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Research Article

Methods of Fertility Preservation in Young Adults with Cancer

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Abstract

Cancer treatments cause numerous adverse effects, which include gonadal failure, resulting in fertility impairment. Difficulty becoming pregnant after cancer treatment is a problem that is increasingly likely to be raised both by young female patients and by doctors. International guidelines highlight the importance of providing young patients with information about the risk of infertility and fertility preservation options.

Keywords: embryo cryopreservation; oocyte cryopreservation; ovarian tissue cryopreservation

Introduction

Cancer in individuals under the age of 40 years is a lot more commonly diagnosed in women than in men [1]. The cancer incidence rate is two times higher in women aged between 30 and 39 years than in men of the same age group, with the difference resulting primarily from the incidence rates for breast cancer, but also thyroid cancer and melanoma. The most commonly diagnosed cancer in women under the age of 30 years is thyroid cancer, followed by melanoma, Hodgkin lymphoma, and breast cancer. Starting from the fourth decade of life, however, breast cancer ranks first [2]. Young female patients diagnosed with this type of cancer below the age of 40 years account for 5–6% of all new breast cancer cases [3]. Breast cancer is diagnosed in 1 in 200 women under the age of 40 years [4].

Cancer survival rates are increasing. The five-year relative survival rates for young patients diagnosed in 2009–2015 are 83–86% [2]. The number of young people being cured of oncological diseases grows every year.

In developed countries, however, the age at which women decide to become pregnant and give birth grows every year. In the EU countries, the mean age of women at the first childbirth is 29.1 years [5]. Consequently, many patients diagnosed with cancer have not completed their plans regarding maternity at the time of diagnosis.

Principles of managing cancer patients of reproductive age

Many cancer-directed therapies may affect fertility either directly or indirectly. However, young patients diagnosed with cancer are usually unaware that cancer treatment may deprive them of the chance to have biological children in the future. Currently, all international guidelines on cancer treatment in young patients recommend fertility preservation counseling.

It has been proven that fertility loss may affect the self-esteem of patients as well as their relations with partners and family members. Importantly, the patients who completed cancer treatment name unawareness of options as the most common reason for making no fertility preservation arrangements [6]. Other reasons why patients decide not to explore such options include fear of delays in the initiation of cancer treatment, the high cost of the procedures, and potential adverse effects on the health of children.

Oncologists often do not recommend fertility preservation methods, mostly for reasons related to the resultant delays in treatment [6].

Not having children has been shown to be the most important factor determining the desire to preserve fertility after the completion of cancer treatment [7].

Providing information about possible complications associated with the planned treatment, including fertility impairment, is recommended for all newly-diagnosed cancer patients of reproductive age.

Given the time-consuming nature of fertility preservation procedures for women, fertility preservation consultation should be proposed at the time of making the first therapy-related decisions.

Risk factors for fertility loss

The risk of fertility loss is largely linked to the type of cancer and its stage [8]. No significant decline in the ability to have children has been observed in patients who completed treatment for melanoma or thyroid cancer compared with the general population. However, fertility is markedly lower after the completion of therapy for Hodgkin lymphoma as well as ovarian cancer, testicular cancer, cervical cancer, and breast cancer. Completing treatment for the latter two malignancies has been shown to have the most pronounced effect on fertility preservation in women.

The surgical treatment of malignant lesions in the lesser pelvis leads to a complete and permanent loss of fertility. However, fertility-sparing surgery is possible in very early-stage gynecological cancers.

Radiation therapy to the pelvis destroys the reproductive cells, thus rendering the patient irreversibly sterile. If radiation therapy to the area of the reproductive organs is planned, ovarian transposition can be taken into consideration as a method of fertility preservation.

The effects of chemotherapy on fertility in men and women are governed by a more complex mechanism. Chemotherapeutic agents used in cancer treatments may cause temporary or permanent infertility because they affect all dividing cells, including the cells during oogenesis in the ovaries. Cyclophosphamide is a chemotherapeutic agent that has the strongest potential to impair fertility in women. Amenorrhea is experienced by most of the women during therapy with cyclophosphamide. Its use in typical breast cancer regimens advances the age of the ovaries by approximately 10 years. Even when menstruation resumes, the female patients treated with cyclophosphamide experience final menopause earlier than the population of women who did not receive such treatment [9].

The fertility of women diagnosed with hormone-sensitive breast cancer is affected by long-term hormone therapy (5–10 years) used in adjuvant treatment. During this period, the ovarian reserve may decrease significantly, which reduces pregnancy chances. Based on the initial results of the ongoing Pregnancy Outcome and Safety of Interrupting Therapy for Women With Endocrine Responsive Breast Cancer (POSITIVE) trial, interrupting therapy after 2–3 years with the goal to permit pregnancy is recommended in young female patients who have a low risk of recurrence, receive hormone therapy, and plan to have a child [10].

In most men treated with chemotherapy, the loss of the ability to produce offspring is short-term. It returns completely or almost completely within two years after the completion of chemotherapy. Nevertheless, most of the men treated with high doses of chemotherapeutic agents after the age of 45 years become permanently unable to produce offspring as a result of a decline in the percentage of healthy sperm cells in the ejaculate [11].

Fertility preservation procedures

Semen cryopreservation, which is a relatively simple procedure with proven efficacy, is the only method of fertility preservation recommended in men.

