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Fertility Preservation Methods in Childhood and Adolescence Cancers: A Review

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Abstract

In childhood and adolescence cancers; survival rates increase with the use of treatment options such as hematopoietic stem cell transplantation, chemotherapy and radiotherapy. One of the long-term effects of primary disease and cancer treatment is the irreversible damage to gonadal tissues, resulting in impaired fertility. Especially chemotherapeutic drugs; causes germ cell defect, affects the secretion of pituitary hormone, and also damages the anatomical structures of internal genital structures such as the uterus.

Gonadal preservation methods are limited in prepubertal male patients. It is a good option to place the testicles in a different area before radiotherapy. Before chemotherapy or whole body irradiation, freezing of testicular tissue and ensuring pregnancy from frozen tissue is still in the experimental stage. After the ejaculation begins, obtaining and storing sperm is successfully done. A limited number of pregnancies were obtained oocytes frozen ovaries in the prepubertal girls. It is possible to freeze oocytes after puberty begins. In addition, recently, as a noninvasive method, gonadotropin-releasing hormone (GnRH) analogues have been used successfully, as it suppresses the hypothalamic-pituitary-gonadal axis and protects germ cells from cytotoxic effects.

This article aims to provide information on fertility preservation methods in patients receiving childhood cancer treatment

Keywords: Childhood cancers, fertility, gonadal protection

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Introduction

The survival rates of child and adolescent cancer patients have recently been increasing with the use of different treatment options such as chemotherapy, radiotherapy, and hematopoietic stem cell transplantation (HSCT). In the last decade, pediatric cancer survival rates have exceeded 80%.[1] These developments have led to a higher desire in patients to have children in the long term.

Before starting cancer treatment, long-term and late effects of the treatment should be considered, as well as its acute side effects. An important issue regarding long-term effects that should be discussed with families is the risk of gonadal dysfunction and infertility. Long-term survival rates have resulted in increased patient concern for fertility, prompting advances in fertility preservation methods. Today, infertility risk and fertility preservation methods are considered together with families before starting cancer treatment to select an appropriate approach to protect gonadal function.

Highlights

- One of the most important side effect of cancer treatment is the long-term deterioration of gonadal functions. This situation can cause infertility and poor quality of life. With the onset of puberty, collection and storage of mature gametes becomes easy. There are various successful and standardized techniques. In the prepubertal period, the same success has not yet been achieved today.

Chemotherapeutic agents, radiotherapy, total body irradiation, and surgical procedures can disrupt gonadal function, causing germ cell defects, affect pituitary hormone secretion, and damage the anatomy of internal genitalia such as the uterus. Although solid tumor and hematologic malignancy treatments have been modified to reduce side effects, there is an ongoing interest in fertility-preserving treatments and assisted reproductive technology.

Alkylating agents are the drugs with the highest level of genotoxicity. These agents, frequently used in childhood cancers, can cause permanent germ cell damage depending on the cancer stage of the patient and the cumulative doses administered. Radiation therapy to the head, spine, pelvis, testicles, or whole body has detrimental effects on pubertal development and eventual fertility. This impact varies depending on the child's age when treated, their susceptibility, and the treatment dose and duration. Besides, the course of the primary disease also impinges on gonadal function (**Table 1** and **Table 2**).

In boys, due to their high mitotic index spermatogonia are highly susceptible to chemotherapy-induced damage, unlike Leydig and Sertoli cells. Posttreatment azoospermia can reach up to 82%, according to the type of chemotherapy.[3] A study on 214 adult male survivors of childhood cancer, who had received chemotherapy including alkylating agents only, reported normospermia in 48%, oligospermia in 28% and azoospermia in 25%.[4] Spermatogonia are more sensitive to radiotherapy than adult spermatozoa; 4 Gy may be sufficient for total destruction. Leydig cells are more resistant but can be damaged at doses of 20 Gy at prepuberty and 30 Gy at puberty.[5]

