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ONCOFERTILITY IN PEDIATRIC, ADOLESCENT, AND YOUNG ADULT PATIENTS: A NARRATIVE REVIEW

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ABSTRACT

The aim of the study is to investigate the impact of cancer treatments on fertility in pediatric and adolescents. It examines the reproductive side effects of cancer treatments, evaluates current fertility preservation methods and global guidelines.

Materials and methods: A comprehensive review of the literature available across reputable databases including PubMEd, Scopus, Google Scholar and Cochrane Library. The study was conducted using a systematic search of keywords including Oncofertility, Gonadotoxicity, Cancer and reproduction, Fertility risk assessment, Embryo cryopreservation.

Conclusions: Despite its importance, oncofertility is often overlooked in cancer treatment planning due to high costs, limited patient understanding, and ethical concerns. Mandatory fertility preservation programs are needed to educate patients, assess eligibility, and provide access to standardized procedures.

Keywords: Oncofertility, Gonadotoxicity, Sperm cryopreservation, Fertility preservation, oocyte cryopreservation, embryo cryopreservation, Assisted reproductive technology (ART), Cancer and reproduction, Fertility risk assessment

INTRODUCTION

Malignant neoplasms in the pediatric population and in adolescents and young adults (AYA), despite their significantly lower incidence compared to the adult population, exert an equally profound psychosocial impact on the lives of young patients and their families. According to World Health Organization (WHO) data, approximately 400,000 children are diagnosed with cancer annually [1]. The spectrum of the most common childhood cancers includes hematopoietic system neoplasms – leukemias (accounting for 36.79%), lymphomas (15%), as well as tumors of the brain and central nervous system (CNS) (14.62%) [2, 3]. In the slightly older cohort of adolescents and young adults, the most frequently identified malignancies are: thyroid cancer (15%), breast cancer (15%), testicular cancer (8%), and melanoma (7%) [4]. Due to the accelerating pace of advanced diagnostic techniques and the availability of modern treatment modalities, a cure rate of approximately 80% for childhood cancers is achieved in developed nations. However, in developing countries, the cure rate within the pediatric population decreases to 30% [5]. This disparity is attributed to limited access to diagnostic infrastructure, lack of modern pharmaceutical agents, and insufficient social support. According to the WHO-led Global Initiative for Childhood Cancer, the strategic objective for the year 2030 is to increase the global survival rate for childhood cancers to a minimum of 60% [6].

RELEVANCE

Progress in curability introduces new clinical challenges, prominently featuring the potential adverse impact of therapeutic interventions on future fertility. This consideration was until recently completely overlooked, deferred, and deemed secondary in the immediate context of fighting for life and health.

NOVELTY

The term oncofertility first appeared in the scientific literature only at the beginning of the first decade of the 21st century [7]. A decade later, scientific research provides an expanding array of feasible fertility preservation methods for implementation prior to initiating oncological treatment. Unfortunately, not all patients are still informed about treatment options, and those who receive information often encounter difficulties in accessing services.

AIM

The aim of our work is to discuss available fertility preservation methods for children and young adults undergoing cancer treatment. We would like to devote particular attention to the available techniques we can offer patients at various stages of development and the barriers we may encounter when implementing these methods.

RESEARCH OBJECTIVES

We want to analyze the mechanisms responsible for the deterioration of reproductive system function during oncological therapies, present currently available methods of fertility preservation, discuss the varying availability of the above-mentioned methods worldwide, and present the problems faced by both clinicians and patients when seeking to implement fertility preservation methods.

METHODS

A narrative review of the literature was conducted to identify current methods of fertility preservation in oncology patients. The search strategy encompassed the PubMed, Google Scholar, and ResearchGate databases. The following keywords and their combinations were used: “oncofertility”, “fertility preservation”, “fertility risk assessment”, “cancer and reproduction”, “gonadotoxicity”, “pediatric cancer”, and “embryocryopreservation”.

Inclusion criteria comprised randomized controlled trials, cohort studies, systematic reviews, meta-analyses, and international clinical guidelines relevant to fertility preservation. Exclusion criteria included case reports, conference abstracts, and non–peer-reviewed publications.

RESULTS

IMPACT OF MALIGNANCIES ON FERTILITY

Malignancies are primarily diseases with systemic effects on the body, inducing a wide range of immune and inflammatory responses that can intrinsically reduce fertility even before any treatment is initiated.

