Editorial

Fertility preservation: Ovarian tissue cryopreservation (OTC) revisited

Every woman is conferred with a secure and nonreplenishable reserve of germ cells. The maximum numbers of germ cells are present at 20 weeks of fetal life when approximately 6–7 million germ cells are existent. Consequently, a regression in the number of germ cells is witnessed, because gametogenesis does not occur any further. There are around 1–2 million germ cells present at birth, but however, by the time of puberty, their number is reduced to approximately 300,000 cells. Subsequently, a number of oocytes begin to mature throughout the reproductive years, with one or a few of them, becoming dominant during each menstrual cycle, whereas the others undergo atresia.[1]

The regression in the total number of oocytes continues with the age notwithstanding whether the woman is ovulating or not. There is an accelerated rate of follicular loss at the age of about 37 years, which ensues when the number of follicles touches approximately 25,000.[2] Only 1000 or fewer follicles remain by the time menopause ensues.

The various diseases affect the germ cell maturation or their numbers due to the treatments offered to nullify the pathology.

The measure of cure of several diseases that affect children and young adults has enhanced considerably thanks to the expansions in the diverse fields of medical sciences. Fertility epitomizes a vital issue in the psychological condition for the couple, which implies conceiving with their own gametes and fulfilling their dream of parenthood. The conceivable alteration in the reproductive potential of young child or adult with protracted illness or genetic disorder is very often accepted as a blow to their aspirations of starting families. This is equally a challenge for the parents and relatives of young unfortunate individuals. The situation has developed into a fundamental subject to be discussed with all the young adults, as a crucial prospect for them to parent their own biological children post-treatment. Providing fertility services to adolescents, adults, and children at a specific risk of premature ovarian insufficiency or failure is a challenge that reproductive medicine specialist across the world are rising too.

Of late, assorted innovative technologies have been established to offer the hope of preserving the reproductive potential in young patients when diagnosed with hematological, autoimmune, benign or malignant diseases, or genetic diseases where fertility is at risk.

The prospect of fertility preservation denotes a vital issue in young women with anticipated premature ovarian insufficiency. Such women are at psychological stress wondering about the effect of treatment on future fertility. The lack of reliable fertility markers makes the job of reproductive biologist even more difficult and challenging.[3] The intricacy of folliculogenesis along with the challenges in the oocyte and ovarian cortex freezing elucidates the reason for difficulty in female fertility preservation even though sperm cryobanking has been available for several years.

Centered on the age of the patient and the type of disease and its extent, the methodologies toward fertility preservation contrast momentously. The conservative fertility preservation methods include administering gonadotropin-releasing hormone agonists for the prevention chemotherapy induced gonadotoxicity or oophropexy to avoid radiation induce preservation in majority of young women is still experimental. Common alternatives for the preservation of female fertility include embryo, oocyte, and ovarian tissue cryopreservation (OTC).[4-6]

HISTORICAL BACKGROUND

One of the pioneering works in the field of human oocyte cryopreservation was conducted by Hovatta.[7] Apart from comparing ovarian tissue freezing using DMSO and sucrose and a combination of 1–2 propanediol, he also stated that the human ovary is cryoresistant to the freeze thaw protocol.

It was in the year 1996 that Newton *et al.*[8] conducted a research into the human primordial follicles and stated that ovarian cortex could sustain cryofreeze procedures. It was 4 years later in the year 2000, when the first

orthotopic transplantation was performed. Oktay and Karilkaya[9] performed it in a 29-year old with harvesting and latter transplant of ovarian cortex. The patient had undergone bilateral oophorectomy for a nonmalignant disease. Strips of tissue were thawed and sutured underneath the pelvic peritoneum by laparoscopy. From the graft, blood flow and ovulation were established. In the year 2001, Radford *et al.*[10] reported ovarian cortical strips grafting orthotopically in a 36-year-old patient who underwent right oophorectomy with cryopreservation of ovarian tissue prior to experiencing high-dose chemotherapy for a Hodgkin's lymphoma. After the transplantation, the patient witnessed a period of fall of Follicle stimulating hormone (FSH) and Luteninzing Hormone (LH) levels.

