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# Oncofertility: the importance of counseling for fertility preservation in cancer patients

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**Abstract. – Scientific and technological advances in the diagnosis of neoplastic disease and the introduction of increasingly accurate and personalized anti-cancer treatments have significantly improved the chances of survival of most cancer patients, particularly at a young age. Since the interest of the research community in the life prospects of young cancer survivors has been growing, a new branch of medicine has emerged in recent years that reconciles the potentially gonadotoxic treatments of cancer with the preservation of fertility: oncofertility. The possibility of preserving one's fertility can be of great benefit for the psychological well-being of cancer patients, whose mental health is already severely tested by the cancer diagnosis. Although national and international guidelines urge doctors to start early a discussion on fertility conservation issues (reproductive counseling), still little is known as to the awareness of oncofertility by young cancer survivors and the information they receive about it.**

*Key Words:*
Oncofertility, Counseling, Decision-making process, Mental health.

## Introduction

Although cancer is commonly considered a disease linked to aging, the number of patients of childbearing age whose reproductive future may be affected by cancer treatments is indeed relatively high. In fact, data from the National Cancer Institute (NCI) and the World Health Organization (WHO) report that there are about 14 million survivors of some form of cancer in the world and that approximately 5% of them are under 40 years of age[1], while in 2018, there were approximately 43.8 million cancer survivors diagnosed within the previous 5 years. If only women are considered, it is estimated that 0.4% of women have had a previous history of cancer and that 8% of these are under 40 years of age[2]. Young cancer patients faced with the devastating news that their lives, careers, college plans or childhood games may be brutally shattered by the fight against a ruthless disease, are often unaware that the life-saving treatments that they will have to undergo can also threaten their future fertility.

Scientific and technological advances in the diagnosis of neoplastic disease and the introduction of new cancer treatments have significantly improved the chances of survival, allowing patients and their care professionals to think far beyond the success of cancer therapy. In consideration of the fact that modern therapeutic strategies often entail the use of radiotherapy and/or cytotoxic treatments, the possible appearance of sterility and infertility secondary to antiproliferative treatments and the psycho-social discomfort associated with it are issues of greater importance, in terms of quality of life and for the future self-fulfillment of young patients.

The need to reconcile cancer treatment with fertility management allowed, just over a decade ago, the emergence of a new topic: oncofertility, that is a new branch of medicine with an interdisciplinary approach that aims to study and propose to cancer patients the most advanced techniques to preserve fertility, in order to face the reproductive future of young women, men and children


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who are faced with a diagnosis of cancer, whose therapies preserve life but threaten fertility. That prospect will be made even more realistic by the continuous advances in medical and surgical procedures aimed at enabling patients with types of infertility commonly deemed irreversible (e.g., absolute uterine factor infertility, AUFI, or infertility derived from complications suffered in previous pregnancies[3,4]), to have genetically related offspring, such as uterine transplantation[5] and tissue bioengineering[6].

Currently available oncofertility options have been summarized in Table I.

It is essential to bear in mind that each and every fertility-sparing intervention for cancer patients needs to be carried out in compliance with internationally validated guidelines and best practices, following a thorough, highly specialized and individually tailored patient assessment[7-14], including possible genetic risk factors[15]. Only documented and provable compliance with national and international validated guidelines can in fact ensure the clinically and ethically sound implementation of fertility-sparing procedures, while ensuring that health care professionals are shielded from malpractice charges and litigation, particularly under tort law statutes.

### Oncofertility as a Means to Preserve Reproductive Functions and Not Only

The term "oncofertility" was coined in 2007 by Teresa K. Woodruff[23] to describe the intersection of two apparently distant disciplines: oncology and reproductive medicine. This medical branch includes all the aspects that lead the patient to undergo treatments, including invasive ones, for the ultimate purpose of preserving their gametes: from technical procedures to counseling addressing the psychological impact and ethical and legal issues[24]. For many years, men and boys have had their sperm collected and cryopreserved in the United States, prior to the initiation of cancer treatment[25]. Nonetheless, young women who had the same hope of survival (in terms of diagnosis, treatment and prognosis) had few options available to them for preserving fertility. There are three main gaps responsible for such a discrepancy: firstly, an information gap, limited and inadequate dialogue between oncology or reproductive medicine specialists and young cancer patients for the purpose of providing reproductive counseling. That may be partly caused or compounded by a certain degree of reluctance on the part of the patients themselves to bring up and openly discuss such an issue with their doctor.