Many tumors generate an increase in the concentration of proinflammatory cytokines (mainly IL-6, IL-8, TNF-α). Studies in rats have shown that disturbed homeostasis of proinflammatory factors can damage the blood-testis barrier, leading to the apoptosis of reproductive cells [8, 9]. Consequently, symptoms such as fever, a common manifestation in the course of Hodgkin's lymphoma, can negatively affect semen parameters, such as sperm motility, morphology, and concentration [10]. Cachexia resulting from prolonged illness may also impair spermatogenesis [11].

The functionality of the human reproductive system is dependent on the Hypothalamic–Pituitary–Gonadal (HPG) axis. This axis regulates reproductive functions through the pulsatile secretion of Gonadotropin-Releasing Hormone (GnRH) from the hypothalamus, which stimulates the pituitary gland to secrete Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH). These hormones, in turn, stimulate the gonads to produce sex hormones and gametes. The system operates via a negative feedback loop mechanism.

Disruption of any component of this cascade—such as the destruction of the pituitary gland due to central nervous system tumors, or the loss of function in gonads involved in the neoplastic process—results in the loss of gamete production capacity [12, 13].

Furthermore, specific hormones secreted by certain tumors can disrupt the function of the HPG axis, thereby impairing the processes regulating the maturation of both spermatozoa and oocytes. An example of this mechanism is observed in testicular germ cell tumors that produce Alpha-Fetoprotein (AFP) and Beta-Human Chorionic Gonadotropin (B-hCG), which subsequently inhibit spermatogenesis [14].

IMPACT OF CANCER TREATMENT ON FERTILITY

In recent years, due to medical progress, survival statistics for cancer patients, especially among the younger patients, have significantly improved. However with this success appears another problem: the long-term side effects of various methods of cancer treatment, which includes its impact on fertility. The main modern methods of treatment include surgery, chemotherapy, radiotherapy, hormone therapy and immunotherapy. Depending on their gonadotoxic potential, these methods often are associated with both transient or permanent and irreversible fertility loss. [15, 16]

THE IMPACT OF SURGERY ON INFERTILITY.

The main treatment for testicular cancer is radical orchiectomy of the testis with tumor. Approximately 9% of patients develop azoospermia after surgery, particularly those who had poor semen quality before the operation. Furthermore,a significant decline in semen parameters occurs in about 85% of patients.[17]

Radical surgical intervention is often essential for ovarian cancer treatment. This procedure involves hysterectomy and bilateral oophorectomy resulting in irreversible infertility. However, in selected cases, Fertility-Sparing Surgery (FSS) may be utilized. Its efficacy depends on the histological type of the tumor: pregnancy rates for Borderline Ovarian Tumors (BOT) vary from 32% to 88%, after Epithelial Ovarian Cancer (EOC) 67% patients have achieved pregnancy after FSS and for Non-Epithelial Tumors. (MOGCT i SCST) the rate is between 75% to 86%. [18]

THE IMPACT OF CHEMOTHERAPY ON FERTILITY.

The gonadotoxicity of chemotherapy arises because the proliferating cells are the most sensitive to cytotoxic agents. Mutations in gonadal stem cells disrupt spermatogenesis. The damage occurring at an earlier stage of this process leads to more permanent consequences. [19] Data show that chemotherapy treatments carry a higher threat of infertility for men (HR = 0.63, 95% CI = 0.58 do 0.68)compared to women (HR = 0.87, 95% CI = 0.81 do 0.94). [20]

Alkylating agents are considered the most gonadotoxic chemotherapeutics, often leading to permanent infertility in both sexes. As non-cell-cycle specific drugs, they can damage all reproductive cells, including germ cells, primordial follicles, and resting oocytes. [21] Patients during chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin (CHOP-Bleo) develop azoospermia in 100% cases. After treatment, sperm parameters recover over 5 years and stabilize after 7 years. However, significant semen impairment still persists in 60% of patients [22].

