CHAPTER 7

Fertility Sparing Team

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Abstract: Cancer is a leading cause of death in the female population, accounting for 6.7 million of new diagnoses worldwide. Cancer and its treatment can often impair the chances of having children, and the fertility sparing issueis an emerging need. In fact, more often, women are delaying conception and therefore, an increasing number of women are diagnosed with malignancy before the desired completion of childbearing. The care of these patients is challenging, and complex, and there is a total lack of validated guidelines. The problem of fertility in a cancer patient encounters not only clinical and technical problems, but it raises many other queries about ethical and psychological perspectives. Since an international consensus statement should be produced, the need for a dedicated multidisciplinary approach is mandatory to offer a clinical range of treatment options. Cancer survivors and the medical community have acknowledged the importance of patient counseling and the pursuit of options for fertility preservation. In 2006, the American Society of Clinical Oncology published the first recommendations on fertility preservation; however, despite the increasing awareness regarding these recommendations, fertility preservation services are still underutilized. ASCO guidelines advised oncologists to discuss fertility risks and preservation strategies and make referrals to fertility specialists for interested patients as early as possible.

There are some programmatic requirements to set up a fertility preservation service, the most significant of which is the availability of a multidisciplinary medical team. A treatment planning approach in which medical figures are experts in different specialties aims to deliver a global treatment tailored to the patient and its disease. A multidisciplinary approach to debating with fertility-sparing issue in oncological patients has mainly two objectives: firstly, to ensure the oncological safety and, in second place, the verification of the fertility preservation desire, that should be not only the intention of the patient but also compliant to “minimum requirements” and therefore a step-wise and careful selection of the women candidate to conservative treatment is necessary. Counseling of patients pursuing fertility preservation should include a discussion of all methods of fertility preservation as well as the alternatives. Because of the sensitive and urgent nature of fertility preservation, a team approach to patient counseling is recommended.

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Effective provision of fertility preservation options requires an ongoing collaborative relationship among medical and surgical oncologists, reproductive endocrinologists and other medical figures.

Oncologists have the initial responsibility to discuss the reproductive risks of intended therapies with the patient and subsequently make referrals to experienced specialists to discuss available reproductive options, which have to be discussed both for surgical decisions and chemotherapy and/or radiotherapy administration. Multidisciplinary teams should include: oncologists, gynecologic oncologists, radiation therapy specialists, reproductive endocrinology and infertility specialists, andrologists, fertility-dedicated biologists, and nurses in the specialties of oncology and infertility, onco-psychologists and social workers. All of these are required to work together in order to achieve a successful collaborative approach.

Keywords: Cancer, Fertility, Multidisciplinary team.

INTRODUCTION

Cancer is a leading cause of disease in the female population, accounting for 6.7 million new diagnoses worldwide. In females, the age-standardized rates in 2012 vary around three-fold, ranging from 103 every 100.000 people in South-Central Asia to 295 per 100.000 in Northern America. The incidence rates of cancer are related to the Human Developing Index (HDI) values; in fact, rates vary around two-fold between very high HDI countries (253 cases per 100.000) compared to low HDI countries (123 cases per 100.000). For example, breast cancer in women was the second most common cancer, with nearly 1.7 million new cases in 2012, most of them diagnosed in high HDI countries. Although not all these women would end up having children, most of them want to at least have the option. Fertility issues are typically raised in high HDI countries according to the most affordable and available access to early diagnosis and treatment of cancer. The burden of cancer in the low HDI countries is widely underestimated, and therefore fertility-sparing is usually not considered before or during treatment. HDI countries can offer technologies and knowledge beyond the treatment of the neoplasm and therefore, there is a commitment in this field. Cancer and its treatment can often impair the chances of having children, making this a harder or even challenging option, or it can raise doubts about whether having children is even the right thing to do.

Actual scenario worldwide (in HDI countries) for the treatment of all types of cancer is an effective multidisciplinary approach, with scheduled meetings among all the specialists involved in treating the particular type of cancer. It's well-known that this type of clinical approach has led to a better outcome for the patients whose treatment has been discussed and reviewed. The evidence suggests

a multidisciplinary approach for all types of cancer; recently, it's going to be mandatory for a hospital to have this clinical organization. More frequently, the "fertility sparing" issue has been mentioned during all the multidisciplinary meetings since it's an emerging need. In fact, more often, women are delaying conception and therefore, an increasing number of women are diagnosed with malignancy before the desired completion of childbearing. The care of these patients is challenging and complex. There is a total lack of security guidelines since most fertility-sparing techniques are of experimental and non-standard nature. The impact of cancer on fertility for a woman is much higher when compared to a man since there is a major objective difficulty in obtaining and preserving the gametes and afterward establishing a viable pregnancy.

