

*Short Communication*

# Fertility Preservation in Oncological Patients

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## Abstract

**Background:** Lately, attention is given to fertility preservation in reproductive-age patients undergoing oncological treatment. This should become a routine part of today's assisted reproductive technologies. **Methods:** Available oncofertility preservation methods, next to their clinical, ethical and legal implications are discussed, within the context of the right to health and its broader aspects as delineated in the 1946 Constitution of the World Health Organization. **Results:** Possible egg and sperm freezing, as well as ovarian tissue cryopreservation, should always be explained and suggested to fertility-age patients before starting oncological treatment. Sperm, oocyte, and embryo cryopreservation should become standard practice. **Conclusions:** All ethical, cultural, and moral aspects of fertility preservation in cancer patients are multifaceted and need to rely on principles that are based on widely-accepted guidelines and evidence-based practices. Adequate policy, legislation, and regulations should be agreed upon and implemented.

**Keywords:** fertility preservation; oncology; ovarian cryopreservation; IVF; sperm freezing

## 1. Introduction

Fertility preservation is a relatively new era in the reproductive discipline which was developed in order to preserve the potential for becoming parents of young patients at risk of sterility due to cancer treatment. Egg freezing is already an established routine [1], and so is embryo freezing [2]. Novel techniques such as oocyte vitrification have made great progress and are being increasingly harnessed with remarkable success [3].

Fertility preservation in pediatric patients should be routine, and sperm preservation should be routinely provided when the risk for infertility from the treatment exists. Preservation of spermatogonial stem cells can be offered, although still experimental [4].

Ovarian tissue cryopreservation, which is an option in order to preserve fertility in young women who undergo chemotherapy is also an option. It was shown that ovarian tissue transplantation did restore hormonal cycles and fertility [5].

All the available options to preserve fertility are considered experimental and thus, they raise ethical issues. In this study, we reviewed the informed consent and the risk-benefit analysis of provided experimental procedures for both adults and children when they are in vulnerable situations. In particular, children represent a special category of patients, and their assent to treatment to be sought at any time should be possible. Overall, there should be no ethical objections to offering these services as they are offered with the scope of preserving future fertility.

These days, when genetics, as well as early detection of cancer counseling, is widely spread in developed countries. Advances in oncology treatment in the young population have resulted in an improvement in life expectancy, not just due to the modern treatment, but also due to greater alertness among the clinicians as well as the patients for early cancer symptoms and signs [6].

Therefore, it is of utmost importance that physicians will be aware of the fertility options, and will be able to share their knowledge with patients in a thorough and understandable fashion. Such, and the given information should become an integral part of the consultation, as cancer patients might not be aware of the option of fertility preservation due to their mental situation. Psychological support should be a part of the process [7].

The American Society of Clinical Oncology (ASCO) periodically publishes up-to-date recommendations concerning fertility preservation for young cancer patients. They recommend that information and discussion should be initiated by the physicians, and in the case of young patients, the parents should be involved. Patients should be introduced to reproductive specialists. Information should be given about the potential fertility risks early in the process as well as the given options for fertility preservation. It is recommended for medico-legal reasons that the discussion is documented [8]. Collaboration between oncologists and reproductive specialists is needed in order to increase their knowledge of fertility preservation for patients and develop fertility preservation services. For further progress, increasing awareness of physicians and the general public is needed recommended.



As a result, fertility preservation and the desire for paternity have become significant issues in this group. However, a major concern is the negative impact of chemotherapy, radiotherapy, and the malignancy itself on fertility. Thus, men about to undergo treatment for malignant conditions may have their sperm cryopreserved before commencing chemotherapy or radiotherapy. Ejaculated sperm cryopreservation is the most common technique used. Some patients with cancer may present initially with oligospermia or azospermia. In cases when a sample is not produced due to medical, social, or religious reasons, sperm can be retrieved using penile vibratory stimulation, electroejaculation, or testicular sperm extraction. Fertility preservation in prepubertal boys presents a great challenge, as sperm banking is not possible. Alternative strategies have been developed, but all are currently experimental.

Sperm, Oocyte, and embryo cryopreservation are considered already standard practice. A controversial opinion exists concerning the recommended use of gonadotrophin-releasing hormone agonists (GnRH) and other ovarian suppression methods. In young women with breast cancer, GnRH may be used in order to overcome chemotherapy-induced ovarian insufficiency [9]. Ovarian tissue cryopreservation is becoming already standard therapy [10].