In female patients anti-Mullerian hormone (AMH), inhibin B and follicle stimulating hormone (FSH) are used as fertility markers. Chemiothery lowers the levels of ovarian markers (AMH and inhibin B) and increases levels of FSH, which corresponds to reversible amenorrhea that often occurs during treatment. [23] Recent studies suggest the superiority of monitoring AMH levels compared to other markers, although it has a limited ability to precisely determine the degree of ovarian reserve damage or predict when menstruation will return after long-term amenorrhea [24]. Inverse relationship between age and gonadotoxicity, the younger the patient, the lower the risk of side effects of chemotherapy. Ovarian failure affects 50% of women older than 40 and only about 15-30% women under 35. These divergences result from decrease of the primordial follicle pool with aging, predisposing patients to Premature Ovarian Failure (POI) [25].

Cyclophosphamide is widely used chemotherapeutic in oncology for treating various cancers including lymphoma, leukemia, neuroblastoma, retinoblastoma, and breast cancer. Patients at the age of 20 faced nine times increased risk of developing premature menopause, with overall occurrence of premature ovarian failure in 60-80% in all patients. In addition to age, higher cumulative dose of cyclophosphamide correlates with higher risk of premature menopause. Due to this high gonadotoxicity, recent breast cancer protocols less frequently use cyclophosphamide. [24] Therapy with other chemotherapeutics, such as anthracyclines and their derivatives have lower risk of developing amenorrhea and fertility disorders. As for taxanes, there is no strong evidence to link them to post-treatment infertility. [26]

THE IMPACT OF RADIOTHERAPY ON FERTILITY

Radiotherapy has a negative effect on both testes and ovaries. Gonads may be exposed when radiation treatment targets the total body, when treating nearby areas such as the abdomen, pelvis, spine or lower limbs due to scattered radiation. The primary protective method includes using focused, precise radiation and shielding the gonads from radiation. Spermatogenesis is negatively impacted by doses starting at 0.1-1.2 Gy, while a dose of 4 Gy results in irreversible damage. In contrast, Leydig cells show greater resistance to radiation, tolerating doses up to 30Gy [27]. However, among women patients, radiation doesos of 3, 3-5 and 5Gy results in destruction of 11%, 60% and 100% ovarian follicles, respectively. White young patients usually retain fertility, the oocyte reserve decreases with age, thereby increasing the risk of complications. Radiotherapy- related infertility risk is considered to rise markedly after the age of 30 [28]. Moreover, the uterus may be affected independently of ovarian effects by radiation. After radiotherapy, the uterus is often thin and fibrotic. This condition endangers future pregnancies and labor, because it increases the risk of uterine rapture and stillbirth Finally, combining radiotherapy with chemotherapy leads to a synergistic impairment of fertility [29].

THE IMPACT OF HORMONE THERAPY ON FERTILITY

Tamoxifen is a selective estrogen receptor modulator that binds estrogen receptors that are located in breast tissue, among other sites. In modern oncology, it is classified as a cytostatic rather than cytotoxic drug. Its usage has been the standard treatment for hormone-sensitive breast cancers. Tamoxifen does not reduce ovarian reserve. The reduced birth rate among women treated with tamoxifen is not due to direct effect on the ovaries. However, because it's contraindicated during pregnancy, women need to delay maternity for the duration of treatment, typically lasting 5 to 10 years. Delayed reproductive plans correlate with decline in fertility with age, resulting in lower birth rates among the patient population[30].

THE IMPACT OF IMMUNOTHERAPY ON FERTILITY

Immunotherapy is a modern cancer treatment that uses the patient's own immune system to target and kill cancer cells. Immunotherapies include immune checkpoint inhibitors, monoclonal antibodies, immunomodulators and CAR-T therapy. Unfortunately, the treatment is associated with a systemic elevation of pro-inflammatory cytokines and other immune- related side effects, which could lead to fertility problems. Among male patients hypospermatogenesis and aspermatogenesis have been observed particularly after treatment with immune checkpoint inhibitors. In females, damage to ovarian reserve, recurrent miscarriages and implantation failure have been observed resulting from reactions between immune cells[31]. Current clinical data concerning the monoclonal antibody Transtuzumab, utilized in HER2+ breast cancer therapy, states that the conception is considered safe after at least 6 months from stopping the medication [32].

The table below categorizes chemotherapeutic agents according to their associated risk level by grouping them into high, medium, low or no, and unknown risk categories.