The problem of fertility in a cancer patient encounters not only clinical and technical problems, but it raises many other queries about ethical and psychological perspective. Since Assisted Reproductive Technology (ART) is subjected to guidelines emphasizing the value of existing standards to ensure ethical practice, the cancer irruption in this field requests more attention, caution and concentration on oncological knowledge. Since an international consensus statement should be produced, the need for a dedicated multidisciplinary approach is mandatory to offer a clinical range of treatment options to cancer women with fertility issues. Spurred on by this high need for Health Technology Assessment, it seems inevitable, as already suggested by some scientific societies, to establish a permanent Fertility Sparing team that can solidly address these issues. Of course, creating a multidisciplinary team is possible only in highly specialized reference structures with high experience in treating cancers (tertiary level hospitals) that can affect women of childbearing age. Therefore, there are requirements not only from a professional point of view (skills and large experience), but there are also organizational, logistic and finally, technological steps that have to be addressed and verified.

OBJECTIVES

Over 100000 individuals less than 45 years of age are diagnosed annually in the United States: an estimated 30% to 75% of men and 40% to 80% of women in this group face the risk of infertility as a result of their treatment [1].

Over the past four decades, advancements in cancer therapies, particularly chemotherapeutic drugs, and especially in young patients, have led to a dramatic improvement in survival. Given the reproductive risks of cancer therapies and improved long-term survival, there has been growing interest in expanding the reproductive options for cancer patients.

Indeed, both cancer survival and the medical community have acknowledged the importance of patient counseling and the pursuit of options for fertility preservation. In 2006 the American Society of Clinical Oncology first published recommendations on fertility preservation, reviewed and updated in 2013, stating: " as part of education and informed consent before cancer therapy, oncologists should address the possibility of infertility with patients treated during their reproductive years, and be prepared to discuss possible fertility preservation options or refer patients to reproductive specialists" [2].

Despite increasing awareness regarding these recommendations, fertility preservation services are still underutilized. In addition, although patients with cancer frequently report anxiety about their ability to have children in the future [3], many do not recall discussing potential infertility with their physicians or other health care providers [4], and some remain unsure of their reproductive status after completion of treatment [5]. Studies suggest those who receive information regarding their reproductive health have lower levels of psychological distress than those who do not [6].

ASCO guidelines advised oncologists to discuss fertility risks and preservation strategies and make referrals to fertility specialists for interested patients as early as possible.

Nonetheless, studies continue to indicate providers are not routinely offering fertility information and referrals to their patients [7]. In fact, a 2011 survey found that a substantial majority of National Cancer Institute (NCI) designated Comprehensive Cancer Centers had no formal procedures to address fertility preservation, nor were they following the ASCO fertility guidance.

Before the ASCO recommendations, patients' advocates had begun to call for improvement in this arena. One effort was led by Fertile Hope (FH), a nonprofit organization focused on addressing unmet needs associated with cancer-related infertility. In 2005, FH launched the FH Centers of Excellence (FHCOE) program to recognize cancer centers that had institutionalized their approach to fertility, hoping to inspire the replication of similar systems nationwide.

In 2010, LIVESTRONG (a nonprofit organization with the mission of supporting and empowering cancer survivors) acquired several of the programs and assets of FH. The latter then undertook a comprehensive review of its FHCOE program to evaluate the program criteria, describe the means of compliance with its design, and issue program recommendations to LIVESTRONG.

FH identified four fertility-related criteria that cancer center programs on fertility preservation should satisfy.

- *PROFESSIONAL EDUCATION*: professional education raises the knowledge base on cancer-related infertility and fertility preservation and the comfort level of providers with regard to this topic; Lack of content knowledge indeed has been identified as an important barrier to discussion with patients. Professional education can be provided by holding live presentations, grand rounds and role-playing sessions.
- *PATIENTS EDUCATION*: patients' education increases basic comprehension on the subject and provides substantive detail for patients to review after notification. It is provided mainly through printed brochures or supplemental web-based patient materials.
- *NOTIFICATION PROCEDURES*: they include all systems to notify eligible patients of fertility risk and options, verbally and in writing, before initiation of therapy. Notification is the key point of the entire system; all the other criteria have been established to enhance the likelihood that notice will occur and that it will be substantive and useful.
- *REFERRAL*: Referring patients to appropriate reproductive specialists makes the information received actionable. For this reason, a multidisciplinary approach is essential in managing cancer-related fertility issues.