Few years later, Leporrier *et al.*[11] reimplanted the left ovary subcutaneously into the arm before the radiotherapy initiation in a patient with Hodgkin's disease. Oktay *et al.* had performed heterotopic transplantation of fresh tissue in the forearm in two patients. He reported performing percutaneous oocyte aspiration with *in-vitro* maturation (IVM) and Intracytoplasmic Sperm Injection (ICSI).[12]

In 2004, Donnez *et al.*[13] reported the first live birth in a patient with Hodgkin's lymphoma after autologous orthotopic transplantation from frozen-thawed ovarian cortex. Ovarian cortex was cryopreserved before the gonadotoxic treatment was initiated, and thawed cortical strips were transplanted beneath the hilum of the inactive right ovary into the peritoneal window. In the year 2005, Meirow *et al.*[14] reported pregnancy from *in-vitro* fertilization in a patient with Hodgkin's disease, postchemotherapy, that resulted in a live birth. Spontaneous pregnancy with live birth from the transplantation of ovarian cortical graft in monozygotic twins was reported by Sibler.[15] Fresh ovarian tissue was harvested from one healthy sister and was transplanted to her monozygotic twin, who was undergoing premature ovarian failure, which led to spontaneous pregnancy and eventually, live birth.

In the recently revised Practice Committee Opinions, OTC and its current status are still experimental. It was further recommended that embryo and ovarian cryopreservation should be offered in all patients undergoing gonadotoxic treatment.[16,17] The surgical removal of ovarian tissue yields an abundance of primordial follicles and causes no delay in cancer treatment initiation. OTC is the only option to preserve fertility in young patients with cancer who have recently been exposed to chemotherapy treatments, because it mainly preserves primordial follicles, which are not subject to the deleterious effects of chemotherapy on growing and mature follicles.

INDICATIONS FOR OVARIAN TISSUE CRYOPRESERVATION

OTC is an option for patients who require urgent gonadotoxic treatment with alkylating agents for bone marrow ablation in young or to manage aggressive malignancies when there is scarce time to perform the ovulation induction, oocyte retrieval, and cryopreservation of oocytes and/or embryos. The only option available for fertility preservation in young girls who are prepubertal or in women who have hormone-sensitive or aggressive malignancies is OTC.[14,18-23] As brought out earlier, women anticipating hematopoietic stem cell transplantation for the treatment of benign hematologic diseases (sickle cell anemia, thalassemia major, aplastic anemia) and women with autoimmune diseases that have failed to respond to immunosuppressive therapy may resort to prophylactically cryopreserve ovarian tissue.[21] Fertility preservation in patients with genetic mutations that pose a high risk for premature ovarian failure is other potential indications. Turner syndrome is a common indication for performing OTC. This technique should not be offered to women who wish to delay childbearing or women with benign conditions such as ovarian cysts that are best managed with fertility-sparing surgery.

It has been observed that the management of malignancy is usually influenced by the fertility concerns of the patient. Indeed, a web-based survey conducted by Partridge *et al.*,[24] in the year 2004 showed that in as many as 29% of patients with breast cancer, the management protocols were modified on the basis of the fertility status.

The studies of OTC and transplantation date back to 1950s. Although it is considered to be experimental by the American Society of reproductive medicine (ASRM) and American Society of Clinical Oncology (ASCO), its unmistakable benefits have led to the increased use of this technology and promising results in recent years because of the ever-increasing research in the field of cryoprotectants and better cryofreezing equipment. The technology is no longer considered experimental in Israel.

Ovarian tissue autotransplantation in postpubertal women is efficient of restoring fertility with over 80 live births currently reported with a corresponding

pregnancy rate of 23–37%. The freshly reported successes of live births from transplant, both in orthotopic and heterotopic locations and the emerging methods of IVM, suggest new fertility options for young women and adolescent girls.[25]

A related study claims that nearly 95 children have been born or will be born in the near future from OTC in coming days. The data are reassuring and further suggest that the cryopreservation of ovarian tissue is becoming an established fertility preservation method.[26]

CONCLUSION

Current studies' available data in the literature indicate that ovarian tissue transplantation is feasible and effective for preserving fertility. Therefore, young women undergoing gonadotoxic chemotherapy should be advised to undergo cryopreservation of ovarian tissue. It should be noted that ovarian-tissue reimplantation could have a risk of remetastasis from ovarian cortical transplants, the exact incidence of which still needs to be studied. The autotransplantation of ovarian tissue in women with a history of systemic hematological malignancies is not recommended. In these situations, the reimplantation of isolated ovarian follicles might represent an interesting option in the future. In humans, research on whole-ovary freezing, IVM, and transplantation is still at its initial stages.

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