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REVIEW ARTICLE

Reproductive Tissue Cryopreservation for Cancer Survivors: Barriers and Challenges in Low-Resource Settings

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Abstract

Reproductive tissue cryopreservation is done for fertility preservation (FP), which is a critical aspect of cancer survivorship, especially for children, adolescents, and young adults undergoing gonadotoxic treatments such as chemotherapy and radiotherapy. Preserving reproductive potential has become more crucial as cancer survival rates have increased. However, obstacles to FP make it challenging to use and implement, especially in environments with limited resources.

This review aims to examine the effects of cancer treatments on reproduction, the FP procedures that are available for both male and female patients, the difficulties in making FP decisions, and the obstacles to putting FP strategies into practice in settings with limited resources.

Fertility is greatly impacted by chemotherapy and radiation, with pelvic radiation and alkylating drugs presenting the most significant hazards. Male tissue freezing include sperm cryopreservation from ejaculated semen and testicular sperm or tissue in case of azoospermia. Techniques for females include cryopreservation of oocytes, embryos, and ovarian tissue. A multidisciplinary approach involving oncologists, reproductive specialists, and psychosocial support teams are necessary to enhance fertility preservation (FP) accessibility. However, implementing FP opportunities in low-resource settings is challenging due to several barriers.

Due to cultural preconceptions, exorbitant prices, a lack of medical knowledge, and limited awareness, the acceptance of FP remains low despite advancements. In low-resource settings, financial constraints, inadequate infrastructure, and insufficient training of healthcare professionals further exacerbate FP access issues.

Barriers to FP at the patient, provider, health system, and societal levels were identified, along with potential remedies.

Establishing oncofertility patient navigation systems, integrating FP discussions into oncology care, and creating financial support programs can facilitate informed FP decisions and improve implementation in low-resource settings.

Keywords: Cancer Survivors, Chemoradiation, Fertility Preservation, Low-Resource Settings,

Introduction

Among millions of cancer patients, a large proportion are children, adolescents, and young adults. The most recent Global Burden of Disease (GBD) 2019 study reported 1.19 million new cancer cases and 396,000 cancer-related deaths globally among adolescents and young adults (AYAs).[1,2] Cancer treatment regimens have evolved over the past two decades, leading to enhanced survival rates. Recent years have seen a steady increase in the survival rates of these patients, attributed to the improved efficacy of novel oncological treatments. The 5-year survival rate for pediatric cancer patients is approximately 85%.[3] Treatments involving chemotherapy or radiotherapy frequently lead to compromised reproductive function or complete infertility. The age at treatment initiation influences the severity of the effects of chemoradiation, the duration of therapy, its intensity, and the specific type of treatment administered. Patients receiving high doses of alkylating chemotherapy or radiotherapy face a considerable risk of future fertility issues.[4-6]

In light of this success, the late effects of both the disease and its treatment are gaining significance. To

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enhance the quality of life for survivors, fertility preservation (FP) before chemoradiation is a critical option for restoring future fertility. Reproductive tissue freezing for fertility preservation denotes the safeguarding of an individual's or couple's capacity to initiate a family at their preferred time. The concept of onco-fertility has emerged as an interdisciplinary network that integrates medical methods aimed at optimizing the reproductive prospects of cancer patients through the provision of various fertility preservation techniques. Despite increasing acknowledgement of the significance of fertility preservation within cancer care, societal acceptance remains relatively low in numerous contexts. Decisions concerning family planning can be complex, and insufficiently informed decision-making may result in future regret and distress.

There remains a lack of consistent, up-to-date, and evidence-based guidance for healthcare providers. Patients are often not given adequate information or timely referrals to fertility specialists before starting cancer-directed therapy. This gap highlights the urgent need for comprehensive clinical practice guidelines to support clinicians in discussing fertility risks and preservation options with patients undergoing cancer treatment.

This article provides a short overview of the reproductive effects of cancer treatment, the reproductive tissue freezing as fertility preservation and family-building options available to adolescent and young adult patients, the barriers and challenges related to fertility preservation decisions, and the key factors that influence clinical care in low-resource settings.

