

Oncofertility in Patients with Breast Cancer

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Breast cancer is the most common malignancy occurring in young women. Improving the prognosis of breast cancer patients is of utmost importance in terms of increasing survival rates. Modern medicine has therefore prioritized better quality of life for patients, even after the disease, through a better management of the potential long-term side effects induced by anticancer treatments. Fertility preservation and family planning are therefore crucial issues to be addressed in all cancer patients of reproductive age. Along those lines, a new branch of medicine with distinct multidisciplinary characteristics has developed over the years: oncofertility.

Keywords: breast cancer ; oncofertility

1. Introduction

Breast cancer is the most common malignancy occurring in young women, who account for 7% of the total number of breast cancer cases diagnosed each year in Western countries ^{[1][2]}. Most available data point to young age having negative prognostic relevance at the time of diagnosis. Therefore, young patients are often candidates to be managed with aggressive multimodal therapies that seriously jeopardize fertility. Breast cancer, according to the data presented in the 2019 AIOM-AIRTUM report (Italian Association of Cancer Registries) ^[3], represents the most frequent neoplasm in women of any age, with 30% of cases of the total diagnosis. Furthermore, in the 0–49 age group, its incidence reaches 40% even though such an age group has the lowest incidence. The AIOM guidelines for breast cancer ^[4], using the 2018 estimates, highlight a slightly increasing trend in the annual incidence (+0.3%), coupled with an average drop in mortality on a yearly basis (–0.8%) which, in the younger groups, rises to 0.9%. The shift in the minimum age to qualify for mammograms in some regions contributes significantly to the increase in incidence in the 45–49 age group, with a consequent increase in early diagnoses, which explains the parallel decline in mortality mentioned above.

Breast cancer is the leading cause of cancer-related deaths in women, with a survival rate standing at 87% in Italy overall, which has remained steady in the 15–75 age group, while it is lower in patients over 75. The age bracket accounted for in this study (15–44 years) has a 5-year survival rate of 91%. Although there is a North-South discrepancy in incidence, with the North being at a higher risk (probably due to environmental factors), the survival rate is higher in the North than in the South, possibly due to the less efficient regional healthcare systems in Southern regions ^[5].

In absolute terms, there are about 800,000 women with a previous diagnosis of breast cancer. From what has emerged so far, it seems safe to assume that taking care of the underlying pathology is not enough in patients with breast cancer; in fact, it is recommendable, both from good clinical practice and from an ethical point of view, to devote the right attention to the quality of the aftercare life.

2. Histological and Molecular Classification

The diagnosis of breast cancer relies on two different tests aimed at evaluating the nature of the lesion. In 2012, with a recent 2021 update, the World Health Organization (WHO) laid out the histological classification ^{[6][7]} of breast cancer. Numerous different histotypes are known in the literature; however, in clinical practice, the most common is invasive ductal carcinoma, with a 70% to 80% frequency. Another purpose of the biopsy examination is the staging of the lesion based on the TNM system, which is based on three parameters:

- Primary tumor (T), wherein the local extension of the tumor is examined;
- Regional lymph nodes (N), wherein the impairment of the draining lymph nodes are assessed. In the case of the breast, the axillary lymph nodes are of primary interest;
- Distant metastasis (M), wherein the presence or absence of systemic metastases is studied.

The purpose of staging according to the TNM system is to facilitate clinical decisions and an accurate clinical evaluation, so as to be able to set the best therapeutic path, combining maximum benefits with less stress for the patient. Gauging the local extension of the tumor is fundamental for planning the surgical removal, which must guarantee total eradication of the lesion by exporting as little healthy tissue as possible. Local extension or the involvement of the regional lymph nodes is a useful parameter for an oncological evaluation as to when to start radiotherapy or chemotherapy to eliminate any neoplastic foci. Over time, clinicians have come to realize that although the clinical manifestations and stage of disease were equivalent, patients did not respond in the same way to therapy. In light of such clinical evidence, research has then focused on the molecular profile of breast cancer. Biological investigations have led to the classification of invasive carcinoma into four subtypes [8][9][10][11][12]:

