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SPECIAL ARTICLE

Gynecology

Cancer therapy and reproductive impact

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Abstract

All patients where the cancer treatment has gonadotoxic potential should be referred for oncofertility advice. The effect of chemotherapy and radiotherapy on the human ovary can vary from no impact to full-blown premature ovarian failure due to hormonal and follicular depletion. Total contraindications to fertility cryopreservation include acute malignancy that requires immediate lifesaving therapy. In prepubertal girls, the only option for urgent fertility preservation is ovarian tissue cryopreservation. Prepubertal testicular tissue cryopreservation is experimental.

KEYWORDS
cancer therapy, chemotherapy and radiotherapy effects, cryopreservation, fertility preservation, gonadotoxicity, oncofertility, ovarian failure, reproductive health

1 | INTRODUCTION

Over the past decade a therapeutic revolution has started in the fields of modern cancer management and fertility preservation procedures.

GLOBOCAN estimates that in 2020 there were 19.3 million cancer cases with 10 million deaths.[1] According to the statistics of the National Cancer Institute (USA),[2] the average 5-year cancer survival rate is now nearly 80% for individuals younger than 50 years of age and in 2016 approximately 1 in every 250 adults survived a malignancy. Yet, it seems that the lives of cancer patients of reproductive age are swaying between survival and quality of life. It is important to note the potential delayed diagnosis and treatment of cancer patients after the COVID-19 pandemic due to disruptions to healthcare facilities.[3]

In the USA alone about 2 million cancer patients were diagnosed in 2015 with over 2 million new cases estimated in 2024.[3] Approximately 10% were younger than 40 years, 1% under 20 years, and 25% of breast cancer patients were diagnosed before the age of 45.[4]

In 2023, cancer remained a leading health concern, affecting millions across all age groups and sexes. Statistics indicated that about 1.9 million new cancer cases and approximately 609 820 cancer-related deaths were anticipated in the USA for the year. Among men, the most commonly diagnosed cancers are prostate, lung, and colorectal cancers, which account for nearly half of all cases. For women, breast cancer is the most common, followed by lung and colorectal cancers, making up over half of diagnoses in females.[5]

The incidence of various cancers among women in the USA according to the National Cancer Institute (NCI) statistics (from most frequent to least frequent) are breast, lung, colon, uterine, pancreatic, ovary, and cervical cancers. Hematological malignancies such as leukemia and lymphoma conclude the list.

Breast cancer, the most frequent cancer in women, is diagnosed in 25% of women before menopause and in 15% before the age of 45.[6] Today, the detection rate (stages I–III) in high-resource countries is fairly high, up to 90%, and the 5-year survival rate is about 95%.[7]

An increasing number of patients become infertile due to diminished or absent ovarian reserve, which is a direct consequence of adjuvant therapy. In addition, in cases of severe malignancy there must be at least a two-year recurrence-free interval before fertility treatments can be initiated.[8]

Childhood and adolescent cancers are much less frequent but are still significant, with around 14 910 diagnoses expected annually in those aged 1–19 years. In children and adolescents, the type of cancer most commonly diagnosed differs from adults, with

leukemia, brain, and central nervous system tumors and lymphomas the most frequent. Survival rates in this group have improved over time, yet cancer remains a leading cause of disease among children.[9]

Regarding boys and girls under the age of 16, according to statistics from the UK's Ministry of Health, 1 in 444 boys and 1 in 594 girls are cancer survivors, with a 10-year survival rate of 80%.[10] As evident from global statistics data, fertility remains a primary concern for cancer survivors.

As reported in an extensive review, cancers are divided into three categories for infertility risk: low risk as in acute lymphatic leukemia; medium risk as in acute myeloid leukemia; and high risk, which mainly refers to incidents where total body irradiation is part of the treatment protocol.[11]

2 | PATIENT CLASSIFICATION

Classification of patients according to chemotherapy and radiotherapy types, with a focus on expected ovarian damage, is essential for determining the reproductive risks associated with various cancer treatments. Ovarian damage risk is related to the type and dose of chemotherapy and radiotherapy as well as patient age and the pretreatment ovarian reserve.

2.1 | Chemotherapy-induced ovarian damage

Chemotherapy drugs vary in toxicity to ovarian follicles, with some causing higher rates of ovarian failure. Chemotherapy regiments can be classified as:

1. High risk (severe ovarian damage)

- Alkylating agents: Drugs such as cyclophosphamide, busulfan, and chlorambucil are associated with high rates of ovarian failure. Alkylating agents damage DNA across both proliferating and nonproliferating cells, making them mostly toxic to ovarian follicles.
- Common regimens: Doxorubicin, vincristine, bleomycin, and others used in lymphoma.

