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Fertility - preserving treatment strategies for adult and pediatric malignancies - current state of knowledge

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Abstract

Introduction and purpose:
The global incidence of malignant tumors is rising, including among young adults who may not yet have considered parenthood. While improved oncological treatments have increased survival rates, they often carry the risk of gonadotoxicity, leading to infertility. This growing challenge has contributed to the development of oncofertility - an interdisciplinary field combining oncology, reproductive medicine, endocrinology, embryology, psychology, and ethics. This article aims to review current literature, highlight recent advances, and discuss available fertility preservation strategies for cancer patients.

Material and methods:
A literature review was conducted using PubMed, Embase, and Google Scholar databases with relevant keywords.

State of knowledge:
Fertility preservation is feasible in many oncology patients, provided it is discussed prior to initiating treatment. Informed consent, particularly for minors, must involve guardians. For postpubertal males, sperm cryopreservation is the standard; testicular tissue preservation remains experimental, especially in prepubertal boys. Female patients have more options: oocyte or embryo cryopreservation are preferred, depending on partner status and treatment timeline. Ovarian tissue cryopreservation, though still experimental in children, is an option. Ovarian transposition before radiotherapy and hormonal protection are considered complementary approaches.

Conclusions:
Cancer therapies can significantly impair reproductive function, affecting quality of life. Despite rapid advances in oncofertility, no method guarantees future fertility. Early patient education and individualized care are essential to maximizing reproductive outcomes post-treatment.

Keywords: oncofertility, fertility, reproductive adjunctive techniques, cancer patients

1. Introduction

It is estimated that approximately eighteen million people worldwide are diagnosed with cancer annually, one million of whom are young [1]. Malignant tumors occurring in young patients, including children, often require aggressive treatment, including chemotherapy using alkylating agents and ionizing radiation, which can lead to gonadotoxicity and, consequently, loss of fertility [2]. This directly determines patients' mental state, social situation, and quality of life after treatment. The risk of developing malignant tumors increases with age, due to the natural aging process and cumulative exposure to carcinogens throughout life [3].

At the same time, in developed countries, we are observing the phenomenon of postponing fatherhood and a significant shift in motherhood to later years – to the age of 30 and beyond [4], approaching the age at which the risk of oncological diseases increases. The most commonly diagnosed malignant tumor in men aged 20-44 is testicular cancer, accounting for as much as 25% of all cancers in this age group [5]. In women, breast cancer is the most common cancer. Treatment for both of these cancers can impair fertility and reproductive capacity [6]. The degree of gonadal damage depends on the histological type and stage of the tumor, the patient's age at diagnosis, and the type and intensity of treatment [7]. This applies to women of reproductive age, who by undergoing oncological treatment simultaneously take the risk of disrupting or even terminating their reproductive process, as well as men undergoing treatment for multiple cancers – primarily testicular cancer, prostate cancer, and lymphoma. Loss of fertility can be temporary or permanent [8]. In women, complete removal of reproductive organs causes permanent infertility, while some anticancer drugs can – in both women and men –permanently or temporarily suppress gonadal function. It is important to emphasize that currently, not all oncological therapies involve loss of fertility [9], thanks to the holistic approach to patients, which has been ensured by the development of a new branch of medicine – oncofertility, officially recognized in the United States in 2015 as a separate medical specialty. This interdisciplinary field combines oncology, reproductive medicine, endocrinology, and embryology, as well as psychology and clinical ethics, aiming to protect the reproductive potential of cancer patients by providing them with multidimensional care [10]. This is particularly important due to the fact that fertility disorders in this group of patients are influenced by a number of factors - in addition to the type of cancer and its treatment, the scope and technique of the surgical procedure are also of crucial importance, as well as the patient's general condition, including comorbidities that may impair fertility. In women, oncological treatment may lead to premature cessation of ovarian function and difficulties with embryo implantation in the uterus due to the effect of chemotherapy, hormonal drugs or radiotherapy on the endometrium. In men, it may lead to a reduction in the number and motility of sperm and damage to the genetic material contained in the sperm nucleus, which may lead, among other things, to lethal defects in the fetus [2]. One of the primary goals of oncofertility is to present patients with available strategies for specific clinical situations and to implement optimal fertility preservation methods before initiating oncological treatment [11]. Currently, oncofertility offers both well-established methods and options that were previously considered experimental, but are now becoming clinical standards. Before initiating anticancer therapy,

