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Short Review

How to Guarantee Fertility During and After Cancer Treatment?

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Abstract

A significant number of oncologic patients are diagnosed under 45 years old when fertility is a significant factor. A better understanding of tumor biology and therapeutic options has been associated with fertility preservation resources development and, as a result, patients benefit from a more tailored therapeutic plan. Special consideration should be offered by a multidisciplinary approach for this population. In this review, oncologic therapy impact on fertility and current resources available for young cancer patients are revisited.

Introduction

Each year, approximately 1.9 million people are diagnosed with cancer in the United States. Usually associated with people of advanced age, recent statistics show that, of that number, 9% occur at patients below 45 years of age/45 years old. The forms of malignancy most frequently found in Americans aged 20 to 44 are breast, lymphoma, skin (excluding basal cell and squamous cell carcinoma) and leukemia. Within this context, there is a higher rate of therapeutic success based on more advanced and aggressive treatments that, in turn, are also related to a greater number of cases of infertility, sterility or early menopause in young patients [1]. The need for effective but less morbid curative treatment for this group of young patients is mandatory. Thus, over the past 20 years, we have observed a significant increase in studies assessing the potential risks and benefits of fertility-preserving therapeutic options [2].

Despite the growing interest of cancer patients in maintaining fertility, and the fact that up to three-quarters of men and women undergoing treatment under the age of 35 do not have children [3], there are still barriers to the fully implementation of the concept of infertility. Among these, we have structural and scientific difficulties. The pursuit for preservation of fertility should be based on the concept of multidisciplinarity, combining clinical resources focused on the development of methods for maintaining or recovering reproductive capacity in young patients diagnosed with cancer. The management of these patients is complex and should always include the wide exposure of the information to the patient to be treated. The professional involved in the treatment of young patients at risk of infertility must be perfectly familiar with the concept of infertility. Thus, it is mandatory that clinical oncologists, oncology surgeons, radiotherapists, gynecologists, urologists, hematologists, and pediatricians have adequate training that allows adequate clinical guidance about the diagnosis in question. We include/present/show/list on this article knowledge about potential options available for preserving fertility and counseling about paternity / maternity after cancer treatment.

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Gender differences and barriers

Among men and women, the realities are completely different regarding this approach. The use of the sperm bank, although difficult in prepubertal male patients, is an easy option for boys already at puberty and for men undergoing cancer treatment who are suitably advised. Conversely, obtaining and maintaining mature eggs from young women is much more complex, invasive, and time-consuming [3,4]. In a primordial way, the harmful potential of each treatment in future fertility must be defined; the available and appropriate options for preserving fertility for each patient in a specific way must be surveyed; questions about the pregnancy itself after cancer treatment and questions still without definitive answers must be asked. Examples of such questions are: who should finance it? Who defines the conditions that are too serious to consider oncofertility? At what age should preservation of fertility be discussed?

All patients should be referred to a fertility specialist before therapy

The American Society of Clinical Oncology, in a very practical way, indicates that there should be initial recommendations for this patient profile in the referral services. Therefore, the health professional must: discuss preservation of fertility with all patients of reproductive age (and with parents or guardians in cases involving children or adolescents) if infertility is a risk of the treatment in question; refer patients with an interest in preserving fertility to specialists in reproduction; define whether maintaining fertility can have an impact on cancer treatment; offer documentation on this topic in the medical record and, in a very important way, guide the patient so that the process of preserving fertility is sought as quickly as possible, ideally before the oncological therapy begins.

Cancer therapy and fertility

Cancer treatment can result in subfertility or infertility through the removal of gonads or permanent damage to germ cells. The risks are related to the patient's age at the time of treatment, as well as

the dose of therapy used, location and type of treatment used. Specifically in the case of gynecological neoplasms related to fertility, there is a huge range of procedures that can be adopted in order to reduce therapeutic morbidity. This becomes even more important when we observe that, in general, contemporary women are postponing pregnancy. In the United Kingdom, annually, more than 1000 women with cervical cancer, 120 with endometrial cancer and more than 500 with malignant ovarian cancer will be under 45 at the time of diagnosis [2]. In the treatment of cervical cancer in this group of young patients, most popularly based on Daniel Dargent's publications in 1994, we have radical trachelectomy as an appropriate option for selected cases. Most authors recommend that the technique be aimed at patients with lesions smaller than 2 cm in diameter (FIGO 2018 IB1), being an inappropriate option for metastatic disease [5-7]. In very early microscopic lesions (IA1 with lymphovascular invasion and IA2) the incidence of metastatic lymph node disease or parametrial involvement is extremely rare, and both radical trachelectomy and conization with lymph node evaluation have been studied in this context [8-10]. In patients whose treatment essentially involves radiotherapy of the pelvis, ovarian transposition can be considered as an alternative to early ovarian failure and, later, as a possibility of collecting oocytes for *in vitro* fertilization in a surrogate pregnancy [11]. More recently, an ongoing research showed that it is possible to offer a minimally invasive uterine transposition procedure. This technique consists on the repositioning of the uterus and attachments in the patient's upper abdomen, vascularized by the infundibulo-pelvic ligaments, for the duration of the pelvic radiotherapy [12].