2. Moderate risk (variable ovarian damage)

- Platinum-based agents: Drugs like cisplatin and carboplatin used in ovarian and breast cancer have a lower but significant risk for ovarian damage.
- Anthracyclines: Doxorubicin and epirubicin may also pose moderate risks.

3. Low risk (minimal ovarian damage)

- Antimetabolites and taxanes: Drugs such as methotrexate, fluorouracil, and paclitaxel generally have a low impact on ovarian function especially when used alone.

2.2 | Radiotherapy-induced ovarian damage

Radiotherapy can also cause significant ovarian damage especially when applied near the pelvic region.

1. Direct pelvic irradiation: Radiation directly to the pelvic area, such as for cervical or rectal cancer poses a high risk for ovarian failure. Doses as low as 6 Gy to the ovary can lead to ovarian failure in adult women.
2. Total body irradiation: Often used before bone marrow transplants. Total body irradiation has a very high risk of causing ovarian failure due to the high doses affecting all reproductive organs.
3. Abdominal radiation: Radiation to the abdominal area as for Hodgkin lymphoma can lead to ovarian damage depending on dosage and age. Shielding or ovarian transposition (moving ovaries out of the radiation field) can reduce risk.

2.3 | Patient factors affecting risk

1. Age: Younger patients have a higher likelihood of ovarian recovery after treatment due to a larger initial follicle pool. However, treatments in prepubescent girls can still lead to primary ovarian insufficiency.
2. Baseline ovarian reserve: Pretreatment ovarian reserve and estimation of anti-Müllerian hormone levels help predict the degree of ovarian damage.

3 | FERTILITY PRESERVATION IN PATIENTS OF REPRODUCTIVE AGE

In line with the American Society of Clinical Oncology (ASCO) guidelines,[11] oncologists, surgeons, gynecologists, and reproductive specialists should address and discuss with patients of reproductive age the possibility of fertility preservation prior to the oncologic therapy. The patient should be immediately referred to an institution that possesses the appropriate facilities for these procedures, including the means for oocytes, sperm, and ovarian or testicular tissue cryopreservation and storage.[12]

The trajectory for this referral should begin with the first-line therapists where the diagnosis was initially raised, continue in the oncology center where the diagnosis is confirmed, and proceed in a tertiary hospital that has direct connections with an assisted reproductive technology unit and women's hospital performing these procedures.

From diagnosis there are four options for oncology treatment: surgery only, adjuvant chemotherapy, adjuvant radiotherapy, and various combinations. The key to an effective referral process is to consider discussing fertility impact early in the process to facilitate timely referral for fertility advice and potential cryopreservation.

Chemotherapy destroys growing follicles and causes ovarian atrophy and apoptosis of ovarian cortex cells. As described by Meirow

et al.,[13] the destruction is caused by two mechanisms: one causing a vascular injury and therefore an impaired blood supply to the cortex, and the other a direct toxic effect. However, Gosden et al. and Oktay et al.[14–16] have shown in experiments and in respective publications that primordial follicles are not affected by chemotherapy. To safeguard a patient's reproductive potential, pretreatment with GnRH agonists for downregulation prior to initiating chemotherapy may be considered. However, the evidence remains limited and sometimes contradictory, leaving the use of GnRH agonists for all patients a subject of ongoing debate.

Unfortunately, GnRH agonists do not protect the ovary from the insult of radiation therapy. In cases of irradiation with more than 600 cGy, total ovarian failure will occur. Where less than 300 cGy is used, about 10% of patients will develop premature ovarian failure.

4 | THE IMPACT OF CHEMOTHERAPY OR IRRADIATION ON HUMAN OVARIES

The chemotherapy or irradiation effect on the human ovary can vary from no impact to full-blown premature ovarian failure due to hormonal and follicular depletion.

Treatment options should always be discussed with the patient and their family by the surgeon (general or gynecologist), the oncologist, and the reproductive medicine specialist that are working as a team in the field of oncofertility.

The protocol for the treatment and fertility preservation process is based on the following data: patient age, type of cancer, the extent and spread of the disease, the extent of emergency to treat, time availability, and whether the patient has a partner or not.