- Luminal A, neoplasms with the expression of hormone receptors for estrogen and progesterone, associated with HER2 negativity and low Ki67 levels [13];
- Luminal B, neoplasms that express hormone receptors, like Luminal A, which are associated with high values of proliferative activity. These, in turn, are divided according to the expression of HER2 into HER2 negative and HER2 positive, in which the levels of Ki67 are not relevant, the strong replicative activity is at the basis of a high risk of recidivism [14];
- HER2-positive, highly expressed HER2 (3+ in immunohistochemical reactions) with an absence of estrogen receptors [15];
- Basal-like or triple-negative, absence of both receptor expression for estrogen and progesterone and HER2, matched by high basal cytokeratin levels [16][17].

Thanks to this classification, the behavior of individual breast cancer subtypes can be assessed in relation to the risk of metastasis [18][19]. The presence of estrogen receptors was found to be a favorable prognostic factor, and the triple-negative subtype is the more aggressive variant. From a clinical standpoint, each subtype has a different metastatic dissemination pattern.

3. Treatment of Breast Cancer

Since they are based on each patient's therapeutic path, countermeasures must be taken to protect the quality of life in the long term. The initial development of the surgical practice was driven by the will of the medical community to counter the major cause of distress and post-operative psychological outcomes: the demolition of the patient's breast with evident aesthetic damage that can compromise the woman's sense of femininity. Currently, radical mastectomy is only carried out in advanced cases with adverse prognosis [20][21]. Although surgery is not the main focus of this article, which is centered around the type of non-surgical therapies adopted in the various stages of cancer, the surgical element is still highly relevant in terms of defining the difference between neoadjuvant and adjuvant therapies (the former take place before surgery, while the adjuvant therapies follow it). Ductal carcinoma in situ (DCIS) is a pre-invasive lesion with the potential to evolve into invasive carcinoma and represents the first stage of malignant breast cancer [22][23][24]. Radiotherapy of the operating field is usually considered. In case of positivity to the immunohistochemical tests for estrogen receptors, tamoxifen can be administered. Surgery alone does not significantly reduce the risk of recurrency [25][26]. As previously observed, hormone therapy causes a risk of infertility [27][28] which, although lower than that of most chemotherapy drugs, must be taken into account in the oncological consultation, particularly for patients of childbearing age. In fact, the risk for infertility lead to a decrease in the use of tamoxifen in this group of age. There is no evidence to support chemotherapy in the treatment of DCIS.

Lobular carcinoma in situ (LCIS) is considered a benign lesion, although it can be associated with an increased incidence of both ipsi- and contra-lateral invasive breast cancer [29]; therefore, it does not require any neoadjuvant or adjuvant treatment.

The treatment of infiltrating carcinoma [29], if immediately operable, requires subsequent conservative surgery, adjuvant radiotherapy, the administration of adjuvant chemotherapy and hormone therapy. Moreover, in ER- and progesterone receptor (PgR)-positive histotypes, biological drugs combined with each other must also be evaluated [30].

Neoadjuvant chemotherapy is used, particularly for most cancers larger than 2 cm, possibly associated with biological drugs. The purpose of this therapeutic approach is to reduce the size of the carcinomatous lesion, favoring less impactful forms of surgery and ensuring better aesthetic results and fewer post-operative complications. Response to adjuvant chemotherapy is a favorable prognostic index. For carcinoma that is not primarily operable, neoadjuvant chemotherapy treatment is instrumental in allowing subsequent surgery. The response to neoadjuvant chemotherapy in this case becomes a favorable prognostic factor.

Only 5% of tumors are diagnosed in the metastatic phase, and when it happens, patients routinely undergo a thorough multidisciplinary evaluation of their general health conditions. Only in 2–3% of such patients can long-term survival or even recovery be the main objective [31][32].

These patients undergo chemotherapy cycles, often as polytherapy; thus, they are at high risk of infertility. In addition, patients who have to undergo neoadjuvant chemotherapy should be able to rely on timely reproductive counseling in order to avoid delays in the initiation of therapy that could result in worse prognosis.