The reasons why many physicians are reluctant to endorse fertility programme (FP) even with national guideline recommendations in place include a lack of physicians' knowledge about fertility, their perception that FP may not be a priority for certain patients (parous patients, older women, *etc*), and physicians' lack of adequate FP referral information [3]. Oncologists' attitude toward FP is significant in patients' decision-making as these vulnerable patients are strongly influenced by the messages they receive from their oncology team [4]. Another obstacle to referral to a fertility specialist is the oncologists' focus on initial cancer treatments. While prompt and appropriate treatments are essential, oncologists may focus most of their attention on these vital immediate issues and minimal focus on future complications, such as infertility [3]. However, the ability to have biological children in the future is extremely important to a vast majority of cancer patients [4]. It is important for these patients to be aware of the risk of infertility and to be able to make a choice to pursue or forego FP independently based on information provided by health care providers.

The programme described provides examples of systems that can be assembled in different types of clinical settings, depending on the availability of resources and infrastructures.

Widespread adoption by cancer centers of programmes that incorporate the baseline elements identified will comply with national guidelines and address patients' reproductive needs and fundamentally affect their future quality of life.

Of course, there are some programmatic requirements to set up a fertility preservation programme.

First of all, for each cancer center, a single and easily identifiable contact point should be available for referring health care providers and patients to provide rapid access to a programme offering fertility preservation services.

Fertility-preservation programme should be associated with an experienced assisted reproductive technology (ART) programme capable of providing a full complement of fertility sparing techniques, including embryo and oocyte cryopreservation. An analogous infrastructure for cryopreservation of sperm and testicular tissue should also be provided.

In addition, the programme should be able to accommodate patients rapidly and be available year round. Ideally, programmes also should be able to counsel prepubertal patients and provide access to procedures (under institutional review board-approved protocols) such as ovarian and testicular tissue cryopreservation, both of which are still considered experimental.

Essential is the availability of an interdisciplinary medical team. The most significant change introduced by the updated ASCO guidelines in 2013 [5] concerns who is responsible for discussing fertility preservation with patients; the original language used by ASCO in 2006 was revised. The word “oncologist” was replaced with “health care provider”, to include medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatrics oncologists, reproductive specialists and surgeons, as well as nurses, social workers, psychologists, biologists and other non-physician providers.

A treatment planning approach in which a number of medical figures are experts in different specialties aims to deliver a treatment tailored to the patient and its disease. Moreover, oncologists must be familiar with the latest ART (Assisted Reproductive Technologies) and the impact of subsequent pregnancies on cancer survivors. Improved fertility preservation education among the oncology team (via Grand Rounds, informal educational sessions, distribution of fertility preservation educational materials and resources to providers and patients, *etc*.) could help allow oncologists to be more involved and make them aware of new developments in fertility preservation. A multidisciplinary approach debating with fertility sparing issue in oncological patients has mainly two objectives.

Firstly, the oncological safety of the treatment has to be clearly defined; in fact, the standard, updated to recent guidelines and best medical-surgical-radiotherapy treatments have to be available on-site at patient or physician request and, of course, should be taken in account during the global planning of the treatment.

The patient must be informed about the prognosis and the outcomes if the standard of care is applied. Of course, standard treatment might be considered even as a salvage option in case of failure of fertility sparing approach. In fact, there is no standard of care for a treatment that preserves fertility in any cancer. Only recently, most scientific societies have been promoting consensus conferences to address this topic. The level of evidence in fertility-sparing approach is very low in most of the available reports, and only in few cases there is a clear and reliable state of the art. Most likely, the oncological safety in conservative treatment might be equal or, in some cases, less safe. In those latter cases, thorough counselling should be offered to the patient and a clear definition of the therapeutic risks. Despite many efforts have been made in oncology to find ways to prevent fertility loss without lowering the cure rate of selected patients, the concerns for the long-term side effects of infertility are still very high.

In the second place, the fertility preservation desire should be verified not only as a real intention of the patient but also according to a "minimum requirements," and therefore, a step-wise and careful selection of the women candidate for conservative treatment is necessary. For *e.g.*, in literature, the fertility-sparing option is considered in patients younger than 40 years old and particularly without children. Since no efficacy data according to patient age is available, as well as fertility and obstetrics outcomes, there is a reasonable open question about that. However, available data demonstrate that the age of the patients strongly influences the risk of sterility in females receiving cytotoxic drugs at the time therapy is administered. Therefore, there is a strong commitment to offering a fertility preservation service in young patients with a childbearing desire.

The entire process of assessing and treating a woman affected by cancer with a fertility desire is highly variable since the physicians enrolled in the discussion come from various specialties according to the cancer type. Hence the need to hold regular meetings with all the various medical figures to promote the adoption of a similar and systematic approach in patient selection and in the treatment planning to highlight pitfalls and criticism, and prevent errors and misunderstanding.