It may be quite difficult to provide scientifically accurate information as to the risks to fertility and reproductive function posed by specific anti-cancer treatments. That is mostly due to difficulties in predicting what patients are likely to be affected in their reproductive functions, and should therefore be prioritized for oncofertility counseling.

Furthermore, there are relatively few options and considerable difficulties in implementing fertility preservation strategies in a timely fashion, i.e., in the window between cancer diagnosis and treatment. Oncologists and reproductive specialists are often not accustomed to setting quick consultations for patients who need urgent care before undergoing cancer treatment, whose effectiveness, however, is closely related to strict time schedules and limits. Two studies[26,27] have highlighted that young cancer survivors are frequently totally unaware of oncofertility options and attribute such a lack of knowledge to limited and far from standardized reproductive counseling strategies, poor information provision, inadequate support and assistance by healthcare professionals in the decision-making process of patients[28]. Such shortcomings can negatively impact access to fertility preservation procedures before the start of antiproliferative treatment, which can cause frustration and dissatisfaction on the part of survivors themselves[29].

This seems to aim to lingering hurdles and barriers in the multispecialty management of neoplastic patients of childbearing age, especially in consideration of the quality of life and future realization, underlining the need for urgent attention by doctors towards an in-depth knowledge of the issues of oncofertility, the need for specialized and highly informative reproductive counseling, in order to avoid post-treatment regret and to help young women, who have already experienced the drama of a potentially fatal pathology, to carry out a maternity and family project.

In accordance with the 2016 recommendations of the Italian Association of Medical Oncology, Italian Society of Endocrinology and the Italian Society of Gynecology and Obstetrics (AIOM-SIE-SIGO)[30] and with the document of the Permanent Conference for relations between the State, the Regions and the Autonomous Provinces of Trento and Bolzano, issued on 21st February 2019[31], an effective territorial network of Oncofertility Centers should be established, capable of providing all the therapeutic choices to preserve and restore fertility following the remission of the