4. Antineoplastic Treatments and Infertility

Infertility resulting from antineoplastic treatments can be determined by radiotherapy, cancer surgery and chemotherapy. There are two mechanisms by which anticancer therapies may interfere with a woman's reproductive capacity:

- Direct damage due to destruction of primary follicles that cannot be replaced, resulting in premature ovarian exhaustion (POF) as the ovarian reserve has been significantly reduced by the treatment;
- Indirect damage that can result either from the involvement of granulosa cells with hormone production deficiency and, therefore, the development of temporary hypoestrogenic hypergonadotropic amenorrhea lasting about 2 months with the recovery determined by the entry of new follicles in the cyclic phase or due to the compromise of the vascular network and of the ovarian stroma with ischemic suffering of the primordial follicles, which causes the apoptosis of the latter [33][34].

Antineoplastic drugs can be subdivided into five classes, according to the frequency of the aforementioned adverse events:

- High risk (>80%): cyclophosphamide, adjuvant therapy for breast cancer in combination with methotrexate, fluorouracil, doxorubicin, epirubicin in patients >40 years;
- Intermediate risk (20–80%): taxani, adjuvant therapy for breast cancer in combination with methotrexate, fluorouracil, doxorubicin, epirubicin in patients 30–39 years;
- Low risk (<20%) vinblastine, bleomycin, dactinomycin, 6-mercapto-purine, adjuvant therapy for breast cancer in combination with methotrexate, fluorouracil, doxorubicin, epirubicin in patients >30 years;
- Very low/absent risk: vincristine, 5-fluorouracil, methotrexate;
- Unknown risk: oxaliplatin, irinotecan, monoclonal antibodies, tyrosine kinase inhibitors [34][35][36][37].

Such a classification notwithstanding, the risk of iatrogenic infertility is difficult to assess at the beginning of treatment: the presence of menstruation is not a reliable parameter, albeit used as an index of fertility by numerous studies, as it may underestimate the ovarian reserve and the woman's capacity to bring a pregnancy to term. A Chinese study on the risk of chemotherapy infertility, in fact, highlights how the percentage of post-chemotherapy women with low levels of anti-Müllerian hormone (AMH) [38][39] is higher than those who have experienced transient amenorrhea [40]. Regardless of the therapeutic regimen adopted, the greatest risk factor for iatrogenic infertility is the patient's age, with a directly proportional correlation. In women under the age of 35, the risk of POF (premature ovarian failure) is about 10%. It rises to 50% between the ages of 35 and 40, and reaches 85% over the age of 40 [41][42]. Although for younger patients there is a lower risk of undergoing POF, given the greater ovarian reserve, the possibility of future damage must be taken into account. It is therefore of great importance to protect all public administrations clients, as the relationship between risks and benefits is totally in favor of the latter.

A further threat to the patient's fertility is the use of adjuvant hormone therapy to prevent relapses in cases of hormone-responsive cancers, such as most breast cancer. Tamoxifen, for example, a selective estrogen modulator, has a receptor antagonist activity that blocks the growth of some types of neoplastic diseases, although by doing so it interferes with the endocrine function of the ovary, causing a deficit of reproductive function and increasing the risk of iatrogenic infertility from chemotherapy, if given in combination [43][44][45]. Highly relevant studies such as the Pregnancy Outcome and Safety of Interrupting Therapy for Women With Endocrine-Responsive Breast Cancer (POSITIVE) have been undertaken to investigate whether temporary discontinuation of endocrine therapy for the purpose of allowing pregnancy may entail a higher risk of breast cancer recurrence [46]. Certainly, patients who wish to achieve motherhood following breast cancer treatment ought to consider that 5–10 years of endocrine therapy (ET) could negatively affect the likelihood to have a pregnancy. Nonetheless, no prospective study has so far involved a shorter ET run in this population. Ultimately, although birth outcomes following breast cancer have been reported to be no different than those among the general population, higher risks have been found regarding delivery complications, preterm birth, low birth weight and Cesarean section [47].