Table 1. Chemotherapeutic agents and gonadotoxicity. [55]

Risk Category	Chemotherapeutic Agents
High Risk	Cyclophosphamide, Busulfan, Melphalan, Chlorambucil, Nitrogen mustard, Procarbazine, Dacarbazine, Doxorubicin, Carmustine, Lomustine
Medium Risk	Vinblastine, Cytosine arabinoside, Cisplatin, Carboplatin
Low/No Risk	Methotrexate, 5-fluorouracil, 6-mercaptopurine, Vincristine, Bleomycin, Actinomycin D
Unknown Risk	Paclitaxel, Taxotere, Oxaliplatin, Irinotecan, Trastuzumab, Pertuzumab, Cetuximab, Erlotinib, Daunorubicin, Imatinib

MALE FERTILITY PRESERVATION

Fertility Preservation Methods in Post-Pubertal Males

Sperm cryopreservation

Sperm cryopreservation is recognized as a standard method for fertility preservation for men facing gonadotoxic treatments. For any male of reproductive age, this method should be the first choice [16].

The primary and least invasive technique for sperm collection is masturbation. In cases where patients are unable to perform it due to stress, paint and other causes, Penile Vibratory Stimulation (PVS) is the preferred second-line option. The alternative is Electroejaculation (EEJ), which stimulates the prostate and seminal vesicles, however it's done under anesthesia. Surgical options include Testicular Sperm Extraction (TESE), which involves a testicular biopsy or Onco-TESE. In Onco-TESE healthy tissues are retrieved from the testicle with cancer during orchiectomy to identify and bank sperm [33].

Studies indicate that using frozen sperm from TESE for in vitro fertilization (using method (ICSI) is just as effective as using fresh sperm, showing better fertilization rates (60% vs 55%) and almost identical pregnancy rates (27%). TESE can retrieve sperm despite azoospermia and sperm samples can be frozen and used years later with the same success rates [34]. Unfortunately not every man in the reproductive age preserves sperm before gonadotoxic therapy. French registry data show banking rates of 41% for testicular cancer, 40% for Hodgkin lymphoma, and only

7% for non-Hodgkin lymphoma (NHL). For NHL time is critical and because of emergency basis often lose the opportunity to bank sperm. Although 40% is considered as high, more differences show in different age groups. Doctors often refer to younger men (aged 20-34) and overlook older men (aged 35-49), assuming their family planning is complete. Many men don't visit sperm banks due to lack of information from oncologists [35].

Fertility Preservation Methods in Prepubertal Males

Testicular shielding

Pharmacologic interventions using GnRH agonists to preserve spermatogenesis during radiotherapy have proven ineffective. Blocking testicular function during treatment does not protect germ cell DNA from radiation damage [33]. Lead shielding is the standard protection providing some defense, it cannot block all scattered radiation. Spreading the total radiation dose into multiple smaller fractions, instead of delivering it as a single dose, is proven to be less gonadotoxic [36].

Experimental methods

The newest experimental method- Testicular Tissue Cryopreservation (TTC) freezes stem cells instead of sperm. It’s a way to preserve fertility for the boys before puberty who must face gonadotoxic treatment. Currently this procedure has been limited to animal models so far. The main challenge remains safety, as research indicates that cryopreservation process might trigger epigenetic mutations [37].

METHODS OF FEMALE FERTILITY PRESERVATION

Fertility Preservation Methods in Post-Pubertal Females

Cryopreservation of Embryos

Cryopreservation of embryos is considered the gold standard [38, 39] among fertility preservation techniques, representing the most well-established and thoroughly studied practice. This method can be used only in patients who have reached sexual maturity and exhibit regular ovarian activity. It is the most effective technique—in healthy patients, the live birth rate per transfer is approximately 30% [40], a figure only slightly reduced in oncological patients.

This is a time-consuming procedure; it must be initiated at the appropriate time in the menstrual cycle, typically on day 2 or 3. Subsequently, approximately two weeks are required to complete hormonal stimulation using GnRH antagonists [41], after which mature oocytes are retrieved. The oocytes are then fertilized *in vitro* using sperm from a partner or a donor.

This solution is not appropriate when treatment must be initiated immediately, as the waiting period for successful stimulation delays cancer therapy. The requirement for sperm retrieval also raises controversies, as it is not always feasible for single women, and the use of donor sperm can present legal and ethical dilemmas [42]. Furthermore, this method is not suitable for young pre-pubertal girls due to the yet inactive Hypothalamic–Pituitary–Ovarian axis [43].