Fertility-sparing surgical approaches for selected cancer patients

For young patients, with endometrial neoplasia classified as FIGO Stage IA1, endometrioid histological type and without myometrial invasion, there is the possibility of preserving fertility prior to definitive treatment with hysterectomy. It is a minimal subset of patients in any institution and, among them, a large part meet the above criteria. All should be referred for genetic counseling. Many of these patients have Polycystic Ovary Syndrome, and the diagnosis ends up being made in fertility clinics in the initial assessment of the infertility complaint. In this specific situation, using MRI as a standard with accuracy greater than 90% for initial evaluation and screening of eligible patients [11,13]. The treatment consists of completely removing the lesion, preferably by hysteroscopy, the product of which must be fully evaluated by an experienced pathologist. The placement of an intrauterine device such as Mirena (R) or oral progestagen is recommended, and a recommendation for weight loss. It is important to perform a hysteroscopy exam 3 to 6 months after the procedure, or, alternatively, uterine curettage. In the absence of injury, remove the IUD and recommend getting pregnant as soon as possible. If the tumor recurs, the formal recommendation is hysterectomy.

For patients with germline-type ovarian tumors and those with borderline tumors, with a desire to preserve fertility, surgical staging with maintenance of the uterus and, whenever possible, the contralateral ovary should be offered. For invasive epithelial tumors, genetic counseling and surgical staging are necessary, the extent of which depends on factors such as the histological type of the tumor. There is a potential risk of metastatic disease in the contralateral ovary [14,15]. Benjamin et al., observed that on 3/118 (2.5%) cases of early ovarian cancer, and with an apparent disease confined to one of the ovaries, there was a microscopic disease in the contralateral ovary. Which, in the case of preservative surgery, would mean an increased potential risk of recurrence. In a 2011 publication, based on recommendations from a task force, ESGO recommends that ovarian preservation could be discussed with young patients with stage IA, G1 malignant neoplasm [16]. According to the NCCN, for selected patients with invasive ovarian epithelial tumors, it is possible to offer preservation of the uterus (if IA or IB), and the contralateral ovary (if IA), with adequate surgical staging.

Systemic therapy and fertility

In the context of young patients in need of adjuvant chemotherapy therapy for non-gynecological and hematological pathologies, the risks to fertility depend on the patient's age, dosage of the medication used, the site of the primary disease and the proposed treatment modality. In protocols with chemotherapy, alkylating agents such as cyclophosphamide, appear to have the highest risk of ovarian failure, compromising even oocytes at rest [17,18]. In the setting of acute leukemias, the greatest risks to female fertility, in addition to those exposed above, include chemotherapy and / or radiation therapy used as pre-allogeneic bone marrow transplantation. In most cases, the urgency to start the leukemia- induction-chemotherapy-protocol prevents the performance of fertility preservation measures, but these must be considered after the first remission, or even before the induction treatment, especially for myelodysplastic syndromes of high risk [19]. Age over 30 and use of Total Body Irradiation (TBI) are predictors of infertility in this context [20]. For male individuals over 30 years of age, use of TBI and development of GVHD (Graft-Versus-Host Disease) after allogeneic bone marrow transplantation seems to affect spermatogenesis [20].

Fertility resources

Post-pubertal patients can be referred to ovarian stimulation with gonadotropins, followed by cryopreservation of oocytes or embryos. Advances in oocyte cryopreservation have made this technique replicable and more effective than in past decades, reaching fertilization rates of up to 70% with intracytoplasmic sperm injection. [21-24]. An issue to be discussed in particular with patients with hormone-dependent tumors is the use of gonadotropins in ovarian stimulation. Some experts recommend protocols that combine traditional stimulation with aromatase inhibitors, for example [25]. In the case of patients whose treatment initiation does not allow time for ovarian stimulation or are not eligible for it, have as an alternative drug suppression of the gonads [26].

In particular, there are still female children to whom cryopreservation of ovarian tissue and transplantation of ovarian tissue are options to be discussed. Cryopreservation of ovarian tissue does not require hormonal stimulation or sexual maturity, and may be the method available for this child group [27]. In male patients, planning should be carried out in a similar manner to that of women. In the post-pubertal phase, in the chemotherapy treatment of young adults, this group of patients must be referred to specialized counseling. The most effective form available involves cryopreservation of semen. Depending on the therapeutic scheme employed, multiple sperm samples can be obtained. It is extremely important that the collection be carried out before the start of chemotherapy, thus avoiding permanent damage to the genetic material contained therein. When the first collection takes place after the start of chemotherapy, it is strongly recommended that there is a genetic evaluation of the material obtained in the semen collection. Other methods have been used in various parts of the world, such as preserving testicular tissue, but they are not yet considered routine [28-36].

Conclusion

Multidisciplinary strategies for preserving fertility have been increasingly incorporated into oncology centers. With technological advances, a greater understanding of the behavior of tumors and treatment, in addition to the significant increase in patient survival, many resources are at our fingertips. These are issues of significant emotional impact, which should be strongly considered when the specialized therapeutic plan is outlined.

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