In women, radiotherapy and chemotherapy can cause premature decrease of the ovarian follicular reserve, resulting in primary ovarian insufficiency (POI) and infertility. POI is considered menopause before the age of 40. The absence of menstruation for more than three months should instigate relevant assessment. High follicle-stimulating hormone (FSH) values should also be premonitory in this regard. Another indicator of ovarian reserve in childhood cancer survivors is serum Anti-Müllerian Hormone (AMH) concentration. AMH levels are lower in patients with ovarian insufficiency due to cancer treatment than healthy controls, constituting a vital parameter to guide POI diagnosis.[6]

Acute ovarian failure occurs in 6% to 12% of childhood cancer survivors.[7] Infertility problems due to decreased ovarian reserve may even occur in women with regular

Table 2
Gonadal dysfunction risks in terms of chemotherapeutic agents[2]

Low	Moderate	High
Vincristine	Cisplatin	Cyclophosphamide
Vinblastine	Carboplatin	Ifosfamide
Bleomycin	Doxorubicin	Procarbazine
Mercaptopurine		Chlorambucil
Methotrexate		Chlormethine
Dactinomycin		Melphalan
		Busulfan

Table 1
Hypofertility risk after cancer treatment in children and adolescents regarding tumor pathology[2]

Low	Moderate	High
Nephroblastoma	Hepatoblastoma	Testicular or pelvic radiotherapy
Acute lymphoblastic leukemia Cerebral tumor (surgery alone or with cranial irradiation < 24 Gy)	Acute myeloblastic leukemia	Soft tissue sarcoma
Retinoblastoma	Soft tissue sarcoma Neuroblastoma	Hodgkin's lymphoma (Alkylating agents)
Soft tissue sarcoma	Osteosarcoma	Ewing's Sarcoma (metastatic)
Malignant germ cell tumors	Cerebral tumor (cranial irradiation > 24 Gy)	Chemotherapy before HSCT
	Ewing's sarcoma	Total body irradiation
	Non-Hodgkin's lymphoma	

menstrual cycles after cancer treatment.[8] The follicle pool is undiminished in the prepubertal period due to the absence of ovulation, so patients receiving chemotherapy are less affected in this period than in the pubertal period.[9]

Ovarian irradiation at doses lower than 2 Gy is sufficient to destroy the follicles. Since girls are born with an established pool of germ cells, susceptibility to radiation-induced damage increases with age.[5] Besides, pelvic radiation may adversely affect the uterine muscle and vessels, entailing a reduced uterine volume. Accordingly, an increased risk of pregnancy complications such as preterm birth, miscarriage, or intrauterine growth restriction may ensue.[10]

HSCT is the highest-risk treatment concerning gonadal dysfunction. The most common complication after HSCT for hematological malignancies, POI, develops in more than 90% of women.[11]

On the other hand, high-dose cranial radiotherapy (35-40 Gy) may affect the hypothalamic-pituitary region, causing hypogonadotropic hypogonadism. Decades of cumulative experience have substantiated no increase in congenital malformations in the biological offspring of survivors conceived naturally.[12]

The burden and cost of fertility preservation options differ for girls and boys. The alternatives should be evaluated concerning whether the patient should receive treatment in the preadolescent or postadolescent period. Some treatments are well-established empirically-supported, while others are still tentative. It is crucial to distinguish between clinically approved treatments and experimental ones when advising patients and families on fertility preservation options.

Fertility Preservation Options for Prepubertal Patients

Prepubertal Boys

Contemporary methods for gonad and gamete preservation in prepubertal male patients are mainly theoretical, except for testicular shielding or relocation from the field of radiation. Most techniques involve interventions to protect the testicles during cancer treatment. Primordial germ cells are sensitive to toxicity at all stages of puberty. During gonadal-sparing irradiation, the gonads can be temporarily relocated on the thigh or anterior abdominal wall.[13] This procedure is named as reverse orchiopexy.

Total or partial testicular tissue cryopreservation has mainly remained theoretical and is not routinely practiced. Similarly, testicular transplantation has not been successfully performed in humans yet; nevertheless, the birth of a primate from sperm produced after testicular autotransplantation has been a remarkable milestone.[14] Besides, animal studies have proven the efficacy of in vitro maturation of frozen testicular tissue as a fertility preservation method.[15] Currently, testicular tissue cryopreservation is successfully applied in patients ranging between 5 months to 34 years of age, but none of these have resulted in spermatozoa formation from the frozen tissue.[16] Only one study has reported spermatogonial stem cell transplantation by injection into the rete testes of seven patients treated for non-Hodgkin's lymphoma.[17]

Transplantation of testicular tissue is more complicated than similar applications involving the ovaries due to developmental differences between male and female gonads. In any case, testicular tissue cryopreservation may prove valuable since future treatment options may potentially render in vitro maturation or germ cell transplantation a reality.

