



Female Pediatric, Adolescent, and Young Adult Oncofertility: A Crucial but Neglected Aspect of Cancer Treatment

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Globally, more than 8.8 million women are diagnosed with cancer each year. About one-tenth of them are under the age of 40, which includes adolescent young women (ages 15 to 39 years) and pediatric girls (> 14 years) (1, 2). In recent decades, pediatric, adolescent, and young adult (PAYA) cancer outcomes have improved dramatically; 5-year survival rates now exceed 80%. As the number of cancer survivors increases, the rate of survived PAYAs who enter adulthood suffering from late cancer treatment complications will increase.

There are increasingly detailed data documenting that cancer treatments, including radiotherapy and chemotherapy, can lead to diminished ovarian reserve (DOR), infertility, and premature menopause, negatively affecting the survivors' quality of life (3). Definite cancer (and cancer treatment)-related infertility rates cannot be calculated because there are no definitive criteria to indicate that the patient had been fertile prior to undergoing the cancer treatments or it developed post-treatment. However, it is reported that women of reproductive age who undergo chemotherapy or radiation have a 40 - 80% chance of losing fertility (4). The effects of radiotherapy depend on the dose, site, duration of exposure, and frequency of treatments; the effects of chemotherapy are related to the type and cumulative dose of received chemotherapy.

In addition to radiation and/or chemotherapy in the case of gynecological cancers, patients may require partial or total surgical removal of reproductive organs, which also has obvious implications for fertility. Besides, cancer and its treatment can cause physical and emotional changes, including depression, anxiety, and sexual dysfunction; thus, the loss of fertility can be even more stressful for young women than cancer itself. For this reason, it is of paramount importance to pursue the best cancer treat-

ments available and discuss available strategies to preserve fertility in these vulnerable patients (5).

In 2006 - 2007, the "FertiPROTEKT network" and "Oncofertility consortium" were established to advance reproductive research and fertility preservation (FP) care for cancer survivors (6, 7). Later, in 2009, the "International Society for Fertility Preservation (ISFP)" was established as a pioneering academic society focusing on the importance of FP for cancer patients. Then, an increasing number of fertility preservation societies and networks were also formed in South Korea, Japan, India, Australia, and other countries. The net goal of all these efforts is to open up the new field of reproductive medicine and promote the advancement of FP in cancer patients.

The aim of FP technologies is to help cancer patients to preserve or protect their reproductive potential prior to exposure to treatments. Currently established and experimental options for FP include oocyte and embryo cryopreservation before gonadotoxic treatment, ovarian tissue freezing and autotransplantation, in vitro maturation (IVM), and ovarian protection techniques (8).

Cryopreservation refers to the cooling and storage of viable cells and tissues at ultra-low temperature, at which all biological function is slowed down or completely halted; thus, they can be preserved for future use (9). Embryo and mature oocyte cryopreservation requires at least one cycle of ovarian stimulation and oocyte retrieval. Therefore, while they have been shown to be a feasible, reproducible, safe, and effective approach, they are associated with important risks due to ovarian stimulation. The major limitations of these methods include delayed initiation of cancer treatment if ovarian hyperstimulation syndrome (OHSS) is developed and increased estrogen levels in estrogen-sensitive malignancies (10).

These two main methods of FP can be offered to post-

pubertal patients with the desire to have their biological children in the future. However, these cryopreservation methods cannot be offered routinely to pre-pubertal girls due to the inactive hypothalamic-pituitary-ovarian (HPO) axis. In these patients, in addition to risks associated with ovarian stimulation, another concern is that the process of ovarian stimulation and oocyte retrieval requires transvaginal ultrasound scans that necessitate a certain level of physical and psychological maturity. Centered on these biological properties, the most suitable FP options for pre-pubertal girls include ovarian tissue cryopreservation (OTC) for future autotransplantation, IVM, and ovarian protection techniques (11).