During the selection of the patients who are candidates for a fertility preservation treatment, two further topics have to be carefully considered: the pediatric age and the presence of a genetic syndrome. In fact, while not common, cancer does develop in children, accounting for 8000 cases in American females each year, but fortunately, the overall cure rate approaches 80%. Therefore, due the substantial potential for a cure a concern for the impact of surgical, radio-therapeutic and drug treatment on fertility is quite justified. Of course, a non-standard treatment in these patients has to be always considered and according to the caregivers

(Fig. **1**). Parents are often interested in information about fertility preservation on behalf of their children with cancer. Impaired future fertility is difficult for children to understand but potentially may be traumatic to them as adults.

Unfortunately, there are no standard modalities available for prepubertal children: current techniques are limited by the patients' sexual immaturity, and all available approaches for children are experimental. For example, there are numerous reports of ovarian cryopreservation in young children, but there are no reports of live births after re-implantation of cortical ovarian tissue cryopreserved prepubertally yet. Efforts to preserve the fertility of children using experimental methods should be attempted only under institutional reviewed board-approved protocols. Several studies confirm that adult survivors of pediatric cancer wish they had been given more information and options about fertility. These survivors are often uncertain about their fertility status or regret no longer having an option [7, 8].

Regarding the presence of a genetic syndrome in an oncological patient with childbearing desire, ad *e.g*. BRCA positive women, the field is totally unexplored. Recently the strong impact and widespread of genetic assessment have changed the therapeutical approach and the prognosis of these patients. Carriers of BRCA mutations may be offered bilateral salpingo-oophorectomy (BSO) as a risk reduction strategy for ovarian cancer [9]. Ideally BSO is performed after childbearing is completed. However, these patients should be candidates either for embryo and oocyte cryopreservation. Ovarian tissue cryopreservation for transplantation is not advisable in BRCA mutation carriers, given the increased risk of occult ovarian cancer in this population. However, at the time of oophorectomy, these patients may consider ovarian tissue harvesting for *in vitro* maturation of oocytes and follicles. The experimental nature of this technique should be discussed with patients, as well as the fact that this approach has not led to live birth to date. In addition, there is concern that cryopreserving ovarian tissue may prevent thorough pathologic examination of the ovaries, thus limiting the diagnosis of occult malignancy. In this subset of patients, another medical figure emerges as fundamental as a member of a Multidisciplinary Fertility Team: the genetic counselor. Genetic counseling is recommended for all these patients, regardless of the childbearing desire. In view of the inheritance of the mutation, the genetic counselor should be available to discuss any potential risks of transmission of disease to resulting offspring and the possible genetic testing available.

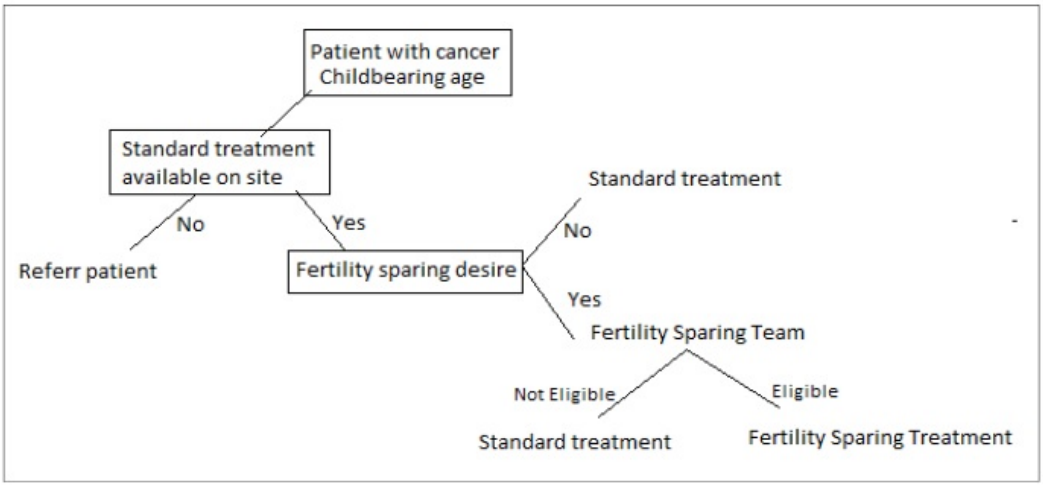

Fig. (1). Decision flow-chart for fertility-sparing treatment.

PRINCIPLES

Counseling of patients pursuing fertility preservation should include a discussion of all methods of fertility preservation as well as alternatives, such as the use of donor gametes, donor embryos, and adoption. The patient's current state of health must be considered, as some individuals with severely debilitating cancer may be too ill to safely undergo fertility preservation procedures. In addition, the potential safety of future pregnancy after cancer should be addressed, taking into account the type of cancer and proposed treatment.