individuals wishing to preserve fertility should be offered cryopreservation of embryos, oocytes, sperm, or a portion of gonadal tissue, ovarian transposition, or hormonal suppression of oogenesis and spermatogenesis [12]. The choice of technique depends on age, gender, cancer type, time available before therapy, and patient preference [13].

2. Purpose

In recent years, the incidence of various types of cancer has been increasing among young people under 50. Approximately 10 percent of patients are under 45 at the time of diagnosis [14]. At the same time, in developed countries, mortality rates for the vast majority of malignant tumors have been significantly declining over the past three decades [15]. A growing number of young people are childless or have not yet decided to have children at the time of diagnosis [16]. Providing them with optimal oncological treatment that allows for complete remission while maintaining reproductive potential after therapy is a new challenge for modern oncology.

This article presents the current state of knowledge regarding available fertility preservation methods that can be offered to young patients with malignant tumors. The aim is to summarize data available in the literature, as well as the latest reports and research on techniques that were until recently considered experimental therapies, but are now becoming clinical standards thanks to the dynamic development of oncofertility, and to assess the benefits and risks associated with them.

3. Materials and methods

A literature review was conducted using the PubMed, Google Scholar, and Via Medica journal databases, as well as the position statements of the Polish Society of Gynecology. Articles were identified using the following keywords: “oncofertility,” “oncofertility in oncologic patients preservation,” “reproduction adjunctive techniques,” “gonadotoxicity,” and “fertility.” A total of 2,378 results were retrieved. After applying exclusion criteria, 43 studies were selected for inclusion in this review. All included publications were published within the last six years, ensuring relevance to the current state of knowledge.

4. State of Knowledge

The last decade of dynamic development in the field of oncological fertility has provided us with not only a wealth of new information regarding specific methods of preserving fertility in cancer patients, but also reports on their impact on quality of life after cancer treatment. Patients often consider marriage and parenthood after cancer to be as important as the need to treat the underlying disease and can significantly influence treatment decisions. It turns out that the loss of the ability to have children is listed as one of the five most important needs of cancer patients, alongside health, work/school, romantic relationships, and friendships [17].

According to Lehmann et al., more than two-thirds of childhood cancer survivors reported feeling stressed if their future parenting goals were not met [16,18]. Other studies have shown that patients with infertility secondary to cancer treatment are at increased risk of emotional distress [19,20]. Considering the above, the need for continuous improvement of previously known fertility preservation techniques, as well as the creation of guidelines and standards of practice in line with the latest medical knowledge, seems even more justified to ensure an individualized approach to each patient, giving young people the opportunity to have children of their own. Before initiating anticancer therapy in individuals wishing to preserve fertility, we can propose one or more of the available strategies: oocyte cryopreservation, embryo cryopreservation, ovarian tissue cryopreservation, ovarian transposition, sperm cryopreservation, TESE (surgical sperm retrieval from the testicle), protection of ovarian function through pharmacological suppression with gonadotropin-releasing hormone agonists, and in vitro maturation (in vitro maturation), which involves the extracorporeal maturation of oocytes [21,22,23]. Cryopreservation of testicular tissue and hormonal suppression of spermatogenesis are currently in clinical trials [24].