In addition, the use of angiogenic factors, such as vascular endothelial growth factor, is reported to positively affect revascularization after testicular transplantation.[18]

Prepubertal Girls

Most fertility preservation methods for girls in the prepubertal period are experimental with unclear long-term results. Using the ovaries to produce mature eggs is not possible in prepuberty, which is also the case for oocyte and embryo cryopreservation.[19] Besides, oocyte in vitro maturation is still in the experimental phase.[20]

Some authors have recommended ovarian tissue cryopreservation (OTC) to preserve fertility in girls treated for cancer. In contrast to oocyte cryopreservation, functional ovarian tissue is cryogenically stored in OTC (removing part of the ovary or its cortex), which is currently the only promising fertility preservation method in prepubertal cancer patients.[21,22]

Preserving gonadal functions by applying this method is theoretically possible in prepubertal children since the ovaries contains more primary follicles in prepuberty. Once the treatment is complete, the stored ovarian tissue is unfreezed and transplanted back to the donor. Limited viability of autotransplant gonadal tissue, therefore, recovery of endocrine function appears more likely than recovery of reproductive function.[23] So far, only one live birth after autograft of cryopreserved ovarian tissue in a 9-year-old prepubertal girl has been reported, the youngest case in the literature.[24]

In adult females, more than 70 cases of live birth with cryopreserved ovarian tissue have been published. However, the functioning of the natural ovarian tissue probably enabled these pregnancies instead of the autotransplant tissue.[25,26]

Flow cytometry studies demonstrated the presence of contaminated leukemia cells in normal ovarian tissue samples from patients with leukemia and lymphoma taken before the initiation of therapy. This finding has raised concerns that tumor cells could return to the body after autotransplantation.[27]

Before radiotherapy, oophoropexy can be performed to protect the ovaries by removing them from the radiation field. However, minimal radiation exposure of the gonad may still be possible. In any case, while ovarian transposition is comparatively effective in preserving the endocrine functions of the ovary (almost 60%), fertility preservation is much harder, and only 15.3% of patients can achieve pregnancy.[28]

Fertility Preservation Options for Postpubertal Patients

Fertility preservation is easier in the postpubertal period when obtaining a mature oocyte or sperm is possible.

Adolescent Males

It is easier to obtain and store semen samples in boys in puberty, especially after ejaculation has begun. Sperm should be collected before cancer treatment to avoid compromising DNA integrity or sample quality. Infertility centers and andrology laboratories facilitate the long-term storage of samples. Some types of cancer, such as testicular cancer, leukemia, and Hodgkin's disease, may reduce sperm quality.[29]

Testicular aspiration or extraction, electroejaculation or obtaining sperm after micturition are alternative sperm retrieval methods.[30] In vitro maturation of spermatocytes into spermatids has been possible in cases of primary testicular failure without ejaculation, but fertility was rarely achieved.[31,32]

Pregnancy rates are higher with fresh sperm samples than frozen sperm. In cases with low sperm count, fertilization and pregnancy can be achieved by with intracytoplasmic sperm injection.[33]

It has been shown in animal studies that the use of G-CSF (Granulocyte Colony Stimulating Factor) after alkylating agent exposure has a protective and restorative effect on spermatogenesis by stimulating the proliferation of immature spermatogonia. It acts by binding to the surface receptor (CSF3R) of undifferentiated spermatogonia.[34]

Studies in mice have demonstrated that antioxidant agents such as melatonin alleviate busulfan-induced toxicity through the elimination of reactive oxygen radicals and apoptosis inhibition of spermatogonial progenitor cells.[35]

Adolescent Females

Pregnancy rates of up to 50% have been reported with cryopreserved oocytes in adult women, with an even higher expectation in younger women and adolescents.[36]