Several factors are involved in making a high-quality medical decision, including the acquisition of information and evaluation of one's personal values or attitudes[10,11]. A thorough understanding of the disease and treatment options is essential to making high-quality decisions[12]. In addition, a patient's participation in decision-making with her healthcare provider has been shown to lead to more favorable patient outcomes[13,14]. Importantly, all these steps are based on efficient communication between patients and healthcare providers.

Because of the sensitive and urgent nature of fertility preservation, a team approach to patient counseling is recommended. Ideally, if time permits, patients should meet with physicians, nurses and mental health professionals over several visits to discuss fertility preservation options. This allows for a more comprehensive evaluation to explore and understand the psycho-social and medical needs of each patient.

Effective provision of fertility preservation options requires an ongoing collaborative relationship among medical and surgical oncologists, reproductive endocrinologists and other medical figures.

Oncologists are initially responsible for discussing the reproductive risks of intended therapies with the patient and subsequently making referrals to experienced specialists to discuss available reproductive options. A detailed description of appropriate fertility preservation techniques should be provided. Ideally, referrals would be made for all adolescents and individuals of reproductive age who are planning to receive gonadotoxic therapies. Interdisciplinary communication among providers is critical to determine the optimal strategy and timing of fertility preservation techniques, considering the overall severity and prognosis of an individual's cancer.

An inter-professional healthcare approach is a process by which two or more professionals collaborate to provide integrated and cohesive patient care to address the needs of their population[15]. Interprofessional involves continuous interaction, open communication, knowledge sharing, understanding professional roles and common health goals.

In summary, the aims of a collaborative and multidisciplinary team approach to fertility issues in cancer patients are:

1- To state the real and strong interest of the individual patients in fertility preservation: it may be difficult for physicians to know how important fertility preservation is to their patients unless they ask because many patients may not bring up the topic. The failure of patients to mention infertility concerns or interest in fertility preservation can result from a variety of factors; they may be overwhelmed by and focused exclusively on the cancer diagnosis, they may be unaware that potential fertility loss may occur, or they may be concerned that pursuing fertility preservation will delay their treatment, leading to increased morbidity or mortality. However, there is evidence to suggest that, at least among women, patients may make cancer treatment decisions based on fertility concerns.

2- To define the stage of disease discuss the optimal standard disposable treatments and the related prognosis, pointing out how fertility can be affected. It is fundamental to point out if fertility can be permanently or temporarily affected, the significance of possible amenorrhea, the risk of premature ovarian failure and anticipated menopause.

3- To assess the feasibility of a conservative treatment taking into account the patient's age and needs, the disease' stage, the disposable controlled clinical trials on fertility-sparing approach, and obviously the oncological safety.

The multidisciplinary action of a fertility-sparing team has to be codified according to the best treatment choice. A sum of all the effects of the treatment regimens included in therapy has to be evaluated according to key principles. Since there is a total lack of a clarified step-wise approach, empirical principles and relative certainties should be applied.

It's obviously not possible to conceive a full list of minimum principles of action, but a brief overview of all the treatment options available, their mutual integration and the main side effects on fertility could be a good basis to proceed. Nonetheless, all the members involved in a fertility sparing team should know the principal side effects of all the treatments for the main types of cancer approached. Since it’s impossible to obtain a comprehensive knowledge of each group of cancer, a wide overviewof all the treatment modalities is mandatory for all the members. Furthermore, the state of the art of Assisted Reproductive Technologies requires a continuous connection with a dedicated full-time gynecologist and constant feedback from the oncological counterpart to apply the latest procedures available to preserve fertility or may increase the success rate of an ART procedure. In fact, a fertility-sparing team can successfully co-operate with a gynecologist experienced in ART procedures from the beginning because not in all patients can a conservative treatment be accomplished, hence the need for a prior step of cryoconservation of the embryo or the ovaries.

Principles During Surgical Procedures

Surgical procedures performed to treat the different type of cancers shows real concerns in the case of gynecological malignancies. In fact, surgery for extra-genital disease can interest the genital area (uterus-tubes-ovaries) only in case of severe spread of the disease. In these cases the feasibility of a treatment respective to the genital area might not be accomplished, hence the need for a careful patient selection.

After the diagnosis of genital cancer, the gynecologic oncologist takes care of women in every step of the treatment, from pre-operative care to tailoring the adjuvant therapy.

Factors that will impact the patient’s desire to preserve fertility and the physician’s recommendation include her age, obstetrical history, family history, a history of infertility, and the cause of infertility, if known. Ideally, fertility potential can be preserved, when appropriate, without compromising curability. The extent of the patient’s cancer is a major determinant of whether fertility-sparing surgery should be recommended. Thus, optimal cancer therapy should always supersede fertility preservation as a primary objective.