4.1. Gonadotoxic effects of chemotherapy and radiotherapy

Female newborns are born with a certain number of primordial follicles, ranging from one to two million; their total number then decreases with age and under the influence of damaging factors, including cytotoxic drugs used in cancer chemotherapy. Regardless of the type of chemotherapy used, a portion of the patient's ovarian reserve will be irretrievably lost during the treatment process. Similarly, in the case of radiotherapy to the abdominal and pelvic areas, in addition to the increased risk of damage to the ovaries, fallopian tubes, and uterus, oocytes, which are highly sensitive to X-rays, may be destroyed. Wallace et al. calculated that as many as 97% of women who received a total radiation dose of 20–30 Gy to the abdominal area during childhood develop ovarian failure [22]. It is also estimated that treatment with ionizing radiation causes an average of 10 years earlier menopause [22].

According to many authors, it is important to note that in patients whose ovarian side effects were significantly minimized, thereby preserving their reproductive and endocrine function, radiation damage to the uterus cannot be definitively ruled out, which may contribute to problems with fertilization and embryo implantation in the uterus, as well as miscarriages. In boys and men undergoing oncological treatment, most often for testicular cancer, prostate cancer, and lymphatic system cancers, a transient deterioration in ejaculate values often occurs, lasting on average from several months to two years. The lowest semen parameters are observed within six months of treatment completion and are associated with acute testicular tissue damage from the chemotherapeutic agents. The toxic effect of radiotherapy on the male gonads depends primarily on the treatment regimen used, with even the lowest radiation doses of 0.1–1.2 Gy leading to a transient reduction in the number of spermatozoa in the semen, and irreversible azoospermia occurring with total doses of 4 Gy or fractionated doses of 1.2 Gy [24]. The age at which the man was subjected to radiotherapy is also important - in pre-pubertal boys, irradiation of the testicles at doses exceeding 20 Gy leads to permanent damage to the Leydig cells in the testicles, which are responsible for testosterone production, whereas in men whose puberty was completed before the start of oncological treatment, the function of these cells remains normal even up to doses of 30 Gy [24].

4.2. Methods of preserving fertility in women undergoing oncological treatment

4.2.1. Oocyte cryopreservation

This is a well-known, internationally established method. According to the guidelines of the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), it should be offered as a recognized, routine family planning option [25]. The method involves hormonal ovarian stimulation, collection of mature oocytes, and cryopreservation (freezing) of oocytes. It is particularly recommended for patients without a partner who do not wish to use a specific donor's sperm, for patients who refuse embryo cryopreservation for religious or ideological reasons, and for prepubescent children. A clear advantage of this method is the ability to collect oocytes for cryopreservation or undergo in vitro fertilization (IVF), followed by cryopreservation of embryos regardless of the day of the menstrual cycle, which does not delay the start of oncological treatment. The procedure's drawback has long been considered to be a lower pregnancy rate compared to freezing fertilized oocytes. Unfertilized cells were significantly more likely to be damaged during freezing and thawing due to their large size and high water content, resulting from the formation of ice crystals within and outside the oocyte, hardening of the zona pellucida, and disruption of the mitotic spindle structure.

Currently, specialized oncofertility centers have an innovative oocyte vitrification procedure, which improves on the previously used technique. It involves very rapid freezing of oocytes previously placed in a high-osmolarity cryoprotectant. Specially selected substances – cryoprotectants - prevent the formation of ice crystals. This ultimately results in higher pregnancy and live birth rates compared to the slow freezing technique [26]. Reproductive outcomes achieved with oocyte cryopreservation, especially in young patients, are similar to those achieved with unfrozen oocytes. The procedure's effectiveness is estimated at 40-60% of clinical pregnancies per embryo transfer [27].