A recently introduced therapeutic alternative is based on monoclonal antibodies, molecules directed towards specific tumor antigens. Although they have not been studied enough for possible side effects on female fertility, an early multicenter clinical trial seems to suggest that monoclonal antibodies are not associated with iatrogenic amenorrhea ^[48].

5. Oncofertility

Fertility preservation in cancer patients has been gaining ever greater attention, largely thanks to the progress in cancer care with increasingly effective chemo-radiotherapy protocols leading to significantly higher survival rates and life expectancy.

Oncofertility is the branch of medicine born from the synergy of oncology and fertility preservation procedures. Its primary objective is to study, outline and implement the most advanced techniques to preserve the patients' fertility and reproductive potential ^[49]. The high incidence of neoplasms in individuals of childbearing age, along with longer life expectancy rates, has prompted health care professionals to pay ever greater attention to the psycho-physical well-being and therefore to the quality of life of patients in the stages following the disease. The increasing incidence of neoplastic diseases in childbearing age is also a financial burden for National Health Systems in terms of care management and long-term follow-up. The World Health Organization (WHO), in an analysis of data from 2015, highlighted that, worldwide, there are 14 million survivors following a diagnosis of cancer, of which about 5% (700 thousand) are under 40 years of age ^[50]. As for Italy, the joint report of the Italian Association of Medical Oncology (AIOM) and the Italian Cancer Registries Association (AIRTUM) 2019, published on the Ministry of Health website, estimates that new cancer diagnoses amount to 371 thousand, with a decrease, therefore, of about 2000 cases compared to the previous year, in the female sex. On the other hand, there is an increase in breast tumors and, in contrast to the male sex, also in pulmonary neoplasms. This is due to an increase in smoking in women of all ages. The 5-year survival percentage has increased, reaching a rate of 63% for women and 54% for men, resulting in a consequent increase in those who live after diagnosis, who number almost 3.5 million ^[1]. For the purposes of this report, the main analysis was focused on the female population, where various critical issues emerged compared to the male counterpart, as reported by a British study ^[51], in light of the anatomical and physiological differences that complicate the process of preserving fertility in women and the different methods applied for this purpose.

Available strategies for ovarian function and/or preservation of fertility in young breast cancer patients prior to administration of chemotherapy include ovarian suppression with gonadotropin-releasing hormone (GnRHa) agonists during cytotoxic therapy, cryopreservation of oocytes and embryos and the cryopreservation of ovarian tissue.

6. Preservation of Fertility in Breast Cancer

There are many techniques available for the preservation of fertility in cancer patients. The first distinction must be made based on the patient's sex for obvious anatomical and physiological reasons. Furthermore, not all techniques are viable for every type of neoplasm.

For example, for breast cancer, given the well-circumscribed field of irradiation, it is not necessary to take precautions against the gonadotoxic effects of radiotherapy. At the present time, there are three main strategies that are adopted to preserve fertility in this class of women. Embryo freezing is illegal in Italy under law 40/2004, mainly on ethical grounds, despite being a well-established and effective practice ^{[52][53]}. Cryopreservation of oocytes is the standard technique for the preservation of fertility in women, and since 2013, it is no longer considered an experimental technique ^{[54][55]}.

The method involves three phases:

- Induction of multiple follicular growth: this entails an ovarian stimulation phase, obtained through the daily subcutaneous injection of gonadotropins, associated with the subcutaneous injection of a similar luteinizing hormone-releasing hormone (LHRH) to avoid early spontaneous ovulation. The duration of the stimulation can vary between 9 and 15 days, causing a delay in the start of chemotherapy;
- Ultrasound-guided egg retrieval: this consists of a short-term invasive procedure, which can be performed under general or local anesthesia. Complications are rare;
- Evaluation, selection and cryopreservation of oocytes: this is a laboratory phase in which the collected oocytes are processed. Those in metaphase II are selected for cryopreservation through vitrification ^{[56][57][58]}.