Oocyte cryopreservation before treatment has become routine in patients who are planned for gonadotoxic treatment.[37] This method involves controlled ovarian hyperstimulation (COH) with subcutaneous gonadotropin hormone injections over approximately ten days. Then, the patient is sedated and the oocytes are collected by fine needle aspiration under the guidance of transvaginal ultrasound. Since this method is invasive, its application in the adolescent age group is limited. In some cases, cancer treatment may need to be started immediately, and a week or more delay may be unacceptable. Besides, adolescents and their parents may be reluctant to ovarian stimulation and egg retrieval due to psychological and emotional reasons. Also, high estrogen levels can be reached during COH, leading to spontaneous ovulation before the eggs are collected. Furthermore, there is a risk of triggering hormone-sensitive cancers. However, these risks are reportedly eliminated using aromatase inhibitors and selective estrogen receptor modulators without causing pregnancy loss.[38]

Babies born from cryopreserved oocytes are increasing day by day, so it has become necessary to investigate their potential health problems and chromosomal abnormalities. Studies have reported a higher rate of birth defects, chromosomal abnormalities or developmental anomalies in these babies than other procedures such as spontaneous pregnancies and IVF.[39]

Evidence has already shown the successful transplantation of cryopreserved ovarian tissue in adults, with more than 90 babies born with this technique so far. About 50% of these are considered spontaneous fertilization.[40,41]

Pelvic irradiation may cause permanent damage to the uterus, tuba, and vagina, preventing conception or continuation of pregnancy. Parents may have a child through egg donation and surrogacy in such cases, but these are not legal in every country.

If gonadal protection is not possible, gonadotropin suppression may be an option, although its efficacy has not been fully proven. In general, there is limited information on the mechanism of action of gonadotropin-releasing hormone (GnRH) analogs (GnRHa) for gonadal protection, but some evidence suggests their efficacy. Accordingly, rapidly dividing cells are particularly more vulnerable to cytotoxic drugs, and the administration of GnRHa during cancer treatment may slow their proliferation rate that otherwise leads to gonadal function arrest and protection of cells from apoptosis. In this way, suppression of the hypothalamic-pituitary-gonadal axis leads to decreased egg and sperm production, rendering it more resistant to chemotherapy.[42] This method cannot be applied in prepubertal girls since the axis is not active yet.

The American Society of Clinical Oncology (ASCO) 2018 guidelines suggest that GnRHa will be an alternative option for the preservation of gonadal function when other methods are not feasible.[43]

Various studies and meta-analyses have shown that the administration of GnRHa in combination with chemotherapy reduces POI and increases the pregnancy rate.[44-48] Some studies indicate that the combination also improves menstruation, but available data is insufficient to evaluate outcomes for ovarian function and fertility.[49] Besides, Moore et al. have reported that combined therapy with GnRHa resulted in more favorable disease-free survival and overall survival rates, as well as the preservation of ovarian function.[50] In another study, lymphoma patients undergoing total body irradiation were started on GnRHa 10 to 14 days before treatment. The normal ovarian cycle was restored in 66.7% of the patients who received GnRHa, whereas in 11.1% of those without GnRHa. The use of GnRHa is especially considered beneficial in women undergoing HSCT for lymphoma.[51]

The use of GnRHa (triptorelin, goserelin, leuprolide) combined with chemotherapy as a noninvasive, inexpensive, and accessible option to prevent POI in pubertal and adult patients has recently been integrated into clinical guidelines as well.[52,53] The updated European Society for Medical Oncology (ESMO) recommendations include using GnRHa in adolescents and young women, among other options.[54,55]

Conclusion

All the treatment options mentioned above have been a source of hope for the fertility of cancer patients. Fertility-preserving treatment options should be evaluated by a specialist team of oncologists, radiation oncologists, endocrinologists, urologists, and gynecologists, considering the diagnosis and stage of the primary disease, the chemotherapy to be administered, the gender and pubertal stage of the patient. The patients and their families should be fully informed throughout the process. In the future, standardized fertility preservation protocols must be established for experimental and approved treatment options. A broad range of experimental and clinical studies on this subject is necessary for further advancements.

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