Cryopreservation of Oocytes

This method involves the retrieval and freezing of mature oocytes, which is the standard procedure for children post-puberty [43]. A distinct advantage is the absence of a requirement for partner sperm at the time of oocyte retrieval, making it suitable for single women. At a later stage in life, the oocytes can be utilized in the *in vitro* fertilization process [44, 45].

The live birth rate per oocyte is distinctly lower than that achieved with embryo cryopreservation, amounting to approximately 6% in healthy women [46]. The procedure protocol is similar to that for *in vitro* fertilization preparation—it also requires time-consuming stimulation. This technique is also unsuitable for young girls.

In the context of the two methods described above, it is important to note that for patients with hormone-dependent tumors, such as breast cancer [47], the stimulation protocol requires modification—for example, protocols utilizing Tamoxifen or Letrozole are employed instead of GnRH antagonists. While these interventions appear to be safe, their long-term safety profiles have not yet been fully established [48].

Fertility Preservation Methods in Pre-Pubertal Females

Cryopreservation of Ovarian Tissue

This is currently the only non-experimental technique for fertility preservation in pre-pubertal girls and in patients where the timing of treatment initiation is critical and cannot be delayed [49, 50]. The procedure involves the laparoscopic removal of a fragment of the ovarian cortex and its subsequent cryopreservation. The secured tissue can be transplanted in the future onto the remaining ovary or to an ectopic site [51, 52]. This procedure restores natural

hormonal function and enables natural conception [43].

A notable advantage of this technique is the possibility of its rapid application—there is no need for ovarian stimulation, and the surgery can be performed practically the day after treatment planning. However, this method carries the risk of reintroducing malignant cells with the transplanted tissue (the risk is particularly high in hematological malignancies) [51, 53]. Therefore, it is essential that all retrieved tissue undergoes histopathological examination [54]. The procedure may also be associated with a significant reduction in ovarian reserve due to ischemia [24].

Experimental Fertility Preservation Methods

Experimental fertility preservation methods remain within the sphere of research and have not yet attained the status of standard care.

Ovarian Suppression – post-pubertal patients receive GnRH agonists, which place the ovaries in a state of rest by inhibiting the secretion of gonadotropins (LH, FSH) . This is intended to protect the gonads from the toxicity of anti-cancer therapies. Researchers hypothesize that the smaller the number of developing follicles susceptible to chemotherapy, the lower the potential for gonadal destruction [55, 56]. However, the efficacy of this method remains controversial due to insufficient clinical data [57].

Ovarian Transposition (Oophoropexy) is a method that may be successful in radiotherapy treatment. The technique involves the surgical repositioning of the ovaries outside the radiation field—the ovary can be shifted within the pelvis, e.g., to the opposite side, but also to distant sites, such as the subcutaneous areas of the forearm and retroperitoneal space under the abdominal wall [58]. However, the efficacy of this method is debatable and heavily depends on the dose and type of radiation [59].

A promising experimental method is **In Vitro Maturation (IVM) of Oocytes**. This technique is expected to completely eliminate or maximally shorten the stimulation time so that it does not delay the initiation of treatment. Immature oocytes can also be retrieved regardless of the menstrual cycle phase. This method requires further clinical safety studies [60].

Global Initiatives and Guidelines for Fertility Preservation in Oncological Patients.

In the face of increasingly successful cancer treatment, challenges related to the side effects of applied therapies are escalating, including those related to infertility treatment. According to statistics from the American Society of Clinical Oncology (ASCO), approximately 1/3 of patients who underwent aggressive oncological treatment experience infertility issues [38]. In order to establish the best possible guidelines for fertility preservation, associations and national programs are being established to safeguard reproductive function.

The year 2006 was a turning point in the field of oncofertility, witnessing the publication of the first global ASCO guidelines on fertility preservation [57]. With the establishment of these guidelines, the issue of fertility protection first achieved the status of a standard of care, rather than being a mere curiosity or an eventual option, as it had been previously. In the same year, the world's first global organization that shaped this subspecialty of medicine was founded—the Oncofertility Consortium, dedicated to research, education, and the implementation of fertility-conserving solutions. They are pioneers in research concerning the cryopreservation of ovarian and testicular tissue and the development of *in vitro* oocyte maturation techniques.

Following the American lead, Japan established the Japan Society for Fertility Preservation in 2012. This organization is a leader in the Asian market, offering comprehensive care for oncological patients.