In considering the option of fertility-sparing treatment for girls or young women with gynecologic malignancies, the physician must articulate the standard therapy for the patient's condition. Any deviation from the standard treatment with the objective of preserving fertility must be discussed in the context of associated risk.

Unfortunately, there are several instances in which fertility preservation is not discussed with the patient and her family. Particularly with regard to the clinical management of ovarian masses, initial surgical treatment may be rendered by a non-oncologist who does not possess the expertise necessary to appropriately counsel the patient. Expertise of a gynecologic oncologist and gynecologic pathologist is critical in optimizing a patient's potential for fertility preservation; however, such experts may not always be available in the community. Therefore, patients wishing to preserve fertility must be directed to the physician or center with the most experience and expertise.

Girls or women of childbearing age with several ovarian cancer subtypes have a high probability of unilateral ovarian involvement, and, thus, may be candidates for fertility- sparing surgery.

with preservation of a contralateral normal ovary and uterus. These subtypes include ovarian tumors of low malignant potential, malignant ovarian germ cell tumors, and ovarian sex cord-stromal tumors. Fertility-sparing surgery may be an option for women with invasive epithelial ovarian cancer who have early-stage disease. In some cases, fertility-sparing surgery may be followed by postoperative chemotherapy. For women with invasive cervical cancer, fertility-sparing surgery may be possible. Options include conization alone for stage IA1 or IA2 disease, radical trachelectomy with stage IA2 or IB disease, or ovarian transposition for women undergoing chemo-radiation. Non-operative options, such as hormonal therapy, may be considered for women with early-stage, low-grade endometrial cancer. For all women of childbearing age with gynecologic malignancies, *in vitro* fertilization techniques or cryopreservation of ovarian tissue may be an option prior to definitive treatment.

Principles During Medical Treatment (Chemotherapy)

Evidence suggests that the risk of sterility in patients receiving cytotoxic drugs is strongly influenced by the age of the patient at the time the treatment is delivered. Lately there are many regimens employed in routine clinical practice that could preserve fertility in young patients.

The indication for medical treatment with cytotoxic drugs is widespread. Even in pediatric patients, aggressive multi-agent cytotoxic chemotherapy is employed in most childhood cancers. Since these treatments can have a profound effect on fertility, there are a series of situations that as to be considered. Ad *e.g*. temporary amenorrhea is very common in premenopausal women, and the duration of the amenorrhea can be highly variable, ranging from a few months to up to several years following the discontinuation of treatment. Interestingly menopausal symptoms are generally not present in women with temporary amenorrhea, but they can be early and heavy in a patient with permanent failure of the ovarian function. Even if a woman recovers her ovarian function after the treatment, damage to the primordial follicles may induce premature menopause. The age of the patient is a key concept in the risk assessment for ovarian failure after chemotherapy, older is the patient higher the risk. On the other side, patients under twelve years old are less likely to experience premature menopause or infertility.

According to the literature, the cytotoxic drugs associated with chemotherapy-induced sterility are alkylating agents, including nitrogen mustard, cyclofosfamide, melphalan and thiotepa. Delivered dose cumulative appears to be the strongest predictor of permanent infertility. Cisplatin, mostly used ad radiosensitiser or as front line therapy in some types of cancers, can induce permanent ovarian failure. However, patients treated with less than 400mg/mq appear to have a lower risk of developing sterility. In the treatment of Hodgkin’s disease the replacement of MOPP (Mustargen, Oncovin, Procarbazine and Prednisone) with ABVD (Adriamycin, Bleomycin, Vinblastine and Dacarbazine) showed no connection with sterility issues following the treatment. As a mainstay principle, the “older” premenopausal woman, the greater the risk that remaining follicles will undergo failure leading to infertility.

Principles of Radiotherapy

Generally, the most frequent indication for radiotherapy in cancer treatment is gynecological cancers (cervix and vulvar cancer) and other non gynecological-cancer as the colorectal, anal, bladder, Hodgkin's and non-Hodgkin lymphoma.