Impact of cancer therapy on fertility

Chemotherapy and radiotherapy serve as fundamental components of cancer treatment. Cancer treatments may adversely affect spermatogonia in males and ovarian follicles in females. Spermatogenesis in males may continue for several years if spermatogonial stem cells are not eliminated.[7] However, in females, the loss of follicles is irreversible. Alkylating agents present the highest risk of long-term infertility compared to other gonadotoxic chemotherapy agents.[8]

In male

Chemotherapy and radiotherapy, mainly when aimed at the pelvic region, can profoundly affect male fertility by harming sperm-producing cells in the testes, frequently resulting in diminished sperm count, transient or permanent infertility, and possible complications with sperm quality, depending upon the treatment type and dosage administered.[9-12] It is crucial to take into account the patient's age and pubertal status at the time of diagnosis, together with the probable effects of the disease.[13]

The germinal epithelium is susceptible to RT, dosages as low as 0.1 Gy leading to a short-term halt of spermatogenesis, 2-3 Gy disrupts spermatogonial stem cells and produces long-term azoospermia, 6 Gy (e.g., total body RT with 10 or 13 Gy) produces long-term or permanent infertility. Leydig cell insufficiency and testosterone deficit have been described at RT doses of 20-24 Gy.[14] A potential deleterious influence of cancer on semen parameters has been described for patients with testicular tumours and Hodgkin's lymphoma.[15]

In Female

Effect of chemotherapy

Effect on the gonads and oocyte

The adverse effect of chemotherapy on the ovarian follicle reserve results from both damage to the ovarian vasculature and the direct effects of chemotherapeutic drugs on primordial follicles. The extent of damage depends on the type of chemotherapeutic agent administered, the dosage, the patient's age, and her baseline ovarian reserve. Age-related diminished ovarian reserve, rendering them more prone to premature ovarian failure (POF).[16]

The drug-induced apoptosis leads to advanced recruitment of follicles, referred to as the "burnout mechanism",[17-19] causing extensive loss of follicles.[20,21] The clinical presentation of this follicular loss varies from total amenorrhoea to early menopause and differing levels of infertility. Anti-Mullerian hormone (AMH) is a key indicator that accurately reflects ovarian reserve after chemotherapy[22, 23] and is unaffected by hormonal treatments.[24]

Patients are advised to delay conception till 6 months after completion of treatment. It is also recommended to wait for the fertility preservation technique for 6 months after completion of therapy. It is not recommended to do fertility preservation between the chemotherapy cycles.[25]

Mechanism of action of chemotherapy.

Each chemotherapeutic drug targets distinct action sites and is formulated to affect dividing cells. While alkylating chemicals target DNA, antimetabolites influence DNA synthesis, and spindle toxicity affects the mitotic process. The development of the oocyte is intricately connected to the growth of the granulosa cells. Consequently, damage to the granulosa cells will result in harm to the oocyte [26]. Doxorubicin, an anthracycline, and cyclophosphamide, an alkylating drug, primarily impact granulosa cells, while cisplatin predominantly targets the oocyte.[27]

Effect of radiotherapy

Radiotherapy is widely acknowledged to damage the ovarian reserve. Nonetheless, predicting the magnitude of the harm is challenging. The estimated radiation dose necessary to eliminate 50% of primordial follicles, referred to as median lethal dose (LD50), is less than 2 Gy.[28]

Acute ovarian failure and premature menopause are associated with hypothalamic, pituitary, and pelvic radiation, with or without the use of alkylating agents [29]. Exposure to 20-30 Gy of radiation or 15 Gy of total body radiation may result in diminished ovarian function.[30]

Rate of gonadotoxicity of different chemotherapeutic agents.

Not all chemotherapeutic agents are equally toxic to the gonads. Cytotoxic drugs are classified by risk as follows (Table 1)[31]: Alkylating drugs exert a profoundly detrimental impact and are associated with the highest age-adjusted odds ratio for ovarian failure rates.[32]

Table I: Classification of chemotherapeutic agents according to severity of toxicity[31]

High Risk	Intermediate Risk	Low Risk
Cyclophosphamide	Cisplatin	Methotrexate
Ifosfamide	Adriamycin	5-Fluorouracil
Chlorambucil	Carboplatin	Vincristine
Melphalan	Doxorubicin	Bleomycin
Busulfan		Actinomycin D
Nitrogen mustard		Vinblastine
Procarbazine		
Mercaptopurine		
Nitrosoureas		

Chemotherapy regimens classified as intermediate or medium risk have been reported to induce primary ovarian failure (POF) in 40–60% of women aged 30–39 years [33-34]. A low-risk chemotherapeutic agent induces primary ovarian failure in fewer than 20% of individuals under 30 years of age.