The increasing survival rates for various cancer types in patients of reproductive age along with advances in reproductive techniques have become an issue that concerns health insurance companies as well. A registration system for fertility preservation is needed in order to evaluate the safety and efficacy of the currently available mode of treatment.

A preliminary study was conducted in order to learn about the outcome of fertility preservation treatment, which involved 159 patients who underwent fertility preservation via gonadotropin-releasing hormone agonist, ovarian tissue cryopreservation, or combined hormonal protection and ovarian tissue cryopreservation. Among patients in remission after a mean follow-up of 61.5 months, 29 (31.9%) women attempted pregnancy. The pregnancy rate was 55%, most of them after spontaneous conception [11].

## **2. Fertility Preservation as an Essential Means to Uphold Reproductive Right**

In addition to the essential clinical assessment that needs to be conducted on a case-by-case basis for each patient eligible for fertility preservation procedures, it is of utmost importance to take into account the added value that such interventions can bring in terms of upholding the fundamental reproductive rights of cancer patients, which fall within the category of inalienable human rights. Fertility preservation for cancer patients is extremely relevant in light of the data showing that 0.4% of women have had a previous history of cancer, 8% of whom are under 40 years of age [12]. Although interventions aimed at preserving the patient's fertility are certainly not life-saving, but they are

characterized as “life-enhancing”, or “life-giving”. Such concepts are in keeping with the broad-ranging notion of health that encompasses well-being that goes beyond the mere absence of disease, in adherence to the 1946 Constitution of the World Health Organization [13].

Cancer-induced or iatrogenic infertility as an outcome of cancer treatment can trigger emotional and psychological responses and give rise to psychiatric illnesses. In addition to the often harmful psychological repercussions linked to a cancer diagnosis [14], the prospect of infertility itself can exacerbate the emotional and mental anguish afflicting cancer patients. Infertility can be perceived as no less than a life crisis, which explains why infertile patients often come to experience lower self-esteem, anxiety, depression, and a noxious sense of personal worthlessness that can cause negative emotions to spiral out of control and trigger major psychiatric conditions. The risk of severe outcomes that may undermine the patient's prospects for recovery warrants the implementation of a multidisciplinary therapeutic approach catering to the needs and expectations of each individual patient [15]. That is possibly even more essential when surgical approaches are weighed, and prognostic pre-op techniques take on substantial relevance [16,17]. 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 by such adverse outcomes [18,19]. Moreover, the need to make extremely consequential therapeutic decisions can generate an amount of strain liable to negatively affect relationships and further burden patients in a state of emotional susceptibility [20,21]. Overall, the incidence of emotional and psychological sequelae for infertile couples has been found to be as high as 25–60% [22,23]. A considerable share of infertile women reportedly experiences such disorders, with 40% meeting the standards for a psychiatric diagnosis, most commonly depressive disorder, dysthymia, and anxiety. A 9.4% incidence of suicidal ideation has also been reported among infertile women, although evidence is still inconclusive to establish a clear correlation [24]. In light of the above-mentioned findings and the alarming linkage between infertility and mental issues, the essential nature of counseling cannot be overstated. Despite the high incidence of psychiatric comorbidity, in fact, relatively few women actively seek professional psychiatric assistance [25,26]. Yet, making sure that such care is accessible and effectively delivered without discrimination and inequality is essential from a medical, moral, ethical and legal perspective. Certainly, fertility preservation techniques can be ethically controversial for the same reasons assisted reproductive technologies (ARTs) are: when scientific and technological advances outpace the cultural, moral, and ethical evolution of our societies, legislative actions aimed at governing such innovations may mirror such discrepancies. ARTs have in fact been regulated through broadly varying levels of restrictions in Europe and worldwide, and that is