The ovaries are the most sensitive tissue in the human body to radiation damage and the probability of castration is related to dose and patient age. A mainstay principle affirms that the gonadal toxicity is reached at increasing ages at lower radiation doses. In fact, it's generally agreed that doses above 24Gy delivered in standard fractions uniformly cause ovarian failure [4]. The role of the gynecologist in addressing the issue of ovarian function is to consider the opportunity to perform a laparoscopic transposition of the ovaries outside the

irradiation field in patient candidates for primary radiotherapy. The risk of hidden metastasis in the ovaries has to be considered (especially in cervical cancer and lymphomas). If the irradiation field includes the ovaries and a transposition of the gonads outside the treatment field is impossible, cryoconservation of oocytes or ovaries should be considered. Recently a random stimulation protocol permits a collection of oocytes within a few days, and this is for sure the next big step in a patient requiring an expeditious treatment (ad *e.g.*, hematological disease). Ovarian tissue can be re-implanted (heterotopic or orthotopic) or kept frozen for vitro follicle maturation. The tolerance of the uterus and the cervix to high-dose pelvic radiotherapy is limited and usually, the uterus can't sustain a pregnancy, although endometrial function might be present in young patients. Case reports of pregnancy have been cited solely for brachytherapy treatment only. In the case of lymphoma, the dose of the treatment directed to the internal genitals is lower, and there, it is more likely that a pregnancy could be carried. The damage to the uterus and cervix is related to late effects of the radiotherapy on the ultrastructure of the tissue: ulceration and necrosis will result in a small, firm uterus with an atrophic cervix and dense collagen deposition in the myometrium.

Final Consideration of Principles

In order to consider the final effect of the treatment, a multidisciplinary team has to evaluate the cumulative effects of all the treatments delivered to the patient. Nonetheless, the sequence of the treatment can modify the fertility of the patient, leading to therapeutical spaces for ART procedures, like oocytes prelevation or ovaries conservation. In patients affected by cancer with childhood desire, a therapeutical horizon should be traced and an individual treatment has to be built around the woman to maximize effects and fertility. The goal of a multidisciplinary team is to lead to a composite outcome (oncological, fertility and obstetric). Nowadays, there is a total lack of measurable outcomes; hence there isn't a benchmark for the current practice. Global networking of physicians is recommended to build a common framework and platform for future guidelines.

MEMBERS OF FERTILITY-SPARING TEAM

Effective multidisciplinary teams should include: oncologists, gynecologic oncologists, radiation therapy specialists, reproductive endocrinology and infertility specialists, andrologists, fertility-dedicated biologists, and nurses in the specialties of oncology and infertility, onco-psychologists, social workers. All of these are required to work together in order to achieve successive collaborative approaches.

Medical Figures

All the physicians related to the site disease should be enrolled in the team (ad *e.g*. General Surgeon for breast cancer, Haematologist for haematological neoplasia), while a gynecologist specialized in ART procedures, reproductive endocrinologists, and a gynecologist oncologist should be permanent figures in the team.

A clinical and medical oncologist and a radiation therapy specialist should be enrolled full-time in the team action.

The physicians related to the site disease should have the role of defining the best treatment on the basis of disease stage and patient's prognosis, driving the choice of alternative fertility-sparing approach.

Oncologists and radiation therapy specialists are fundamental to discussing the potential impairment of fertility after chemotherapy and/or radiation therapy.

Gynecologists specializing in ART and reproductive endocrinologists should address the patient with the most suitable and functional techniques for fertility preservation.

Fertility preservation options in females depend on patient age, diagnosis, type of treatment, presence or participation of a male partner, time available, and the likelihood that cancer has metastasized to her ovaries.

An experienced anesthesia team may play a central role in evaluating patients for surgical FP procedures. On occasion, FP patients pose complex medical scenarios that require advanced anesthesia planning. The pathologist is a crucial contact for discussing the disposition of ovarian and testicular tissue obtained for banking. The participation of these specialists in the multidisciplinary team is mandatory in order to avoid the risk of delay in cancer treatment, ensuring an early referral to fertility preservation techniques. A strong connection between the oncology team and the fertility specialist is required for comprehensive fertility preservation (FP) program. Oncologists' support for FP treatment is important in several aspects. First, the fertility preservation process begins with oncologists addressing the possibility of infertility in patients who face fertility-threatening therapies before or during their reproductive years; strong collaboration between oncologists and fertility specialists might contribute to the higher referral rate for sparing fertility in cancer patients.

Second, it is well known that the primary physician's support and opinion have a significant influence on patient's decision-making [4]. Finally, since FP always occurs in conjunction with primary cancer treatments, open communication

between the fertility specialist and oncology team is crucial, especially if modifications are needed for the treatment plans.

Effective multidisciplinary teams that include oncologists, nurses in the specialties of oncology and infertility, social workers, reproductive endocrinology and infertility specialists, andrologists, and embryologists are required to work together in order to achieve success.

Non-medical Figures

Biologists and laboratory personnel who are highly experienced in clinical tissue banking are key members of FP team to freeze cells or tissues and explain the technical effectiveness and potential limits of the procedures.