**Table I.** Currently available oncofertility interventions.

| Technique | Definition | Specifics | Comments |
|---|---|---|---|
| Oophoropexy (surgical ovarian transposition) | It entails surgically moving the ovaries to a location outside the radiation field in the upper abdomen, either laterally toward the pelvic wall or medially behind the uterus, in order to stave off or minimize radiation damage | Surgical procedure.<br><br>It should be carried out shortly before radiotherapy in order to prevent the ovaries from returning to their original position<br><br>It may require surgical repositioning. It does not protect ovaries from chemotherapy induced-gonadotoxicity and therefore has limited role when chemotherapy is administered | Preservation of ovarian endocrine function of approximately 70%. Spontaneous pregnancies are reported[16] |
| Gonadal shielding | In order to minimize radiation damage to ovaries and testes, the genital and pelvic region is protected with a lead apron during radiation therapy. Use of shields to reduce scatter radiation to the reproductive organs | Gonadal shielding is highly advisable especially in young patients, and ought to be routinely used during pelvic irradiation to achieve some degree of ovarian protection | Similar to oophoropexy, gonadal shielding cannot provide ovarian protection from chemotherapy-related gonadotoxicity and has therefore a limited role when chemotherapy is administered. Both oophoropexy and gonadal shielding are hardly ever beneficial when hematologic malignancies are involved: most treatment protocols in fact do not entail local radiation to pelvis without a concomitant chemotherapy[17] |
| Ovarian tissue cryopreservation and further autotransplantation | The procedure involves surgical removal of the ovary and dissection of the cortical tissue for cryopreservation. When fertility is desired, the ovarian tissue is thawed and transplanted orthotopically or heterotopically to the remaining ovary or ovarian fossa. Transplanted follicles can then be maturated by appropriate hormonal stimulation. | The extracted ovarian tissue can be transported to cryobanks. Ovarian tissue freezing is carried out via slow freezing as standard; however, vitrification has been attempted in numerous research trials with promising results | Immature oocytes could be retrieved directly from the extracted ovarian tissue for oocyte *in vitro* maturation (IVM) and vitrification.<br><br>Not feasible in the presence of high risk of ovarian involvement[18]. |
| Oocyte cryopreservation (OC) | OC entails hormonal stimulation, transvaginal retrieval of oocytes from the ovaries, oocyte freezing by slow freezing or vitrification, and storage. When ready to conceive, cryopreserved oocytes have to be thawed and fertilized using standard ART procedures | Patients are accessing and receiving oocyte cryopreservation for a wide range of indications, and there has been a marked increase in patient numbers and OC cycles. OC is also becoming more acceptable as a solution for age-related infertility. | OC requires 10-14 days of ovarian stimulation, as well as an invasive procedure for oocyte recovery (day surgery)[19] |
| Embryo Cryopreservation (EC) | Embryo cryopreservation is the process of freezing embryos created using IVF and storing them for later use. Embryos that are cryopreserved can be treated with cryoprotectants and stored for many years. When the woman has completed cancer treatment and is ready to carry a baby, the embryo will be thawed along with implantation procedures. | It is important to note that sperm is required for the production of embryos; hence this process requires a willing partner or donor sperm. It may lead to legal issues in case of relationship changes if the partner's sperm was used. In Italy, Law 40/2004 bans the procedure | 10-14 days of ovarian stimulation are usually necessary[20] |

*Table continued*

**Table I.** *(Continued).* Currently available oncofertility interventions.

| Technique | Definition | Specifics | Comments |
|---|---|---|---|
| Temporary ovarian suppression with Long-acting luteinizing homone-releasing hormone (LH-RH) analogs | Temporary ovarian suppression with LH-RH analogs are among the well-established oncofertility strategies and are aimed at protecting ovarian tissue during chemotherapy | Clinical trials with promising results, particularly in breast cancer patients | Carried out before and during chemotherapy<br>Relatively simple and inexpensive<br>Can be used in conjunction with cryopreservation techniques[21] |
| Fertility-sparing Surgery (FSS) | Interest in FSS has been growing, particularly as an option for young women with gynaecological cancers such as borderline ovarian tumours and epithelial ovarian cancer | Fertility-sparing surgery (e.g. Radical vaginal trachelectomy with laparoscopic lymphadenectomy small early stage cervical cancers) is generally deemed safe in patients with early-stage cervical and ovarian cancer | FSS can already rely on vast case data reports[22] |

underlying disease. Such centers should be located within public facilities (in the form of Fertility Medicine and Surgery Units) and, as regards the collection of oocytes or ovarian tissue, within MAP centers relying on highly-specialized experienced professionals.

For this purpose, it is necessary to initiate a constructive dialogue between health professionals and institutions and to foster dialogue and collaboration between specialists who treat cancer patients, so that they are directed to the oncofertility centers located throughout the territory that are most suitable for specific needs.

It is essential to improve the interpersonal and communication skills of medical staff, in order to involve and support patients in the decision-making process and to initiate them to the fertility preservation procedures currently available in Italy.

Besides, it could be helpful to create multidisciplinary teams within health care facilities, which should include oncologists, surgeons, endocrinologists, gynecologists, psychologists and, above all, specialists in Reproductive Medicine, in order to address the issue of reproductive risk in a multispecialist and all-encompassing way and to propose various options to reduce such a risk. These teams should undertake reproductive counseling at the time of diagnosis or in the immediate aftermath, in accordance with the recommendations of national and international scientific societies, regardless of whether the woman with cancer has or wants children, considering how female fertility status means much more than mere reproductive capacity in the eyes of the woman herself and society[32].