4.2.2. Embryo cryopreservation

This widely used method, an integral part of most in vitro fertilization programs, is primarily aimed at women of reproductive age with a stable partner, as it requires in vitro fertilization (IVF) with donor sperm as a subsequent step before cryopreservation. The process begins with hormonal stimulation of the ovulatory cycle to simultaneously obtain several mature oocytes in metaphase II. The patient's follicular growth is monitored by ultrasound measurements of their diameter and determination of serum estradiol concentration. Then, at the appropriate time after the ovulatory peak, a transvaginal ovarian puncture is performed under ultrasound guidance, obtaining properly prepared oocytes. These are then subjected to in vitro fertilization using sperm obtained from a sperm donor. The resulting embryos are frozen in liquid nitrogen at -196 degrees Celsius, allowing for complete inhibition of metabolic processes and optimal utilization of their potential in the future. As with oocyte cryopreservation, the currently dominant technique is embryo vitrification, which involves slow freezing of embryos using cryoprotectants at three developmental stages. With regard to fertility preservation strategies, freezing embryos at the 2PN stage (two pronuclei) is preferred [27]. When presenting this method to patients, it is important to consider the approximately two-week time required for hormonal stimulation and the need to initiate the procedure within three days of the onset of the menstrual cycle. Therefore, it is not recommended in cases requiring immediate oncological treatment or in cancers that preclude the use of hormonal stimulation.

However, there are reports that initiating hormonal stimulation at any time can also be successful. A separate aspect, which is an undoubted advantage of this method of fertility preservation, is the opportunity to perform genetic testing before implantation into the uterine endometrium, eliminating the possibility of pregnancy developing from an embryo whose genetic material contains a defective gene responsible for the development of malignant tumors in offspring. This is particularly important in patients with genetic tumors. The effectiveness of the procedure is estimated at 45-65% of clinical pregnancies per embryo transfer. Studies have shown that the live birth rate per transferred embryo in breast cancer patients is comparable to that in the cancer-free population, i.e., 45.0% vs. 38.2% [27,28,29].

4.2.3. Ovarian tissue cryopreservation

This is a relatively new method of preserving fertility in patients, which is constantly being refined and refined to create appropriate treatment algorithms. Although the first attempts at ovarian tissue transplantation took place over 100 years ago, it was only in 2019 that the American Society for Reproductive Medicine (ASRM) recognized it as a standard, rather than experimental, method for patients undergoing cancer treatment [28]. To date, several hundred live births have been reported following cryopreservation and autotransplantation of ovarian tissue. The procedure involves the removal of a whole ovary or a fragment, most often during a laparoscopic procedure. The material is then prepared and frozen at -196 degrees Celsius using vitrification. Ovarian tissue prepared in this way is stored in specialized tissue banks in liquid nitrogen indefinitely. At the appropriate time, the tissue is thawed and transplanted back into the woman's body, either orthotopically (in place of the anatomical gonads), or heterotopically (into the greater omentum, subcutaneous tissue, or near the uterus). This method of preserving fertility does not require the patient to reach puberty, making it the only option for prepubescent girls.

However, in the pediatric population, it is still considered an experimental therapy. Its undoubted advantage is the possibility of performing the procedure without the need for prior hormonal ovarian stimulation, thus avoiding delays initiating oncological treatment. The primary disadvantage is the risk of reintroduction of cancer cells during transplantation and the possibility of graft rejection, leading to loss of ovarian function and failure to restore fertility. The procedure's effectiveness, according to current reports, is estimated at 30-35%, with approximately half of these pregnancies occurring naturally [28,29]. It should also be emphasized that so far no evidence has been found of an increased risk of congenital defects in offspring born from fertilized oocytes from transplanted ovaries, and no increase in the frequency of tumors of this organ has been observed.

4.2.4. Ovarian transposition - oophoropexy

This procedure involves surgically moving the ovaries outside the radiotherapy field, intended for both prepubertal and sexually mature women. It should be offered to patients whose planned treatment involves radiotherapy, as close as possible to the planned radiation therapy due to the risk of ovarian displacement [30]. Patients should be aware that gonadal protection is not always completely effective due to the possibility of radiation scattering, and that the procedure does not provide any protection against chemotherapy toxicity.

However, this method maintains normal ovarian function in 70-90% of patients [30,31].