Pelvic irradiation alone has considerable repercussions. Complete ovarian failure manifests with a dosage of 20 Gy in women under 40 years of age and at merely 6 Gy in older women.[35] A dosage of 4 Gy may lead to the depletion of fifty percent of ovarian follicles.[36]

Options and techniques of reproductive tissue freezing for fertility preservation

Tissue freezing options for males.

Sperm cryopreservation

Sperm cryopreservation, commonly known as sperm banking, is the primary technique for preserving male fertility, involving the collection and freezing of sperm for subsequent use.

Table 2: Risk of permanent amenorrhoea after treatment with chemotherapy and radiotherapy [37]

High risk >80%	External radiotherapy that includes the pelvic region CMF, CEF, CAFx6 cycles. women >40 years
Intermediate risk <20%	CMF, CEF, CAF x 6cycles in women <30 yearsACx4 cycles in women <40 years od
Very low risk or no risk	Vincristine, Methotrexate, Flurouracil
Unknown risk	Taxanes, Oxaliplatin, Irinotecan, Monoclonal antibodies (trastuzumab, bevacizumab and cetuximab), Tyrosine Kinase Inhibitor (erlotinib, imatinib)

CMF: Cyclophosphamide, methotrexate, and fluorouracil, CEF: Cyclophosphamide, epirubicin, and fluorouracil: Cyclophosphamide, doxorubicin, and fluorouracil

It is easy to collect sperm from normozoospermic, oligospermic, and even from azoospermic men. Sperm sample is collected by masturbation or electroejaculation, who are not able to do masturbation. In cases of azoospermia, testicular sperm extraction (TESE) or microsurgical (microTESE) extraction is performed to collect sperm from testicular tissue. No option exists till now for prepubertal boys. Sperm cryopreservation should be done before starting chemo and radiotherapy to avoid potential genetic abnormalities in sperm after exposure to therapy [38].

Testicular Tissue Cryopreservation

Testicular tissue cryopreservation for future implantation is currently under experimental study. It remains in its nascent phase but has potential for fertility preservation in prepubertal children and adolescents. There exists a danger that testicular tissue auto transplantation may reintroduce malignancy.

Tissue freezing options for females.

Cancer survivor rates are significantly higher among females (65%) than among males (35%) in younger age groups. So, fertility preservation should be offered after proper counselling for future fertility and improved quality of life.

Options of fertility preservation should be tailored according to:

- Patient's age
- Type of disease: The overall prognosis for the patient
- Spread of the disease:
- Plan of treatment: The risk of sterility with the proposed treatment
- Time available: The potential risks of delaying chemotherapy.
- Whether she has a partner
- The possibility of tumor contamination of the harvested tissue

Options are

i. Embryo freezing

ii. Oocyte freezing

iii. Ovarian tissue freezing

iv. Immature oocyte collection and In-vitro maturation (IVM)

Oocyte, embryo, and ovarian tissue can be preserved for future use. Oocytes and embryos can be effectively and securely cryopreserved prior to the commencement of anticancer therapies. Women of reproductive age are the appropriate candidates for oocyte and embryo cryopreservation. For embryo cryopreservation, it needs sperm to fertilize the oocyte. Therefore, candidate should be married. But ovarian tissue freezing can be done for all women including prepubertal girls.

Candidates for oocyte cryopreservation are

1. Post-pubertal girls
2. Adult unmarried women

Candidates for embryo cryopreservation are

1. Married women who have partners
2. Unmarried women who want to use donor sperm

Candidates for Ovarian tissue cryopreservation are

1. Pre-pubertal girls
2. Any woman who needs to start chemotherapy within a short time, or in other words, who cannot take two to three weeks to undergo egg or embryo freezing, is a candidate for ovarian tissue freezing.

Procedure for oocyte and embryo cryopreservation

Embryo cryopreservation is a well-established and reproducible technique; however, it requires the use of sperm and the participation of a partner or donor. Oocyte cryopreservation can be conducted without the necessity of a partner, rendering it the preferred option for most post-pubertal women.

