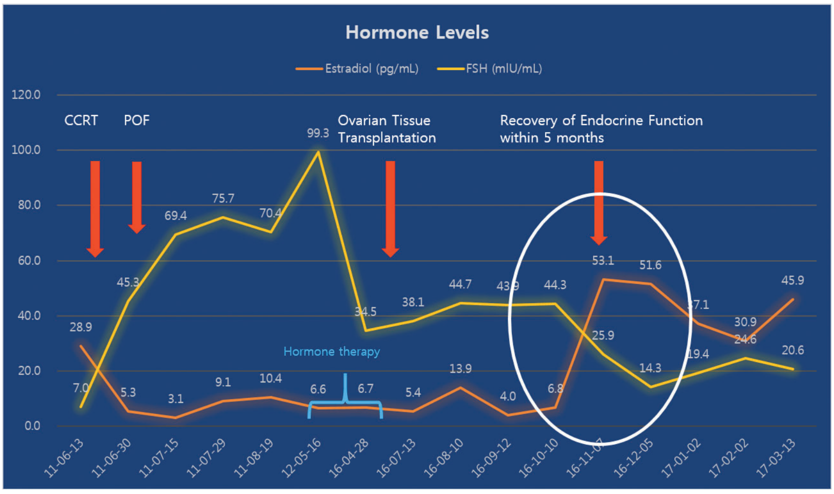

Figure 3. — Recovery of endocrine function occurring within five months after the frozen-thawed ovarian tissue transplantation. A rise in estradiol level (orange) and a decrease in FSH level (yellow) are observed.

preservation. However, human ovarian tissue cryopreservation and transplantation have the potential to preserve fertility in reproductive women with cancer and reduce the risk of premature ovarian failure or infertility in young patients with cancer.

Advantages of ovarian tissue transplantation are not only preserving fertility, but also restores endocrine function in young women after cancer treatment. In a review of successful orthotopic frozen-thawed ovarian reimplantations, restoration of ovarian activity was observed in at least 92.9% of patients between 3.5 and 6.5 months after transplantation [4, 8]. In this case, recovery of endocrine function was detected five months after transplantation.

The duration of endocrine function after frozen-thawed ovarian tissue transplantation is still uncertain. Kim described that the endocrine function lasting for seven years can be established with heterotopic transplantation of cryobanked human ovarian tissue. This information demonstrates that young cancer survivors with premature ovarian failure can benefit from this technique [9]. In the UK, researchers indicated that the duration of graft life is greater than seven years [10]. Undoubtedly, the duration of graft function will depend on several factors, namely on age at the time of cryopreservation, baseline ovarian reserve, history of cancer treatment, techniques of ovarian tissue preparation, freezing-thawing protocols, number of grafted cortical tissue, techniques and sites of transplantation, degree of ischemia after transplantation, and number of follicles in the ovarian grafts [9, 10].

Based on the present review, ovarian tissue cryopreservation and transplantation in women diagnosed with cancer before treatments is an effective option to preserve their fertility and to restore gonadal endocrine function. In this case report, the restoration of ovarian activity is not sufficient for young reproductive women but the authors believe that this successful ovarian tissue cryopreservation and transplantation will open a new research field in human reproductive biology and may offer new opportunities and possibilities for fertility preservation in women with cancer. In order to provide better treatments for preserving fertility in these patients, physicians should recognize and consider many options for fertility preservation and provide timely information and appropriate counseling.

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