4.2.5. Protection of ovarian function by pharmacological suppression with gonadotropin-releasing hormone (GnRH) agonists

Of all fertility preservation methods, this one is the most controversial and is the subject of randomized controlled trials. The essence of this method is the administration of GnRH agonists to patients. These drugs act on the pituitary gland, blocking its secretion of tropic hormones – luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This leads to reduced ovarian activity and may translate into a reduction in the toxic effects of anticancer therapy on the gonads. Their reversibility is intended to ensure that sex hormone levels return to baseline after therapy is completed. There is a growing body of scientific evidence demonstrating the benefits of such treatment, including a higher rate of return of menstruation within 12 months in women receiving GnRH analogues together with chemotherapy (74.5%) compared to patients treated with chemotherapy alone (50%) [32,33].

However, no direct effect on increasing the rate of pregnancy and live births has been demonstrated in patients who received GnRH agonists during chemotherapy, hence the most influential global scientific societies, such as ASRM, ASCO or NCCN (National Comprehensive Cancer Network), do not recommend their routine administration, but only their consideration in women for whom other methods of fertility preservation are not possible [33].

4.2.6. In vitro maturation (IVM)

A fertility preservation method with high developmental potential, based on in vitro oocyte maturation, is extremely valuable, especially in oncological scenarios where controlled ovarian hyperstimulation is impossible. This procedure involves the collection of immature cumulus and oocyte complexes from small antral follicles via the vaginal route during ovarian puncture or isolation from collected tissue. The obtained oocytes mature in the laboratory within 24-36 hours to reach the metaphase II stage of the meiotic division. The advantage of this method is its independence from the cycle phase, unlike embryo cryopreservation, which allows for rapid vitrification of mature oocytes or embryos after IVM in emergency cases or when delaying stimulation is not indicated. The first live birth using this method was reported in 2020, and its current success rate is 25-35% in clinical pregnancies following embryo transfer [34].

However, recent advances in IVM systems offer hope for improved results in the future, which would reduce the currently significant difference between IVM and results following prior ovarian stimulation. It is suggested that, to optimize the chances of conception, a combination of IVM and ovarian tissue cryopreservation be used in patients for whom ovarian stimulation is not possible. The procedure also holds promise for future use in prepubertal girls [34,35].

4.3. Methods of preserving fertility in men undergoing oncological treatment

4.3.1. Sperm cryopreservation

A well-known, readily available method of preserving male fertility, with high efficacy, should be presented to every patient of reproductive age before initiating oncological treatment. It involves freezing several samples of ejaculate, most often obtained through masturbation. However, sperm for this procedure can also be obtained through the use of phosphodiesterase inhibitors, vibratory stimulation, transrectal electrostimulation, or invasively by performing a testicular or epididymal biopsy, obtaining semen along with the seminiferous tubules. After collection, the semen is analyzed for parameters such as sperm concentration, motility, and morphology. If sperm parameters are normal, a cryoprotectant is added and the sample is frozen in liquid nitrogen at -196°C, where it can then be stored under special conditions until the sperm

are used in assisted reproductive procedures. Sperm banking is the most effective method of preserving male fertility and is readily available to over 95% of patients [36,37]. An important aspect of this method is the need to secure semen samples before initiating gonadotoxic chemotherapy, due to the risk of sperm DNA damage, which is possible after a single treatment course. Even if unsatisfactory semen parameters are obtained, which can occur even before the patient begins chemotherapy, cryopreservation is not recommended. In vitro fertilization (IVF) using ICSI selects sperm with the best properties for injection, increasing the chance of success.

Advantages of sperm cryopreservation in terms of fertility preservation include the absence of the need to postpone oncological therapy, the ability to store sperm for very long periods without significant loss of its properties, and good outcomes from assisted reproductive technology (ART) treatments. The method's effectiveness is estimated at >50% in subsequent assisted reproductive procedures [36,37]. The disadvantage is the impossibility of implementing it in prepubertal boys, from whom mature sperm cannot be obtained, unlike in pubertal boys - in about 20% of them, in Tanner II stage, with testicular volume above 10-12 ml, in whom spermiogenesis has already started, semen collection is recommended.