The capability to cryopreserve oocytes has significantly improved in recent years due to the advancement of ultra-rapid freezing or vitrification. Any protocol can be used, but as there remains an urgency for chemo or radiotherapy, the procedure needs to be completed within the shortest possible time. In this regard, the antagonist protocol can be used, which needs less time than the agonist long protocol. The antagonist protocol procedure is initiated during the menstrual phase of the cycle. However, as there is no question of implantation, it is not necessary to start during the menstrual phase of the cycle. Stimulation can be started at any time of the cycle, which is called "random start" of stimulation.[39] After 10-12 days of stimulation by gonadotropin, follicles mature when the

size of the follicles attains 17 mm or more. Antagonist is used to prevent the LH surge and is started on D6 of stimulation or when the size of the follicles becomes 14 mm. When follicles attain the size of 17 mm or more, ovulation is triggered by hCG, and ovum pick up is scheduled 34-36 hours after hCG injection. Collected oocytes and or embryos after fertilization are cryopreserved for future use.

During ovarian stimulation, supraphysiological estradiol (E2) production has raised concerns in hormone-sensitive cancers. Addition of letrozole, an aromatase inhibitor, along with gonadotrophins during OS can effectively reduce the oestrogen production [40,41]. It is administered from the start of OS in a dose of 2.5-5mg daily and continued until after oocyte retrieval, until the E2 levels normalize. Use of Letrozole does not appear to affect the oocyte number or fertilization rate.

In women with diminished ovarian reserve and no immediate requirement for anticancer therapy, double stimulation may be contemplated; this necessitates four weeks of treatment and approximately doubles the quantity of oocytes obtained. The effectiveness of oocyte and embryo cryopreservation in achieving a subsequent pregnancy is closely linked to the quantity of mature oocytes obtained following ovarian stimulation. The quantity of recovered oocytes diminishes in women with diminished ovarian reserve (i.e., low AMH levels resulting from ovarian surgery or advancing age). The quantity of retrieved oocytes depends upon age, ranging from 15.4 ± 8.8 in women under 26 years to 9.9 ± 8.0 in women aged 36-40 years.[42] Recent data indicated a cumulative live birth rate of 61.9% for women aged 35 years who had 12 oocytes cryopreserved, and 43.4% for women over 35 years with 10 oocytes cryopreserved.[43]

Oncologic risks of ovarian stimulation.

Concerns regarding the safety of conventional ovarian stimulation protocols particularly the short-term exposure to high estrogen levels have led to the development of alternative approaches aimed at minimizing estrogen exposure in patients with estrogen receptor (ER)–positive tumors undergoing fertility preservation. These strategies include the use of tamoxifen, a selective ER modulator, or letrozole, an aromatase inhibitor. Available evidence indicates that the number of oocytes and embryos retrieved is not compromised when these agents are used.[44]

Procedure of ovarian tissue cryopreservation

Ovarian tissue cryopreservation (OTC) involves the surgical removal of ovarian cortical tissue, which is rich in primordial follicles, followed by cryopreservation using either traditional slow freezing or the more advanced vitrification method, with subsequent transplantation typically performed laparoscopically. Re-implantation is most often orthotopic, into the ovary or pelvic cavity, although heterotopic sites such as the abdominal wall or forearm may be used when necessary. Evidence shows that OTC not only restores endocrine function but also enables fertility, with reported pregnancy rates of ~32.7% and live birth rates of ~26.5% per patient, while cumulative data place live birth outcomes in the 21–33% range depending on whether conception occurs spontaneously or with assisted reproduction.[45,46] Pediatric and adolescent cohorts further demonstrate pregnancy and birth rates of approximately 34.5% and 24.1%, respectively, underscoring its value for patients requiring urgent gonadotoxic treatment, as the procedure avoids ovarian stimulation and preserves the possibility of natural conception.[47]

Heterotopic transplantations necessitate in vitro fertilization to facilitate pregnancy. The success of transplantation is influenced by the patient's age, baseline ovarian reserve, and the expertise of the surgeon and cryobiologist involved in the procedure. Ovarian function usually resumes between 60–240 days post-transplant and would extend for up to 7 years. This technique is the sole method for preserving fertility in pre-pubertal girls. In 2004, The Lancet published a study by Donnez et al. detailing the first successful delivery following the orthotopic transplantation of ovarian cortical tissue in a patient with Stage 4 non-Hodgkin's lymphoma. Meirow et al. reported a case of a female who, after treatment for non-Hodgkin's lymphoma, subsequently gave birth to a second living child.[48]

Risk of malignancy reintroduction in OTC.

