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Fertility issues among pediatric oncology patients – short communication

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ABSTRACT

Childhood cancer survival rates are constantly improving due to treatment. Fertility research has focused on adult cancer patients, but studies among childhood cancer survivors who reach reproductive age are rare and mainly based on small numbers of patients. This is surprising as childhood cancer survivors constitute a distinct, ever-growing population that may have temporarily or permanently impaired fertility due to cancer treatment. Thus, the basic scientific concern specific to the pediatric population has focused on improving protection techniques and cryopreserved tissue transfer. Research on preservation techniques confirms the safety of surgical retrieval of gonadal (ovarian and testicular) tissue for cryopreservation. Outcomes may improve, but it is clear that large registries of long-term follow-up of patients are needed. Current research efforts imply the need to develop a national strategy in each country to ensure the education and information of pediatric patients undergoing gonadotoxic regimens and their families about fertility options and subsequent outcomes and give them the opportunity to join such programs.

Keywords: cancer, fertility, oncofertility, pediatrics, survival, treatment, strategy

INTRODUCTION

Every year, around 400,000 children and adolescents aged between 0 and 19 years are diagnosed with cancer [1]. In 2019, the incidence of cancer among children under the age of 15 is 17 per 100,000, and that of adolescents and young adults (aged between 15 and 39 years) is 78.3 per 100,000 [2]. Continuous improvement in cancer treatments has led to better survival rates for young patients diagnosed with cancer: children (0-14 years), adolescents, and young adults (15-39 years). Overall survival is now greater than 80% [3]. For this reason, there is increasing emphasis on improving cancer survivors' long-term quality of life. Efforts to reduce the adverse effects of treatment are increasingly intense. When a patient not yet reached reproductive age is diagnosed with cancer, their future fertility must be considered, as chemotherapy, radiotherapy, and some surgical treatments can reduce or lose gonadal function. Thus, one of the most important adverse effects of cancer treatment is the loss of fertility temporarily or permanently [4, 5].

Chemotherapy and radiotherapy are essential treatments for oncological conditions. In recent decades, major advances in these treatments have led to a steady increase in pediatric cancer survivors. According to the US National Cancer Institute, the 5-year survival rate for all childhood cancers was 84.5% in November 2019, and similar data were reported for European countries [6]. Consequently, an increasing number of survivors reaching adulthood will face long-term side effects of cancer treatments.

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Impaired fertility resulting from gonadal exposure to gonadotoxic treatments or surgery is a major concern among cancer survivors [7].

Most adult survivors of pediatric cancer want to become parents and have concerns about fertility and reproductive health. Given the increased risk of infertility from cancer treatment, many survivors will find themselves infertile, a diagnosis with a significant psychological impact [8-10].

RISK OF INFERTILITY AFTER CANCER TREATMENT

The most common types of cancer among children and adolescents up to the age of 19 are leukemias, brain and CNS tumors, lymphomas, neuroblastomas, kidney, bone, thyroid, and malignant gonadal germ cell tumors (testicular and ovarian) [11].

Cancer treatments such as hormone therapy, chemotherapy, radiotherapy, and surgery are associated with infertility and early menopause in adolescent girls [12]. Gynecological cancer surgery involves the removal of the uterus or ovaries, thus leading to permanent infertility. Although in the past radical hysterectomy was performed for tumors such as anaplastic embryonal rhabdomyosarcoma of the cervix, in recent years the goal is fertility-sparing surgery such as radical abdominal trachelectomy [13,14]. Gonadal excision in the pediatric population is usually unilateral in the case of malignant tumors, thus allowing the preservation of menstruation and fertility. Bilateral removal of the female gonads is practiced early, in the first months of life in gonadal dysgenesis to prevent cancer or in the rare cases of bilateral tumors [15,16]. Occasionally, the hypothalamic-pituitary axis may be affected by surgical treatment in the case of brain tumors, producing an alteration in the secretion of gonadotropins [17].

Chemotherapy and radiotherapy disrupt the regulation of sex hormones [18,19] and affect primordial follicles [20-23]. Females are born with a fixed number of primordial follicles that will generate oocytes during the menstrual cycle [24]. The number of primordial follicles decreases steadily until a woman reaches menopause. Chemotherapy and radiotherapy are considered "gonadotoxic" because they damage DNA and accelerate the decline of the primordial follicle population [25]. Depleted ovarian follicle reserves increase the likelihood of infertility, temporary amenorrhea, and early menopause. The risk of treatment-related infertility depends on the patient history and age, as well as the type of cancer and its treatment [26]. Cancer patients routinely treated with high-intensity therapies, such as those with advanced-stage Hodgkin's lymphoma, are at greater risk of ovarian involvement [27,28]. Overall rates of gonadotoxicity in pediatric cancer range from 8 to 30%, although they may increase to 70–90% in high-risk subgroups [29]. Chemotherapy causes gonadotoxicity for both sexes. The risk of gonadal toxicity varies depending on the type of oncological treatment received, the accumulated dose, the state of the gonads before the start of treatment, and, above all, the age of the patient when chemotherapy is administered [30].