The psychological and emotional support in dealing with cancer patients has to be demanded by a specialized psychologist; mental health professionals can help patients and their families with counseling needs. They can discuss various ethical and legal issues to set a realistic expectation of fertility preservation treatments and provide emotional support, which is usually beyond the scope of fertility specialists and oncologists.

The role of "Advanced Nurse Practitioners (ANP’s) or Midwives is now of emerging interest in the relatively novel area of Oncofertility. Several studies highlighted the importance of ANP’s role in cancer care, including counselling skills, holistic patient care provision, and specialist procedures. This indicates the potential for the involvement of ANP’s or midwives in developing guidance and information provision in the context of fertility preservation options for patients of reproductive age diagnosed with cancer.

Early identification of key medical contacts facilitates the navigation of patients across specialties within the tight timelines necessary for FP in cancer patients. It is important that FP services and practices are clearly identified to facilitate referrals of newly diagnosed cancer patients by the oncology team members. For most FP programs based on multidisciplinary teamwork, FP consultations can occur within 24-72 hours of referral.

Establishing an FP patient navigator position can significantly reduce the barriers between patients and specialists. They play a role in shepherding patients and ensuring that patients do not get lost between the complex specialties. Within the multidisciplinary team setting, the FP patient navigator bridges institutional and disciplinary boundaries so cancer patients can receive timely information regarding FP options. Also, they serve as the primary contact for patients and

clinicians. This function of the patient navigator makes it possible for patients to make well-informed decisions prior to the beginning of cancer treatment.

DESIGN OF FERTILITY PRESERVATION CONSULTATION

Fertility preservation (FP) consultation with a fertility specialist is a patients' main informational resource regarding fertility and FP options. In a recent survey study evaluating female cancer patients who pursued FP consultation, 100% of patients answered that FP consultation was the most helpful resource for information, and 73% of patients made up their mind about treatment after the consultation [5]. Because, in most cases, only one FP appointment occurs because of time constraints, it is crucial that this single visit is as efficient as possible to allow for information gathering. Utilization of a decision aid as a part of FP consultation can potentially help patients better understand the complex topics [6]. Patient decision aids are tools that help people become involved in decision-making by making explicit the decision that needs to be made, providing information about the options and outcomes, and by clarifying personal values. The efficacy of decision aids in medical decision-making has been validated in various diseases including cancer [7]. Studies investigating breast cancer patients who pursued breast reconstruction surgery found that patients who used an interactive digital decision aid demonstrated greater factual knowledge, reduced anxiety, and increased postoperative satisfaction compared with patients given preoperative instruction using standard methods alone [8]. Pre- and post-consultation exposure to information resources such as brochures and websites about FP options may be helpful, too. Practically speaking, patients have to be informed on how to access these resources and a patient navigator or oncology team members could assist in providing this information. Also, a brief discussion with a patient navigator prior to FP consultation and may help make a complex FP topic more understandable and accessible. To allow patients to make a high quality decision, it is essential to understand their decision-making process. Various factors such as social status, language barriers, financial concerns, and cultural background can be related to a patient's medical decision-making. In a recent study, decision-making about FP treatment appears to be significantly impaired in patients grappling with financial concerns and when the opportunity to ask questions was not felt to be sufficient [5]. To minimize decisional conflict, it is essential to identify and discuss the unique factors that individual patients find challenging about FP. Having a follow-up visit or additional contact with a fertility specialist after the initial FP consultation was found to be significantly associated with lower decisional conflict [9]. Follow-up communication via phone or email may be ideal and realistic under time pressure.

CONCLUSION

While more fertility preservation options exist for reproductive-age cancer patients, access to these services continues to be limited. A tremendous number of individuals need to be involved in moving a patient from cancer diagnosis to completion of FP in a short period of time. While caring for FP patients can be challenging, helping appropriate patients pursue FP options is important because it can give patients a sense of control over their reproductive options and hope for the future. For this reason, it's ongoing a continuous movement to expand the FP program to all comprehensive cancer centers in Europe over the past few years.

Several recommendations can be made to improve the quality of cancer care in fertility issues. All patients of reproductive age should be informed of the potential for gonadal toxicity of cancer treatments and the option available to preserve future fertility. As patients appear to favor individual consultations, structured face-to-face appointments need to be considered to meet individual needs in the context of the complexities of cancer and related fertility.

A follow-up appointment should also be offered once the patient has completed treatment to allow discussion and information about the clinical use of stored gametes (if appropriate).

This is of particular importance for patients who were not in a relationship at the time of gamete storage and for whom circumstances have changed.

There are several barriers to providing fertility-sparing information, including those which are a caregiver and institutional related. Developing an evidence-based intervention in a systematic way could help overcome these barriers and improve the quality of information provision – in the context of fertility preservation - to produce more reliable findings that can be used to inform decision-making.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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