In Europe, the largest organization of this type is FertiPROTEKT—a clinical network operating in German-speaking countries, providing rapid and professional access to fertility preservation methods, based on consistent, evidence-based guidelines and methodologies.

Additionally, an increasing number of countries are establishing their own procedures and standards concerning fertility preservation management. Currently, countries such as the United Kingdom, France, Italy, Spain, Canada, and Australia have wide and rapid access to oncofertility care. Importantly, many of these programs are fully or partially state-funded.

DISCUSSION

Despite recognizing the immense importance of fertility preservation during oncological treatment and the significant impact that the application or non-application of reproductive protection can have on an individual's life, the topic of oncofertility does not always surface during the planning of cancer treatment. In some cases, even if the topic is raised, its implementation remains incomplete.

One of the reasons for the non-implementation of oncofertility principles is the **cost**. Fertility preservation procedures

are specialized and highly expensive treatments, which are not universally reimbursed, significantly reducing their accessibility to the general population [52, 54, 58]. Another reason is the lack of understanding by the patient [54,59]—and often primarily the parents of a pediatric patient—regarding the complications associated with oncological therapy. Patients and their caregivers, confronted with a life-altering diagnosis, are often unwilling to delay treatment or deliberate over potential, secondary options, seeking immediate commencement of therapy. Issues causing hesitation may also include dilemmas of a religious and ethical nature [14, 54].

The subject of the impact of oncological treatment on fertility remains a topic addressed rather superficially, whereas we should strive for oncofertility to become a mandatory element in the oncological treatment planning process, not merely an optional addition. We should aim for the establishment of official fertility preservation programs whose role would be to educate patients, perform qualification assessments, and carry out fertility-preserving procedures according to current standards.

CONCLUSION

In modern oncological treatment, implementing a fertility preservation protocol is a necessity and a responsibility of medical personnel, particularly given the increasing survival rate of young patients. Cancer and oncological treatment negatively impact the reproductive system of both sexes by inducing systemic inflammation, disrupting the hypothalamic-pituitary-gonadal axis, and directly damaging the gonads. Chemotherapy, radiotherapy, hormone therapy, and immunotherapy can have gonadotoxic effects. Understanding these mechanisms is crucial for selecting appropriate therapeutic approaches.

Currently, a wide range of fertility preservation methods are available. Their selection depends on the patient's age, stage of puberty, type of cancer, and the need for rapid treatment. For post-pubertal girls and young women, the most effective method is cryopreservation of embryos and oocytes. For pre-pubertal girls and in cases where immediate treatment is necessary, the only fertility preservation option is cryopreservation of ovarian tissue. There are also a number of experimental methods—ovarian suppression, ovarian transposition, and in vitro maturation—but their effectiveness has not yet been proven. In males, sperm cryopreservation is the standard treatment. Cryopreservation of testicular tissue has also shown promising results in trials, but the effectiveness of this method has not yet been thoroughly studied.

The availability of these procedures varies significantly between countries. It depends largely on the availability of specialized centers with experienced staff and the existence of regional fertility preservation programs. Reimbursement of these types of procedures also plays a significant role in the availability of services – some high-income countries offer oncofertility procedures in basic health insurance. Access to services in middle- and low-income countries is limited. Regardless of the availability of specialized medical centers or financing programs, barriers remain due to clinicians' lack of knowledge about the availability of appropriate methods, ethical dilemmas, and the reluctance of patients and family members to discuss fertility preservation in the face of a terrifying cancer diagnosis.

There is no doubt that fertility preservation protocols should be routinely implemented in oncology care. This requires the development of reproductive counseling, rapid referral pathways, standardized treatment protocols, and broad collaboration between oncologists, gynecologists, urologists, andrologists, and surgeons. Routine care programs for cancer patients are also essential. The introduction of regional and international oncofertility programs, along with appropriate funding, will help reduce inequalities in access to services and improve the quality of life for cancer survivors.

DISCLOSURE

AUTHORS' CONTRIBUTIONS

Conceptualization: Maria Spychalska

Methodology: Maria Spychalska, Jan Spychalski

Formal analysis: Maria Spychalska, Jan Spychalski

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Writing-review and editing: Maria Spychalska, Jan Spychalski

Supervision: Maria Spychalska

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