The indications for ovarian tissue cryopreservation include the situation when delaying urgent cancer treatment is contraindicated and in cases of prepubertal cancer in young girls.[16]

In some cases of oncologic diseases, cancer therapy takes priority before the fertility preservation procedures, as in the case of prepubertal children with cancer. In such cases, an emergency fertility preservation process should be undertaken. These decisions are made by a multidisciplinary team comprising the oncologist, fertility preservation expert, and a surgeon.[17] The treatment should always be done in a tertiary medical center with appropriate facilities.

A full algorithm concerning the approach to emergency fertility preservation exists for adults and children. It is based on the guidelines and recommendations from the following societies: American Society of Clinical Oncology (ASCO),[11] European Society for Medical Oncology (ESMO),[18,19] American Society for Reproductive Medicine (ASRM),[20] International Society for Fertility Preservation (ISFP),[21] Fertility Preservation Network (FertilPROTEKT),[22] and the Oncofertility Consortium.[23]

According to these societies' recommendations, the approach for emergency fertility preservation is divided into adults (male and female) and prepubertal children (male and female).

In cases of a very aggressive cancer in adult males, the urgent fertility preservation can be done by cryopreservation of several sperm samples, preferably given via as many ejaculations as possible. In cases of azoospermic patients or where a very severe oligospermic result is present or in a male unable to provide a sample for cryopreservation, sperm can be retrieved from testicular tissue and testicular tissue cryopreservation can be performed.[24,25]

One of the most typical examples of female cancer is an aggressive estrogen-dependent breast cancer. In such cases, ovarian stimulation may be contraindicated due to the time interval and elevated estrogen levels in protocols of controlled ovarian hyperstimulation. Nonstimulated ovarian immature oocyte collection and subsequent cryopreservation can be done by implementing a process of in vitro maturation of the oocytes to MII stage of development.[24,25]

In vitro maturation is an emerging reproductive technology where immature oocytes are collected from ovarian follicles and matured in a laboratory setting. It offers significant potential for fertility preservation particularly among patients in whom conventional ovarian stimulation is not feasible, safe, or appropriate.[26]

For prepubertal patients, ovarian tissue can be collected and immature oocytes extracted and matured in vitro. This represents an experimental yet promising method of fertility preservation in young cancer patients.[27]

Additional options are fertilization of the oocytes with partner or donor sperm, and cryopreservation of embryos. Today, another novel option is ovarian tissue cryopreservation. This method would necessitate a future re-implantation of thawed tissue in the female body, orthotopic or heterotopic.[24]

In prepubertal girls, the only option for urgent fertility preservation is ovarian tissue cryopreservation. Most pediatric oncologic societies globally have guidelines for fertility preservation in prepubertal children. The American Children's Oncology Group (COG) summarized these guidelines in 2017.[28,29] The Schneider Children's Medical Center of Israel have summarized their experience. Twenty-nine prepubertal girls aged 2–10 years were treated at the hemato-oncological department of the children's medical center. All girls underwent removal of an ovary by laparoscopy, which was then cryopreserved after being dissected into very thin slices. Prior to the cryopreservation the tissue was irrigated using a special medium, and very young oocytes, in the range of 1–43 per ovary, were extracted from 23 out of 29 ovaries. Of the oocytes, 27% were found to be atretic and the rest were taken for an in vitro maturation process following a special protocol. The maturation rate of oocytes was 38% on average. Metaphase II oocytes were cryopreserved together with the remaining ovarian tissue. The source of the oocytes was the antral follicles that are found in very young ovaries.[27]

In cases of prepubertal boys, the only way to perform fertility preservation is by testicular biopsy performed under microscopic view (micro). In very young boys the tissue itself is cryopreserved, and in older prepubertal boys the spermatogonial stem cells are isolated and cryopreserved together with the whole testicular tissue. All this is done or future implantation of stem cells or of the tissue itself with the seminiferous tubules. This process is still experimental.

The technology of stem cell transplantation has its own advantages. It might prevent cancer cell contamination in future

transplantation as opposed to transplantation of the testicular tissue. It should be emphasized that these procedures are purely experimental and are only performed in a handful of countries. These procedures are thoroughly and extensively discussed by the COG.[24]

To date, no human birth has been reported as a result of transplantation of testicular tissue or spermatogonial stem cells following recovery of these boys from oncologic disease.

AUTHOR CONTRIBUTIONS

Both authors equally contributed to data collection, writing and editing of this article, and agree to be accountable for the final published content.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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