At present, given the lack of studies conducted on large samples, little is known about the effectiveness of the technique in terms of completed pregnancies. The first data that emerged are very satisfactory ^[59].

Cryopreservation of ovarian tissue, on the other hand, is a technique considered experimental; however, it can be useful in cases where it is not possible to postpone the start of chemotherapy. A review published in 2017 reports more than 80 cases of full-term pregnancies following ovarian tissue transplantation ^[60]. The management and clinical outcomes of breast cancer survivors who managed to achieve pregnancy and patients diagnosed with pregnancy-associated breast cancer (PABC) have been elaborated on in great detail in the 2017 PREgnancy and FERtility (PREFER) study, a broad-ranging prospective cohort study encompassing several Italian hospitals linked to the Gruppo Italiano Mammella (Italian Breast Group, GIM). Interestingly, the study points out how a degree of safety in terms of the pregnancy in cancer survivors has been proven by available retrospective findings. That holds true for patients suffering from hormone receptor-positive disease ^[61].

It is also worth remarking that according to the same study, neonatal outcomes in cancer survivors are apparently similar to those among the general population, although higher abortion and birth complication rates were reported in the former group as well ^[62].

7. Rules Governing Oncofertility

The fundamental goal pursued by oncofertility is in keeping with inalienable rights enshrined in international treaties and covenants.

In 1948, the General Assembly of the United Nations in art. 16 of the Universal Declaration of Human Rights stated: “men and women of full age have the right to marry and to found a family, without any limitation due to race, citizenship or religion [...]” ^[63].

In 1950, the European Convention on Human Rights added to Article 8: “Everyone has the right to respect for their private and family life [...] and there can be no interference by a public authority in the exercise of this right, unless such interference is required by law ^[64]”.

The 1968 International Conference on Human Rights in Tehran, on the other hand, represents the first international document that establishes the right to self-determination of the family. In paragraph 16, it states: “The protection of the family and the child remains the goal of the international community. Parents have the fundamental human right to freely and responsibly determine the number of children and the time lapse between one child and another” ^[65].

In 1994, with the International Conference on Population and Development, held in Cairo, a turning point was reached with an international acknowledgment of the importance of sexual and reproductive rights ^[66]. The Action Program that emerged stated: “Reproductive health is a state of complete physical, mental and social well-being—And not simply an absence of disease or infirmity—On all aspects relating to the reproductive system, its processes and functions. Reproductive health therefore implies that people have a satisfying and safe sex life, that they have the ability to procreate and the freedom to decide if, when and how often”. The forerunner in the reception of international declarations is the USA, where the Oncofertility Consortium was founded in 2005 to implement the union between endocrinological-reproductive needs and treatments at risk of infertility, especially in young women ^[67].

In Italy, with the promulgation of Law 40/2004, the State regulates access to medically assisted procreation (MAP) paths guaranteed by the National Health System; however, the restrictions imposed are deemed too strict and ineffective in upholding the rights of all citizens.

Therefore, on 18 June 2014, the Constitutional Court declared the legitimacy of using heterologous fertilization techniques; the following year, a Constitutional Court ruling legalized access to medically assisted procreation techniques for fertile couples who are carriers of transmissible genetic diseases, thus expanding the population to be granted free access to MAP. Furthermore, questions of legitimacy were also raised with regard to other articles of law 40/2004, declaring it in fact an incomplete law, ill-suited to the current needs of the Italian population.

In 2016, following a joint statement of purpose from three different associations, AIOM (Italian Association of Medical Oncology), SIE (Italian Society of Endocrinology) and SIGO (Italian Society of Gynecology and Obstetrics), a new set of recommendations was released, which stressed the need for a national network of oncofertility centers (OCs), highly specialized facilities in a limited number but rationally placed on a regional basis, in order to provide an accessible and efficient service to the entire population. The above-mentioned document also recommends the creation of an oncofertility center in each region that brings together doctors of various specializations, oncologists, gynecologists, reproductive doctors and also psychologists and biologists to establish the best approach for the patient, both from a technical and human point of view. Consultancy should be provided by the local centers to which citizens turn to for the diagnosis and

treatment in order to provide the most effective and updated diagnostic-therapeutic path ^[68]. To achieve this goal, the recommendations lay out a set of criteria which should be met by OCs:

- They should be placed within public health facilities that meet the multidisciplinary criteria and the criteria of structural compliance with the Guidelines;
- They ought to be capable of guaranteeing a dedicated and consistent service and be adequately staffed (gynecologists, endocrinologists-andrologists, biologists-oncologists, psychologists and nurses);
- OCs need to rely on an effective booking system with availability for specialist-patient consultation within 24–48 h on an informative website;
- OCs need to be able to provide adequate counseling on cryopreservation, on any subsequent MAP options and techniques with adequate information material, and create a standardized informed consent form and digital archiving, preferably on a national basis.

The administration's interest is reflected in the 2015 National Fertility Plan issued by the Ministry of Health and the inclusion of outpatient and specialist services among the Essential Levels of Assistance (LEA) for couples requiring medically assisted and autologous procreation that are heterologous, and, at the same time, the collection and conservation of donated gametes for the purpose of heterologous fertilization are guaranteed ^[69].

8. Reproductive Counseling in Cancer Patients

Reproductive counseling refers to the phase in the doctor-patient relationship in which the risks of chemotherapy treatment on the reproductive system's health are discussed, in addition to the best medical options for preserving fertility. The purpose of well-conducted counseling is to help patients overcome both the psychosocial discomfort deriving from a diagnosis of infertility, temporary or permanent, and to envisage a better quality of life after the disease, as also recommended by the guidelines of the American Society of Clinical Oncology (ASCO) ^{[36][37]} and the already mentioned Italian Association of Medical Oncology (AIOM) ^[68]. Therefore, it is essential that all healthcare professionals dealing with cancer patients of childbearing age are adequately prepared to provide information on the risks of likely impaired reproductive endocrine capacity related to anticancer care and to illustrate all options for preserving fertility.

The guidelines emphasize that the discussion on these topics should be an integral part of the specialist assessment and of doctor-patient counseling as a whole, while pointing out that often, the fertility issue is neglected, which means we are still far from a systematic and timely application of counseling, according to the provisions of the Barcelona Recommendations ^[70]. This often deprives patients of access to fertility preservation treatments.

Fertility, for a woman, represents much more than the ability to give birth: it is a sign of femininity and womanly identity, which may at times lead to a presumption of infertility due to the inadequate information received during the diagnostic-therapeutic process ^{[71][72]}. On the other hand, although the effects that anti-tumor therapy has on reproductive capacity are well known and widely documented, not all women facing a diagnosis of cancer are aware of the long-term consequences. Therefore, counseling and providing information for the patient is important not only for the purpose of fertility preservation; it also allows her to acknowledge the course of her disease, and to become aware of its outcomes ^[73].

A US study conducted on a group of young cancer patients reveals that over 70% of those who, at the time of diagnosis, had no children yet, wished to become parents in the future, and, moreover, most of them believed that the experience of the disease could make them better parents ^[74]. From what has been reported so far about the risk of infertility from chemotherapy and the importance that this side effect plays in the psychology of patients who survived the disease, it can be evidently seen how the doctor who takes care of the health of this population segment has a great responsibility both in terms of the physical and mental health of the person concerned. It is in fact of utmost importance to articulate the communication process with the right timing and approach so that the patient is receptive, responsive and ultimately capable of making a reasoned, conscious and free choice as to the most suitable therapeutic procedures to be undertaken ^[75].

