

Ovarian tissue cryopreservation– Where are we today?

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Nowadays, ovarian tissue cryopreservation (OTC) is an increasingly prevalent method of preserving fertility amongst the patients across the globe.

This is the method of choice in pre and peripubertal girls for fertility preservation. Indeed, this is also being utilized for women in the reproductive age group, who do not have the stipulated time of approximate 2 weeks for oocyte or embryo cryopreservation before they proceed for gonadotoxic therapy.

In OTC, apart from preserving fertility, there is an added advantage of resumption of the ovarian endocrinal function following transplantation of the ovarian tissue.^[1]

The procedure involves laparoscopic removal of the ovarian cortical tissue, and in some cases of very young children, even the entire ovary may be removed. This tissue is then processed and fashioned to form strips of $1 \times 2 \times 2 \text{ cm}^3$ approximately. Subsequently, the tissue is then dehydrated and cryopreserved by slow freezing or by vitrification (ultrarapid) freezing methods. These strips are usually stored in independent vials in liquid nitrogen at a temperature of -190°C .

Once the patient is declared free of the disease, the tissues are thawed and reimplanted in the pelvic cavity – over the ovary from which the graft was taken (orthotopic site) or other heterotopic sites as in the pelvic areas usually – ovarian ligament, broad ligament, etc., or even the subcutaneous/intramuscular tissues.^[1]

Although, hematologic malignancies comprise of the major chunk of patients undergoing the OTC. Dissemination of tumor and reintroduction of malignancy posttransplant is of major concern amongst these patients. To rule out malignancy, various methods like immunohistochemistry and molecular biology analysis of the ovarian tissue are performed.^[2,3]

Growing the tissue in immunodeficient mice and then looking for metastasis is another method which is being used for preventing reintroduction of the malignant tissue.

Once performed meticulously, by the slow freezing method or vitrification (ultrarapid cooling), post thawing the ovarian tissue regains almost 95% of the endocrine function, which would be evident both clinically with the resumption of menstrual cycle and on the ultrasound. The resumption of endocrine function is considered if the cases show follicle stimulating hormone (FSH) of $<25 \text{ IU/L}$, luteinizing hormone (LH) of $<15 \text{ IU/L}$, and estrogen of $>200 \text{ pmol/L}$, posttransplant.^[1]

The patient characteristics which further influence the efficacy of the transplant are: the age at transplantation, cryopreservation before gonadotoxic chemotherapy, the amount of ovarian tissues transplanted, and the site of transplant.

The conception rate posttransplant varies widely according to the latest meta-analysis with over 700 patients; the pooled rates were 37% (95% confidence interval (CI): 32%–43%) for pregnancy, and 28% (95% CI: 24%–34%) for live birth.^[4] Fresh ovarian transplants have also been reported amongst twins with similar genetically similar siblings. So far, 15 pregnancies and eight births have been reported. Median for the average duration for which the graft lasted was 2.5 years with a range of 0.7 to 5 years.^[1]

Amongst the patients who have a conception following the ovarian transplantation, almost half of the patients would conceive spontaneously and other half would do so with the assisted reproductive techniques (ART) procedures. The world's first fresh ovarian allogenic transplant was reported by a surgeon in New York in the year 1906.^[5]

Morris *et al.* performed an ovarian tissue grafting directly into the uterine cavity in order to bypass the fallopian tubes. The endocrinological function resumed after a few months, which was confirmed by the onset of regular menstrual cycle.^[5] There was a controversial report of pregnancy also taking place 4 years after the procedure.

In the subsequent years, there were several attempts at transplant between 1950 and 1970, mainly on animal models.

It was later in the year 1999 that a well-documented ovarian transplant was performed with restoration of the endocrinological functions in a patient with premature menopause. The ovarian function was demonstrated for up to at least 6-month posttransplantation by follicular growth in response to gonadotropin stimulation, confirming the long-term survival of the tissue.^[6,7]

In the year 2004, Donnez *et al.*^[8] reported the first successful orthotopic transplant, which was followed by a live birth. The procedure involved removal of the tissue followed by autotransplantation. This was followed by resumption of the endocrinological functions and later pregnancy.

Although this was the first pregnancy, but a few authors expressed concerns as the patient had received drugs of low toxicity and the serum progesterone levels were elevated at the time of transplantation in these patients.^[8,9]

A year later in 2005, Meirow *et al.*^[10] reported a case of pregnancy following autotransplantation of the ovarian tissue in a patient receiving gonadotoxic therapy for Hodgkin lymphoma. Patient had elevated gonadotropins to confirm the menopausal status. Ovarian endocrinological function resumed 8 months following the transplant. Patient had a successful pregnancy with an in vitro fertilization followed by an embryo transfer, and subsequently she had a live birth following it.^[11]

The procedure has gained ground and is now accepted and performed all over the world.

Following which it took another 16 years, in March 2020, for the experimental tag to be removed. In 2017, the Belgian group reported an analysis of 548 cases who underwent OTC and amongst them only 3.9% (4) underwent retransplantation. Following this, seven healthy babies were delivered making the live birth rate as 33%.^[12]

Since the time of inception, over 1000 cases of ovarian tissue transplantation have been performed worldwide.

Newer additions in the ovarian transplantation are the use of robotic-assisted techniques.

Very recently, Oktay *et al.*^[13] reported a case series with robotically assisted autotransplantation and the use of extracellular matrix creating a scaffolding, also called the

artificial ovary, to prevent the loss of the primordial follicles in the early period posttransplantation.

In the current era, the spectrum of OTC has extended beyond the indications of oncofertility preservation.

It is being studied as a cell-based hormone replacement therapy (HRT) to allay the menopausal symptoms. The heterotopic sites are commonly used in cases of cell-based HRT. Anterior abdominal wall and even the wrist are sites which have been reportedly used for reimplantation of the tissue.

It can be used for inducing puberty in patient with anticipated premature ovarian failure. This group of patients would encompass people with Turners syndrome, carriers of fragile X syndrome, etc., who are likely to develop premature ovarian failure at a much younger age than their contemporaries.

It is being studied as a replacement of modern wedge resection in the patients with severe polycystic Ovarian Syndrome (PCOS).

CONCLUSION

OTC is a well-established method for fertility preservation and is widely being used in the prepubertal age group. The indications for its use are expanding as it is now emerging as a form of cell/tissue-based hormonal therapy in patients who wish to postpone menopause or allay the postmenopausal symptoms.

Newer innovations of using extracellular matrix scaffold (artificial ovary) to improve the neovascularization are being studied with encouraging outcomes.

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Conflicts of interest

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Rupali Goyal

Apollo Assisted Reproduction Unit, Indraprastha Apollo Hospital, Sarita Vihar, New Delhi, India


Address for correspondence: Dr Rupali Goyal, Clinical Coordinator, Senior Consultant, Apollo Assisted Reproduction Unit, Indraprastha Apollo Hospital, Sarita Vihar, New Delhi, India.
E-mail: rupalibassi@hotmail.com

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