Fertility preservation methods that should be used in reproductive-age women in which chemotherapy is planned include above all the surgical fertility preservation procedures, and the use of a gonadotropin-releasing hormone (GnRH) agonist should be taken into consideration. The choice of the method depends on the patient's age, the type of the planned treatment, the question of whether the patient has a partner, and the patient's views on ethical and religious issues. Patients should be informed that fertility preservation procedures improve their chances of maintaining the reproductive potential after the completion of cancer treatment but offer no guarantee that they will have biological children.

Embryo cryopreservation is the process of freezing embryos obtained by *in vitro* fertilization of mature eggs. It is also the most effective assisted reproductive technology (ART). Obtaining an adequate number of mature eggs requires controlled ovarian stimulation. In breast cancer patients, standard hormonal stimulation is not recommended for reasons related to high estrogen levels. In this situation, the concurrent use of an aromatase inhibitor and a short-acting GnRH agonist allows the retrieval of a higher number of mature oocytes while minimizing the rise in the level of estradiol [12]. It is likewise possible to retrieve one mature egg without hormonal stimulation, but this means obtaining only one embryo, which may consequently lead to the failure of the procedure in the case of problems with the implantation of the embryo in the uterus after the completion of cancer treatment.

Regardless of the use of stimulation, obtaining egg cells requires time and causes chemotherapy to be delayed by 2–6 weeks [12]. Initiating the procedure during the late follicular phase or the luteal phase makes it possible to speed up the retrieval of cells by approximately 1–2 weeks and obtain a similar number of oocytes [13]. In cancer patients, when chemotherapy should be started as soon as possible, the time window for fertility preservation methods is very limited, and ovarian stimulation can only be performed once. In selected cases, double stimulation may be performed for the purpose of retrieving a higher number of eggs. The procedure is started during the early follicular phase. Egg retrieval is immediately followed by the second stimulation, but according to the protocol for the luteal phase. The procedure takes approximately 30 days [14].

Disadvantages of embryo cryopreservation include the need to have a partner or to use a sperm bank. The method allows pre-implantation genetic diagnosis (PGD) for genes causing cancer (such as *BRCA1/2* mutations) [15].

In some cases, it may be possible to cryopreserve oocytes. In this method, eggs are not fertilized before they are frozen, unlike in embryo cryopreservation. Oocyte cryopreservation is mainly intended for women who do not have a partner or object to embryo cryopreservation for ethical or religious reasons. The whole of the procedure also takes about one month. As a result of the recent introduction of the rapid freezing of oocytes, the outcomes associated with this method have improved significantly, reaching the levels comparable to those of embryo cryopreservation [16].

Extracting immature oocytes from the ovaries is also possible. Currently, this method is considered experimental. It involves retrieving immature oocytes, maturing them *in vitro*, and cryopreserving mature eggs. The efficacy of this procedure is considerably lower than that of oocyte or embryo cryopreservation. So far, very few births have been reported following the use of this method. However, it may become more widely used in the future because it has the advantage of requiring no ovarian stimulation and above all no delays in cancer treatment [17].

Another method that has been recently evolving involves cryopreserving ovarian tissue. A fragment of the ovarian cortex is collected laparoscopically, cut into thin strips, and cryopreserved. After the completion of cancer treatment, the fragments of the ovarian tissue are thawed and transplanted orthotopically or heterotopically into the woman's body [18]. If they are transplanted back into the pelvis, it is possible for the patient to conceive naturally. In the remaining cases, hormonal stimulation is followed by the retrieval of mature oocytes and their *in vitro* fertilization. The time needed to obtain ovarian tissue does not exceed a few days, so this method is good for women who must start cancer treatment as soon as possible. For now, this is also the only method that can be used in prepubertal girls. The procedure has an estimated success rate of over 30%. Half of the patients being followed up conceived spontaneously [19].

This procedure can also be offered to women who do not plan pregnancy but wish to preserve ovarian function after they complete treatment. However, it should be borne in mind that there is a possibility that malignant cells will be reintroduced together with the ovarian tissue. The risk is estimated at approximately 1% and remains highest for hematological malignancies [20].

Temporary ovarian suppression with GnRH analogues (GnRHa) may be performed to attempt to preserve fertility before chemotherapy. Suppressing ovarian function during chemotherapy protects oocytes, increases the chances of pregnancy, and reduces the risk of premature menopause after the completion of treatment [21,22]. The use of GnRHa during chemotherapy can be offered to all female patients who wish to preserve ovarian function after completing cancer treatment. However, it should be stressed that the effectiveness of this strategy as the only method of fertility preservation is insufficient, especially in older patients and those treated with cyclophosphamide. For this reason, the use of GnRHa during chemotherapy does not replace surgical fertility preservation procedures, which should continue to be offered to all female patients who plan to have children. GnRHa should be given to the patient no later than one week before the first dose of chemotherapy and continued until the end of the regimen [23].

Combining several methods of fertility preservation improves the chances of a live birth and therefore currently remains the recommended strategy. Examples include egg and ovarian tissue cryopreservation and the administration of GnRHa to protect the ovaries during chemotherapy.

Summary

A growing number of young cancer patients plan to have children after the completion of cancer treatment, which highlights the need to promote awareness of available methods of fertility preservation both among medical professionals and in the social media targeting young cancer patients. Importantly, pregnancy after the completion of cancer treatment, even in such hormone-sensitive cancers as breast cancer, is safe both for the mother and for the child [24]. The time between the completion of treatment and pregnancy has no effect on the potential recurrence of cancer or the health of the child. However, the highest risk of cancer recurrence is during the first 2–3 years, so planning pregnancy is usually recommended after this follow-up period [23].

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