The adverse effects of radiotherapy on fertility are variable, and sometimes it is impossible to establish a prognosis. Intensity-modulated radiation therapy should always be used to preserve reproductive tissues, and radiation doses to reproductive organs should be evaluated when planning a future pregnancy. Radiotherapy affects the fertility of children with acute leukemia, lymphomas, Wilms tumors, pelvic sarcomas, and brain and nasopharyngeal tumors [18,19,23].

Although hormone therapy is not gonadotoxic in itself, increased duration of treatment may amplify the risk of infertility caused by a decreased ovarian reserve with age. Patients must be informed about the risk of infertility when starting endocrine therapy, and consideration should be given to the duration of treatment. Published data until now estimate that ovarian function could be recovered in 3 months after ovarian suppression following treatment with luteinizing hormone-releasing hormone (LHRH) analogs combined with tamoxifen or aromatase inhibitors. Androgen deprivation therapy generates hypogonadism and low testosterone levels; consequently, it may be associated with oligospermia and azoospermia and cause transient sterility. Data available on the risk of infertility associated with biological treatments are rare and uncertain [24]. Imatinib seems not to cause infertility in men or women. Data about nilotinib and dasatinib suggest that they do not modify the gonadal function in both sexes. Data from the Summary of Product Characteristics (SmPC) and clinical trials indicate that tyrosine kinase inhibitors (TKIs) use is contraindicated for pregnant women. Although angiogenesis plays an essential role in gonadal development, studies showed that both sexes' fertility is moderately affected by sunitinib and other TKIs with antiangiogenic activity, such as sorafenib or pazopanib [31].

SCREENING FOR FERTILITY PROBLEMS

Screening is currently recommended only for survivors with associated risks, which may explain why only 38% have documented endocrine testing [32]. Many more survivors may be at risk of infertility because alkylating agents are used to treat ~50% of all childhood cancers in conjunction with other

gonadotoxic therapies [33]. Another guideline suggests using infertility screening at the request of survivors [34], but it is debatable whether survivors are sufficiently and correctly informed to make such requests. It is the responsibility of physicians to address in discussions with patients all potential late adverse effects of oncology treatment, and precise guidelines are needed for approaching the subject of infertility, choosing the optimal moment of counseling, and interpreting and communicating test results appropriately. Although hormone levels are only suggestive of a potential infertility problem, blood tests can be the first step and allow survivors to make informed decisions about further evaluation, fertility preservation, and family planning timing. At the same time, other barriers to fertility preservation among the pediatric population must be addressed, such as cost, family beliefs, and doctor-patient communication [35,36].

FERTILITY PRESERVATION

Currently, there are several fertility preservation techniques, such as reproductive organ conservation surgery in the early stages of oncological conditions and cryopreservation techniques (of embryos, oocytes, ovarian cortex, sperm, and testicular tissue). The pediatric population is extremely vulnerable, and ethical and legal factors must be considered, in addition to strictly medical factors, before applying these fertility preservation procedures [31,37,38].

FEMALES

Established fertility preservation options for young female patients include ovarian transplantation, radiation protection, and oocyte/ovarian cryopreservation [39,40]. Administration of gonadotropin-releasing hormone analogs for ovarian suppression is commonly used, but efficacy data are mixed, and this option is considered experimental [41].

Cryopreservation of mature oocytes

Cryopreservation of mature oocytes involves ovarian stimulation with gonadotropins for 8-14 days and surgical retrieval of oocytes under transvaginal ultrasound guidance with conscious sedation. This method is most likely to result in a subsequent pregnancy in postmenarchal patients [40,41].

Ovarian tissue cryopreservation

Ovarian tissue cryopreservation (OTC) is currently considered experimental in the United States but is performed as an established fertility preservation procedure in parts of Europe and Israel; it is the only option for patients before puberty [39]. OTC involves the surgical removal and cryopreservation of strips of ovarian cortical tissue or the whole cortex for potential future fertility and hormonal restoration [41,42]. The method is safe and effective, with a risk of minor complications of less than 1%, same-day discharge for most patients, and no treatment delay [43-46].

The recommended technique is unilateral (partial or total) laparoscopic oophorectomy, ideally performed in combination with other necessary procedures, for example, port placement, under a single anesthetic exposure [47].