indeed understandable in light of the different sets of social and moral priorities each society espouses and turns into legislation through its lawmakers. Restrictions of an uneven degree from country to country can however increase the risk of inequality between those who can afford “fertility travels” to countries with permissive legislation and those who cannot, with the latter’s reproductive rights thus jeopardized [27–29]. Taking into account the European Union, that is largely due to the fact that the European Court of Human Rights affords a broad margin of appreciation to member states in matters involving social, moral, and ethical values. Still, there is no denying that oncofertility does have a fundamentally distinctive trait: it is rooted in the moral duty to respect the autonomous reproductive rights and choices of individuals, a core value that a free society can but enforce. If it is true that adults ought to be enabled to exercise such rights, provided that no unreasonably high risk is incurred to the children thus conceived or to others, cancer patients are entitled to see their reproductive freedom enforced as well. From a legal standpoint, the failure to provide information and counseling on fertility preservation opportunities could even entail grounds for a loss of chance lawsuit, if the patient’s reproductive potential is demonstrably impaired as a result, albeit jurisprudence and case law in that sense is still far from decisive [30]. Oncofertility can then be viewed from such a vantage point as a noble effort deeply rooted in non-negotiable ethical, legal and moral precepts such as autonomy, beneficence, and non-maleficence. A specifically and individually designed course for each individual patient must therefore be mapped out, ultimately intended to prioritize the hopes, reasonable expectations, beliefs, and aspirations of all parties involved. Harmonization would certainly be greatly beneficial in pursuing such goals. Still, there is still a lot to be done for the purpose of developing more harmonized and consistently standardized and evidence-based diagnostic-therapeutic protocols for reproductive counseling and fertility preservation for cancer patients, in accordance with the recommendations of scientific societies such as the American Society of Clinical Oncology (ASCO) [31], Japan Society of Clinical Oncology [32], the Italian Association of Medical Oncology (AIOM), Italian Society of Endocrinology (SIE) and the Italian Society of Gynecology and Obstetrics (SIGO) among others [33]. For the same reasons ARTs may present considerable quandaries, and when scientific and technological advances outpace the cultural, moral, and ethical evolution of our societies, legislative actions aimed at governing such innovations may mirror such discrepancies. ARTs have in fact been regulated through broadly varying levels of restrictions in Europe and worldwide, and that is indeed understandable in light of the different sets of social and moral priorities each society espouses and turns into legislation through its lawmakers. Restrictions of an uneven degree from country to country can however increase the risk of inequality between those who can afford “fertility travels”

to countries with permissive legislation and those who cannot, with the latter’s reproductive rights thus jeopardized [27–29]. Taking into account the European Union, that is largely due to the fact that the European Court of Human Rights affords a broad margin of appreciation to member states in matters involving social, moral, and ethical values. Still, there is no denying that oncofertility does have a fundamentally distinctive trait: it is rooted in the moral duty to respect the autonomous reproductive rights and choices of individuals, a core value that a free society can but enforce. If it is true that adults ought to be enabled to exercise such rights, provided that no unreasonably high risk is incurred to the children thus conceived or to others, cancer patients are entitled to see their reproductive freedom enforced as well. From a legal standpoint, the failure to provide information and counseling on fertility preservation opportunities could even entail grounds for a loss of chance lawsuit, if the patient’s reproductive potential is demonstrably impaired as a result, albeit jurisprudence and case law in that sense is still far from decisive [30]. In addition, overlooking genetic risk factors may bring about “genetic malpractice” charges [34,35], i.e., negligently failing to take into account genetic testing and verification. Oncofertility can then be viewed from such a vantage point as a noble effort deeply rooted in non-negotiable ethical, legal, and moral precepts such as autonomy, beneficence, and non-maleficence. A specifically and individually designed course for each individual patient must therefore be mapped out, ultimately intended to prioritize the hopes, reasonable expectations, beliefs, and aspirations of all parties involved. Harmonization would certainly be greatly beneficial in pursuing such goals. Still, there is still a lot to be done for the purpose of developing more harmonized and consistently standardized and evidence-based diagnostic-therapeutic protocols for reproductive counseling and fertility preservation for cancer patients, in accordance with the recommendations of prominent scientific societies.

### 3. Conclusions

In order to be thoroughly effective and beneficial for its intended target, oncofertility needs to rely on professional and comprehensive counseling, for the sake of the patient’s physical as well as mental health. It is therefore essential to ensure that each and every intervention aimed at preserving fertility for cancer patients must be clinically, ethically, and legally sound, in full adherence to internationally recognized guidelines and best practices. Any therapeutic pathway needs to be molded according to a highly specialized and individually tailored patient evaluation, which has to take into account the genetic risk factors as well. Only documented and demonstrable adherence to national and international guidelines can protect doctors and healthcare providers from litigation arising from malpractice. Medicolegal soundness is in fact even more relevant in a realm such as oncofertility, which relies on various

practices still deemed experimental. That can in fact ensure that the worthy and noble practice of fertility preservation protocols for cancer patients is ethically implemented from the clinical and legal standpoints, and the rights of prospective parents and children yet to be born are properly upheld.

## Author Contributions

SZ, MS conceived the idea and wrote the article, and both read and approved the final manuscript.

## Ethics Approval and Consent to Participate

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## Conflict of Interest

The authors declare no conflict of interest. SZ is serving as one of the Guest editors of this journal. We declare that SZ had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to LM.

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