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Editorial

An Established Technology Gets a New Application: Reimplantation of Autologous Ovarian Tissue to Treat Menopausal Symptoms

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Introduction

In 1954 and 1956, Deanesly [1] and Green, et al. [2] were one of the first to experiment with the freezing and thawing of animal ovarian tissue. In the first half of the 20th century, the art of tissue cryopreservation was at its infancy with glycerol being the only cryoprotectant available [3]. Glycerol is a poor cryoprotectant and, therefore, early research showed very limited success [4]. Additional cryoprotectants became available during the 1990s leading to successful ovarian tissue cryopreservation, transplantation, and resumption of fertility studies in animals and humans [3,5,6].

In 1983, Trounson and Mohr [7] reported what appeared to be the first ever pregnancy in a human following preservation and transfer of an [8] cell embryo. This was followed by the report of the first human live birth after ovarian cryopreservation and transfer with more cases to follow [8,9]. Sonmezer and Oktay [10] performed a metanalysis, which included 21 studies on oocyte cryopreservation. They found that the mean oocyte survival rate after thaw, mean fertilization rate, and mean pregnancy rate per cryopreserved/thawed oocyte was 47%, 52.5%, and 1.52%, respectively.10 In a recent interview, Oktay, et al. [11] cited the first report of resumption of ovarian endocrine function following orthotopic transplantation of frozen banked ovarian tissue.

Summary

The preservation and autologous transplantation of endocrine glandular tissue is not limited to the ovaries. In 1977, Wells, et al. [12] introduced reimplantation of autologous cryopreserved parathyroid tissue as a treatment modality of hypoparathyroidism. Wagner, et al. [13] simplified the methods of parathyroid gland cryopreservation and storage. For cryopreservation, the parathyroid tissues were cut into cubes of 1 mm in length. The time between parathyroidectomy and replantation of cryopreserved tissue was 5 months on average (range, 0.5 to 15 months). Follow up examinations in 25 patients were performed 6 months to 120 months (median: 40 months) postoperatively. In all patients, the autografts functioned well and most of the patients did not require any additional medication [13].

Despite technical difficulties with cryopreservation at that time, pioneering research in parathyroid autotransplantation was performed in the 70s by Alveryd, et al. [14] and Wells, et al. [15,16], Alveryd, et al. [14] described six patients with primary parathyroid hyperplasia who had parathyroid autografts. In 1976, Wells, et al.15 reported an additional four patients with primary parathyroid hyperplasia who were treated by total parathyroidectomy and auto transplantation of parathyroid tissue inserted into the forearm muscle. All of these patients remained norm calcemic at 9 and 13 months, respectively. Good graft function was documented further by detection of a higher concentration of parathyroid hormone in the patients' blood. Hormonal activity of auto transplants, if excessive, can be adjusted by removing some transplanted tissue [15]. Additional implantation can be carried out if the amount of tissue initially implanted had been insufficient or if the transplanted parathyroid tissue failed to survive. In the rat model, parathyroid isografts functioned normally after cryopreservation for up to 9-12 months [16]. Wells, et al. [15] grafted autologous parathyroid tissue, frozen for six weeks, into a patient who had had a total parathyroidectomy for renal osteodystrophy. The graft was still functioning 18 months after the procedure.

Research on oocyte and ovarian tissue cryopreservation has gained momentum in recent years [17]. Oktay, et al. [18] reported their experience with auto transplantation of ovarian tissue in cancer patients to alleviate premature menopause and preserve fertility.

Inspired by the success in parathyroid tissue auto transplantation and recent advances in ovarian tissue cryopreservation technology, we propose to apply this technique to treat menopausal symptoms.19 We established an ovarian tissue cryopreservation bank in 2000 in collaboration with Professor E. Zharov (Russian Federation) with the goal to collect and preserve ovarian tissue retrieved with the patient's consent during indicated obstetrical or gynecological procedures (cesarean section-15, minilaparotomies and tubal ligation – 12, gynecological surgeries for benign conditions – 22). Since our computer-assisted search failed to find an ovarian tissue bank with similar goals, we used the experience of the ovarian transplantation program in Denmark for the purpose of preserving ovarian tissue to combat infertility. The ovarian transplantation program started in Denmark in 2000 (800 women have had their ovarian tissue frozen) [19]. For this study, the researchers studied the outcomes of women who had received transplantation between 2003 and June 2014. The functional life span of the grafts varied between one and ten years; grafted tissue robustly restored ovarian function.

In 2000, we initiated a research protocol at Nassau University Medical Center (Petrikovsky BM, Ansari AH, Beers PG, et al. which stated as follows:

After obtaining approval from the Institutional Review Board, patients, ages 40 and under, will be included in this study. Normal ovarian function in these cases is to be established prior to ovarian sampling, using such methods as; hormonal assay, pelvic ultra-sonography and endometrial sampling. Opportunistic ovarian biopsy will be performed by means of laparoscopy or laparotomy. Ovarian cortex will then be separated from its stroma and divided into several pieces. Each piece will be placed in a special cryovial container and filled with a special cryoprotectant solution (dimethyl sulfoxide, human serum albumin factor V). The cryovials are then transferred to a special aluminum case and lowered into a liquid nitrogen tank where it is stored until such time that it is used for autologous transplantation. To assess potential structural alterations, it is the further aim of this study to examine a portion of the ovarian tissue by means of TEM, prior to and after freeze thawing. Whenever, clinically indicated, the specimen will be thawed and reimplanted, subcutaneously, in a cosmetically acceptable body site. The function of the transplanted ovarian tissue will be assessed clinically by re-evaluation of symptomatology, as well as such techniques as bone density analysis, ultrasonography, and hormonal assay."

None of the patients experienced complications directly related to opportunistic ovarian sampling. Now, 20 years later, histological assessment of preserved ovarian strips (15 samples) demonstrated ovarian tissue adequate for reimplantation, 6 samples contained visible icicles and were judged unfit for transplantation.

Conclusion

- Ovarian autotransplantation may be considered for treating menopausal symptoms in carefully selected and motivated patients.
- Opportunistic ovarian sampling is not associated with additional complications.
- The majority of preserved specimen appear fit for transplantation based on their histological appearance.
- Long-term outcomes of ovarian autotransplantation to treat and/or prevent menopause symptoms, remain unclear.

Acknowledgement

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Conflict of Interest

No conflict of interest.

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