A more recent review documented two cases of cancer arising within transplanted ovarian grafts [49] To avoid this chance of malignancy following strategies can be adopted. 1. Careful patient selection, 2. histological and molecular screening of ovarian tissue and 3. avoiding direct auto transplantation by a) in Vitro Maturation (IVM) and b) artificial ovary technology (experimental) in which follicles are isolated, embedded in a biomaterial scaffold, and matured

outside the body to avoid reimplanting potentially contaminated tissue.

In Vitro Maturation (IVM)

IVM is an assisted reproductive technique (ART) in which immature oocytes (eggs) are collected from the ovaries and matured in the laboratory before being fertilized by ICSI. Immature oocyte can be collected from unstimulated ovary, partially stimulated ovary or before processing of ovarian tissue. It Avoids or reduces the need for high doses of ovarian stimulation drugs and reintroduction of malignant cells by ovarian tissue transplantation. It is beneficial for women breast cancer, risk of ovarian hyperstimulation syndrome (OHSS) and for urgent fertility preservation before cancer treatment. Successful live births following IVM have been documented in the literature.[50-53]

Potential Risks to offspring

Long-term cryopreservation does not appear to result in an increased occurrence of embryonic aneuploidy when compared to fresh oocytes.[54-56]

Barriers and challenges in Low-resource settings

Many barriers exist when it comes to fertility preservation. Barriers are at different levels. In various low-resource countries, a significant obstacle to the effective establishment of ART clinics is the acute shortage of medical doctors, nurses, social workers, embryologists, and laboratory technicians with knowledge of reproductive medicine. The shortage of proficient, locally accessible embryologists is prevalent in resource-poor areas, where they play a critical and significant role in an IVF laboratory. Many private clinics, through transnational networking, borrow qualified embryologists from other countries for a short time as flying experts to carry out the laboratory procedures, which might interfere with the ideal treatment environment.

Despite the setting up of ideal laboratory facilities, there are different barriers to fertility preservation in cancer patients. Barriers are

1. Patient-level barriers

Fertility preservation decision is not easy for cancer patients, where survivability is a big question. Patients and guardians remain anxious about the start and outcome of the treatment. They believe that the time required for tissue preservation may lead to treatment delays and potentially poor treatment outcomes.

Patients may lack sufficient information or recollection of the effects of cancer treatments on fertility or fertility preservation strategies. If survivors fail to completely comprehend the potential effects of cancer and its therapies on fertility, they may forgo pursuing fertility preservation.

Moreover, fertility preservation is expensive. Cancer therapy is also costly. In low-resource settings with no insurance coverage, life-saving treatment is the top priority for spending money. For both males and females, the procedural cost and annual storage cost are not bearable for most of the patients. So, decision-making is dependent on the financial condition of the patient.

FP decisions for patients under the age of 18 may be influenced by parents or guardians, even though many minor patients have a strong desire to participate in decisions about FP and their future reproductive health; they frequently feel excluded from treatment decisions. Several factors may influence minors' involvement in FP decision-making, such as: (1) the cost of procedures; (2) evaluations of the child's decision-making ability; (3) perceptions of the child's desire to be included in the decision; (4) assessments of the child's chance of surviving cancer; (5) parents' or guardians' attitudes toward FP; and (6) the family's religious and/or cultural values. However, the reproductive health concerns of minor patients may differ from those of their parents, who may underestimate their child's anxieties about the impact of cancer on fertility.[57]

Furthermore, discussions regarding fertility with the medical team may encompass delicate and potentially uncomfortable subjects (e.g., masturbation, sexual functioning). Patients, especially adolescents, may experience embarrassment during these discussions, particularly when conducted in front of their parents or guardians. Patients expressing embarrassment may be less inclined to pursue FP discussions with their parents/guardians and healthcare practitioners, as well as to contemplate FP options.