It would be greatly beneficial to arrive at a standardized, validated and consistently shared model of reproductive counseling, offered by experienced, adequately trained medical personnel and consistently documented in medical records, in adherence to the legal and ethical standards that any informed consent should meet[33]. Solid and thorough counseling can go a long way towards benefiting the patient's mental health as well. In that regard, it is worth remarking that in addition to the severe psychological toll that comes with a cancer diagnosis[34], the prospect of becoming infertile could compound the emotional distress experienced by cancer patients[35]. To many individuals and couples, infertility is no less than a life crisis, which may give rise to severe psychological suffering[36]. Infertile patients are frequently at a higher risk of anxiety, depression, diminished self-esteem and a harrowing sense of personal worthlessness. In addition, spousal issues frequently arise very often[37] due to the pressure in facing highly consequential therapeutic decisions[38]. The incidence of such disorders is apparently rather high among infertile women: as many as 40% of that group meet the standards for a psychiatric diagnosis, with the most common disorders being major depressive disorder dysthymia and anxiety[39]. Infertile women may also be at higher risk of suicidal ideation (a 9.4% incidence), albeit a direct linkage has not yet been established[40]. Quite alarmingly, despite such a high incidence of psychiatric comorbidity, few women choose to seek psychiatric care[41,42]. Overall, the incidence of emotional and psychological sequelae for infertile couples

has been found to be as high as 25-60%[43,44]. Infertility has also been associated with obsessive-compulsive symptoms possibly triggering psychoticism, substance abuse and eating disorders. Women seem to be more severely affected than men[45] by such adverse outcomes.

## Conclusions

This contribution intends to emphasize, in the face of the ever-improving chances of survival of young cancer patients, the importance of raising awareness as to the opportunities offered by oncofertility and the proposal of a reproductive counseling program by multidisciplinary health care teams aimed at upholding the best interest of said patients. This program should also rely on medico-legal support, in order to promote adherence to national and international guidelines and recommendations for the preservation of fertility in cancer patients. Medico-legal activity, both in the prevention of litigation and in the management of clinical risk, should be focused on the active promotion of all those procedures aimed at reducing the risks linked to the therapeutic assistance of cancer patients of reproductive age, attributable to an inadequacy of reproductive counseling, the lack of a standardized and regulated informed consent and the lawfulness of fertility conservation techniques, regulated in Italy by law 40/2004. Scientific progress and recent technological innovations in the field of reproduction and Medically Assisted Procreation have brought about a remarkable extension of the physiological reproductive window. The main scientific progress in this area (along with the introduction of diagnostic procedures and anti-cancer treatments, which are increasingly accurate and capable of increasing the survival rate of cancer patients) is represented by the fact that today, thanks to oncofertility, neoplastic disease and reproduction are not more irreconcilable. In fact, if on the one hand it can be considered undisputed that both doctors and patients must prioritize the path of life-saving care at every stage of the disease, it is also of utmost importance to inform the woman as early as possible about the possible strategies for preserving fertility, in order to enable them to choose their own therapeutic path with full awareness and self-determination. Several areas of research need to function synergistically in order to optimize the provision of counseling about fertility preservation, and those include the improvement of our ability to assess risk prior to the beginning of any therapy, the establishment of the degree to which fertility is affected during treatment, and the scope and extension of the reproductive window left following treatment. Improvements in reproductive technologies, including the development of procedures aimed at obtaining mature oocytes from cryopreserved ovarian tissue, will likely provide a more reliable option for patients who cannot delay therapy. Importantly, increasing insurance coverage for these procedures will greatly expand the number of individuals who can avail themselves of fertility preservation techniques. Ultimately, what should be fulfilled by any means possible is the legal, ethical and moral duty of the doctor, in accordance with the provisions of law 219/2017 and the Italian Code of Medical Ethics, for the sake of the physical as well as mental well-being of all cancer patients and in a manner that prioritizes results.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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