MALES

Options for male fertility preservation include gonadal radiation protection, sperm cryopreservation, and testicular tissue cryopreservation (TTC). The risk of infertility seems to be greater for male children with cancer than their female counterparts due to the relative chemo- and radiosensitivity of testicular germ cells. Sperm cryopreservation—is the most established option for male fertility preservation and should be offered to all peri- and post pubertal adolescents with a fertility-threatening condition. Sperm quality and DNA integrity can be compromised after a single course of chemotherapy. The stage of pubertal development is considered the best indicator of spermarche (initiation of sperm production), sperm cryopreservation is usually offered to adolescents who are at least Tanner stage II-III for genital development, with motile sperm reported with testicular volumes of up to 6 ml [48-50].

Testicular tissue cryopreservation (TTC) — Lack of mature spermatozoa limits fertility preservation options in prepubertal boys. TTC is an experimental intervention that currently has the greatest potential for this population, although no sperm recovery from this method has been reported to date. TTC involves surgical removal of immature testicular tissue prior to treatment and cryopreservation by slow freezing. Eligibility for TTC generally includes prepubertal children at high risk of infertility or patients who cannot provide an adequate sperm sample [51].

COUNSELING FOR PEDIATRIC ONCOLOGY PATIENTS

Pediatric patients and their families should receive an individualized gonadotoxic risk assessment as early as possible after a cancer diagnosis. Also, timely interventions must be performed to protect their reproductive goals. Oncofertility (OF) is focused on providing information and analyzing fertility issues, managing associated complications,

and offering fertility preservation (FP) alternatives for patients to maintain their reproductive potential [52]. In recent years, OF has become a firmly established discipline and has been declared the universal law [53].

Female childhood cancer survivors treated with gonadotoxic therapies are at risk of ovarian failure, making them less likely to become pregnant than the cancer-free population [45,52,53]. Among survivors who maintain fertility, some studies have found an increased risk for adverse obstetric and perinatal outcomes [10,42,49]. The data obtained so far are contradictory; most studies relied on self-reported outcomes and altered the quality of the results [10,45,54,55].

Thus this population is the focus of counseling and has a greater need for information from virtual environments [56]. Currently, young patients increasingly use social networks to obtain medical information, and they have become a bridge of interaction between healthcare providers, healthcare centers, patients, and relatives [54,55,57]. Almost one-third of patients use social media to seek health-related information, advice, and social support [55].

In recent years, young users have been trying to find dates and support on social media platforms like Facebook, Instagram, Twitter, and YouTube. These platforms could support young patients by increasing their medical knowledge and encouraging them to discuss their doubts and decisions with their GPs. Informed patients have better disease awareness, greater adherence to treatment, and, therefore, better clinical outcomes [54,57-60]. In addition, digital resources increase patient participation in support groups, helping others with the same condition and enhancing their quality of life [61].

Oncology patient-specific online communities pursue interests specific to these categories, and therefore interactions occur between various stakeholders, including patients, families, healthcare providers, and decision-makers. These interactions offer opportunities for non-clinicians, oncology professionals, cancer patients, and those who help them share information, advice, and support [62].

The current practice of fertility preservation counseling and the performance of specific procedures differs between European countries depending on national recommendations, local logistics, technical experience, and cost settlement by the national insurance system. Counseling is a difficult task for doctors and requires an approach that considers the ethnic and cultural background of the patient's family, as well as the maturity and age of the patient. Especially adolescents must be addressed directly, as they usually want to be included in decision-making [63]. It is important for children and adolescents to integrate legal guardians for decision-making and to obtain consent. Besides the shock of a newly diagnosed malignancy or the presentation of side effects, the risk of infertility can be devastating information and should be considered as such [64]. Counseling helps develop a strategy to best deal with the problem and could provide an option for future fertility [65].

ETHICAL ASPECTS

There are ethical dilemmas in fertility preservation for the pediatric population, including parental decision-making, the child's decision-making capacity, the use of experimental fertility preservation methods, religious issues, and disposal of gametes or stored tissue at death. Parents have legal authority over minors' health decisions, and parental permission is required to initiate treatment [66]. Several national and international organizations support deciding on fertility preservation with the parents' help but with the child's consent (age >7 years) [67-69]. There are articles showing discordance between the decisions of adolescents and their parents regarding fertility preservation [70,71]. Systematic reviews of adolescent health decision-making show a strong willingness among adolescents to participate in treatment decisions about future fertility [70,72,73]. Specialized consent forms need to be developed for the adolescent population to allow them to accept procedures alongside their parents [51].

CONCLUSION

The pediatric population diagnosed with oncological diseases has had an increased survival rate in recent years and requires a careful approach to fertility-related problems. Fertility conservation methods before the initiation of cancer treatment have notable results today, and patients are given a chance to have a reproductive life as close to normal as possible. Medical treatments, specific counseling, and careful evaluation of ethical considerations are needed to obtain the best possible results.

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