OTC involves laparoscopic removal of all or part of the healthy ovarian tissue containing eggs, followed by cryopreservation of the tissue for autotransplantation in the future (12). The tissue graft can be placed orthotopically in the patient's pelvic cavity (remaining ovary, ovarian fossa, or broad ligament) or can be heterotopically transplanted outside the pelvic cavity (forearm or rectus muscle).

The major advantage of OTC is that ovarian stimulation is not required, avoiding its potential complications, such as OHSS and delay in cancer development. Additionally, OTC does not require sexual maturity, making it a suitable option for pre-pubertal girls. While OTC is still considered investigational at some institutions, it fulfills the criteria for an "established method" (13). In December 2019, the Practice Committee of the American Society of Reproductive Medicine stated that OTC should no more be considered experimental/investigational, and it is an acceptable technique to be offered to patients seeking FP (14, 15).

However, autotransplantation of ovarian tissue from patients with particular types of cancers is associated with the risk of recurrent malignant disease due to the reintroduction of cancer cells (16). Besides, avascular grafting is associated with an increased risk of post-grafting ischemia and follicle atresia. On the other hand, in orthotopic transplantation, pregnancy can occur due to ovulation from the remaining ovary instead of grafted ovarian tissue (17).

IVM of oocytes is another method that does not require ovarian stimulation; however, it is still commonly considered an experimental approach. IVM was first offered to women with polycystic ovary syndrome (PCOS) or poor ovarian reserve who were at OHSS risk following gonadotropin stimulation (18). IVM approach involves the collection of immature oocytes from ovarian antral follicles with minimal or no stimulation, followed by their subsequent maturation in vitro. IVM can be done at the time of oocyte retrieval, or immature oocytes may be immediately cryopreserved for maturation at later stages. However, the number of reported live births after IVM oocyte cryopreservation is very limited.

Given the importance of FP decision-making for can-

cer patients, especially in PAYA, several guidelines and clinical recommendations have been developed in this context. However, recent studies have reported that most PAYA with cancer and their families did not receive acceptable and satisfying consultation from their healthcare professionals. In particular, they were not always informed about the impact of treatments on their future fertility, available options to preserve their chance to have their child in the future, and alternative family planning (19-21).

Some of the reasons that oncology (or pediatric oncology) clinicians and other medical teams are not willing to have these discussions include, but are not limited to, a lack of knowledge, limited financial resources, concerns about delaying treatment, poor prognosis, and incapability of patients/their family to handle that conversation on top of the many other issues they are emotionally processing (22, 23).

The practice of FP requires a multidisciplinary collaboration between oncologists, fertility specialists, and other involved medical teams prior to the initiation of cancer treatments. Clear information about fertility risks associated with cancer/treatments, adequacy of fertility-sparing approaches, evaluation of reproductive potential, and setting realistic expectations regarding future pregnancy should be provided to all pubertal or post-pubertal patients at the time of diagnosis, whether or not they decide to undergo FP (24, 25). Undoubtedly, FP is associated with unique clinical and ethical challenges regarding consent and beneficence for young cancer patients. FP is time-sensitive as it is better to be done prior to the administration of chemotherapy or radiotherapy. Discussions often take place just days after diagnosis of cancer, with treatment planned to start immediately. During this period, the patient experiences a high level of anxiety and distress. However, many patients claim that the concern about cancer-related infertility is an even more poignant situation than the cancer diagnosis or treatment itself. Besides, reports have demonstrated that the majority of survivors desire to have their own biological children after therapy, with one primary study reporting that 76% of survivors desire future children (26). In such vulnerable situations, healthcare providers play a crucial role in aiding patients and their families in making a shared decision about FP. Therefore, it is of paramount importance that clinician(s) provide clear and easy-to-understand information about cancer-related infertility, options for FP, costs, and logistics to patients and their families shortly after diagnosis.

Footnotes

Authors' Contribution: As a single author, Mino Taheri is responsible for the paper in its entirety.

Conflict of Interests: The author is a member of the editorial board and chairperson of the journal.

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