4.3.2. Testicular sperm extraction – TESE

This method is gaining increasing importance, particularly in patients with testicular cancer, which itself is a risk factor for infertility. Studies have shown that semen parameters in approximately half of testicular cancer patients show abnormalities of varying degrees of severity even before chemotherapy [38]. This strategy is aimed at patients who have failed to obtain sperm-containing semen using the previously mentioned methods and involves surgical sperm extraction from the testicle. It should be recommended for patients with azoospermia, cryptozoospermia, absence of ejaculate, anatomical abnormalities of the vas deferens, or in cases of specific cultural and religious circumstances. The procedure can be performed using a surgical microscope, representing an advanced modification of testicular biopsy and allows for direct identification of the seminiferous tubules in the testicular parenchyma, where spermatogenesis is most advanced, thus enabling the recovery of viable sperm.

Data regarding this strategy are currently limited; it is estimated that a standard testicular biopsy (TESE) procedure provides a 40-50% chance of extracting sperm suitable for in vitro fertilization, while microsurgical procedures, thanks to the possibility of detecting additional spermatogenic foci, may provide up to 1.5 times higher probability of success [39].

4.3.3. Cryopreservation of testicular tissue

A fertility preservation strategy involving the collection of a testicular fragment, its freezing, and reimplantation after completion of oncological treatment is still in clinical trials and can only be used in experimental protocols due to the lack of clear evidence of its effectiveness in humans [40]. Attempts are being made to obtain mature sperm from collected testicular tissue, both in vitro and in vivo, through autotransplantation of the tissue or spermatogonial stem cells isolated from it. This represents a potential and currently the only option for prepubertal boys or adolescents in whom spermatogenesis has not yet begun, provided their testicular architecture is normal [41].

Discussion and conclusions

This paper attempts to review the latest reports and present the most current knowledge on fertility preservation strategies used in cancer patients who, despite their diagnosis, refuse to abandon their reproductive plans. It also explores the opportunities that the modern field of

oncofertility offers for the youngest patients struggling with cancer during their prepubertal years.

Based on a review of the available medical literature on this topic, primarily scientific papers, it can be concluded that oncofertility procedures are constantly improving; this relatively new field is rapidly developing, responding to the growing needs of patients. Despite the increasing incidence of malignant tumors in children and young adults, advances in oncology allow for more effective treatment, resulting in a better prognosis for patients [42], and this not precluding their participation in society as potential future parents.

Oncological treatment, especially chemotherapy and radiotherapy, has a significant impact on the reproductive potential of patients, and the existing threat of complete loss of reproductive function due to its effect on the gonads is associated with a decrease in the quality of life and is an additional factor influencing their mental state [42,43], in addition to the already burdensome role played by the diagnosis related to the risk of loss of life, loss of the sense of security and struggle with somatic complaints, which are a negative effect of the anticancer therapy undertaken.

Importantly, when considering the choice of a specific method or the simultaneous use of more than one, each patient should be treated individually, taking into account numerous variables, including age, cancer type and initial prognosis, planned treatment and the associated risk of temporary impairment or complete loss of gonadal function, the possibility of postponing the start of oncological therapy, as well as the patient's personal preferences related to their expectations, religious or cultural affiliation, and worldview. A discussion with the patient regarding the impact of planned oncological treatment on their reproductive potential and the risk of infertility should be conducted as soon as possible after diagnosis, along with comprehensive information on the options available to protect reproductive function. Therefore, patients should be consulted by oncofertility specialists, preferably in dedicated centers where they can receive comprehensive care from physicians and psychologists.

None of the presented methods guarantee complete fertility preservation [43], therefore further research is necessary to improve their effectiveness, both to increase their efficiency and to increase their availability. It is worth noting that in the case of children and minors, decisions about the implementation of possible reproductive protection strategies should be discussed with the patient, but must be made in consultation with his or her legal guardian.

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