Reproductive counseling, therefore, needs to take on a rather wide-ranging value: it has to be coordinated with the other phases of the diagnostic-therapeutic path, so as not to burden the patient with unnecessary concerns, and inform them as to the best path to be taken both for the treatment of neoplastic diseases and the restoration of acceptable quality of life ^[76]. Given the complex context in which the medical team operates, and despite the undeniable progress that many health systems have made, much work still needs to be done to ensure the best health care is available to young cancer patients. Still, the early involvement of a specialist in reproductive medicine, with the theoretical and practical skills to

conduct an accurate reproductive counseling phase, is currently not part of routine clinical practice ^[77]. It is the duty of health professionals to provide information as to the clinical status, the possible therapeutic pathways and all the viable options for preserving fertility in a thorough, understandable fashion. The entire medical team should make a concerted effort to get through to their patients, striving to meet their needs regardless of social background, level of education and religious belief. Still, even greater attention is necessary when catering to the needs of cancer patients, since such a future risk is often not even conceived by the young patient. At the same time, it is necessary to prepare the patient to undertake a therapeutic choice in a relatively short time ^[78]. The essential role played by reproductive counseling is now widely recognized by the medical community, but still, much remains to be done in order to achieve complete coverage of all patients of childbearing age diagnosed with cancer. A German retrospective study reports that in 20 years, the rate of patients who remembered having engaged in a discussion about the risk of iatrogenic infertility went from a third, in the period between 1980 and 1984, to half in the four years 2000–2004 ^{[79][80]}. An Australian review published in May 2019 ^[81] has collected more than 30 documents drawn up by 19 national and international organizations from Europe and much of the Western world. This list of documents consists of guidelines, clinical recommendations and expert opinions representing a cross-section of the various health systems which, despite the differences between their fundamental principles, agree on the relevance and value of reproductive counseling for fertility preservation. In analyzing the current international state of affairs, it is worth mentioning the 2018 guidelines by the American Society of Clinical Oncology (ASCO) ^[37], which decidedly reaffirm that the dialogue on risks and solutions for the preservation of fertility must be prioritized within the diagnostic-therapeutic process for both oncologists and other healthcare professionals. To better achieve the goal of providing adequate counseling, the guidelines lay the foundations for the correct management of patients of childbearing age diagnosed with cancer who risk compromising their reproductive capacity permanently, through three recommendations for doctors:

- Recommendation 1: cancer patients are to be considered interested in discussing the preservation of their fertility. It is, therefore, the duty of the doctor and in general of any health professional to talk about the risk of infertility as early as possible before treatment;
- Recommendation 2: healthcare professionals should refer patients who express an interest in preserving fertility (and those who are undecided) to a reproductive specialist;
- Recommendation 3: in order to keep all options open, fertility preservation ought to be discussed as early as possible before the start of therapies.

A thorough and exhaustive discussion can ultimately reduce suffering and improve the quality of life. A second consultation may be necessary upon the patient's return for follow-up after completion of therapy and if the patient has considered the desire to become pregnant. The entire counseling process should be reported in the medical record. Recommendation 2 highlights the importance of a specialist in reproductive medicine, which is often underestimated. Referral for second-level counseling to a professional expert in the subject enables the patient to receive much more detailed information compared to what might be offered by the oncologist or surgeon. Furthermore, the dialogue would take place in a different setting that does not focus on the diagnosis of cancer but on the patient's well-being. Still, reports show that this approach is not sufficient to reach the patient's full awareness. Hence, in addition to counseling by a reproductive medicine specialist, the support of paper or digital material freely available by the patient is advisable, so that patients can absorb at their own pace and outside the health facilities the large amount of information received. Moreover, the intervention of a psychosocial consultant should be considered as well to help patients deal with the psychological distress that diagnosis and therapy certainly entail ^[82].

In conclusion, reproductive counseling is universally recognized as an essential phase in the diagnostic-therapeutic process of the cancer patient, resulting in undeniable benefits in terms of health and quality of life. However, several issues linger, including, first of all, the lack of information from doctors who treat patients of childbearing age. A recent Italian study highlights the lack of knowledge of oncologists on the subject ^{[83][84]}, and the shortage of reproductive specialists within the multidisciplinary oncological-surgical teams. Another element that complicates the doctor-patient dialogue is precisely the gender of doctors and of patients: male doctors have been found to have more ease in relating to patients of the same sex, which causes gender disparity, since it is female patients who generally need counseling the most ^[85].

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