2. Provider-level barriers

The following are some of the provider-level barriers to fertility preservation referrals: i) lack of understanding of FP and training in discussing preservation options; ii) low self-efficacy or discomfort with FP discussions; iii) believing that infertility is a side effect of cancer

treatment and/or less relevant to oncology practice; iv) concerns about the costs (financial, emotional, and physical) to patients; v) concerns about the emotional fallout from FP conversations; vi) considering information overload to a patient who is already distressed.[58-60] Referrals for these procedures may be rare because providers may not be well-versed in new protocols that allow for quicker preservation times (such as random-start controlled ovarian stimulation) and surgical procedures for prepubescent patients (such as ovarian tissue cryopreservation).

Fertility discussions may also be impacted by patient and illness characteristics. When patients are female, younger, or have a specific cancer diagnosis, such as breast cancer, lymphoma, leukemia, or testicular cancer, providers are more likely to talk about how medication affects fertility.[61] Furthermore, factors like the level of pain, the patients' satisfaction with fertility-related conversations, and the oncologist's perceived support may influence the decision to preserve fertility [62]

3. Health system level barriers

Cancer care increasingly requires patients to shoulder a greater share of expenses through deductibles and coinsurance [63,64]. Higher out-of-pocket costs have been shown to hinder both initiation and adherence to recommended treatments [65,66]. Similarly, utilization of fertility preservation (FP) services is associated with significant financial hardship.[67]

In many countries, insurance coverage may be available through employer-sponsored plans, Health Insurance Marketplace (Affordable Care Act) plans, Medicaid, military insurance (Tricare, Veterans Administration), or the Federal Employee Health Benefits Program; however, FP coverage varies widely across these options. By contrast, in low-resource settings, insurance policies rarely provide financial support for FP.

Health care policies vary in different countries. Availability of services and insurance coverage for services are important factors contributing to barriers to having reproductive health care. Billing methods that necessitate upfront, out-of-pocket payments for fertility-related testing and procedures may impede patients' capacity to pursue fertility preservation while concurrently undergoing expensive cancer treatments.

Providers may lack awareness or knowledge regarding referrals to fertility centres, potentially restricting patient access to fertility preservation. So, lack of insurance coverage and lack of an appropriate referral system are the main barriers to FP.

Sometimes, oncologists' business finds insufficient time with patients as a significant impediment to discussions regarding fertility preservation. Due to these time constraints, providers prioritize treatment discussions without giving a clear idea to the patient about the impact of treatment on fertility, which affects referrals for fertility counselling and preservation. Cancer survivors frequently endure non-specific symptoms, including stress, worry, and reduced quality of life; yet, numerous cancer patients of reproductive age are insufficiently informed about fertility preservation and do not obtain referrals to reproductive experts.[68]

At the societal level:

Many patients remain unable to access the benefits of innovative prevention strategies, early detection programs, biomarker testing, and novel cancer therapies due to structural barriers such as limited transportation, unstable housing, inadequate insurance coverage, food insecurity, low health literacy, distance from specialized cancer centers, and the high cost of care [69]. Sexual and gender minority populations face additional stigma and barriers to cancer screening, prevention, and treatment, which further contribute to disparities.[70]

Geographic disparities also influence outcomes, as rural patients experience higher mortality rates and poorer survivorship compared with non-rural populations, in part due to fewer specialists and cancer centers. To address these inequities, reproductive care should be integrated into the standard of care for all oncology patients. However, cost, limited access, and time-sensitive nature of established fertility preservation (FP) methods remain significant barriers to optimal reproductive care. Disparities in access to oncofertility services for racial and ethnic minorities and low-resourced patients exist in many societies.

How to overcome?

The goal is not to increase the FP rate per se, but rather to empower patients to make informed FP decisions.

A. Establishment of opportunities for low-cost treatment

Bringing down the cost of cancer treatment and fertility preservation to an affordable level so that both

treatments can be accessed comfortably. Establishment of insurance policy for giving financial support. Cost discussions should be incorporated into shared decision-making.[71] Clinicians are encouraged to familiarize themselves with their state's FP insurance laws to help patients identify potential coverage options. When financial concerns arise, patients should be directed to insurance navigation and financial counselling services, which can provide essential support in navigating this complex and heterogeneous landscape.[71]

B. Setting a multidisciplinary approach for cancer management.

An established collaboration between oncology and fertility units is crucial. Involving psychosocial providers, who can support when a patient is concerned about infertility. Providers must be equipped with appropriate knowledge regarding the impact of cancer treatment on fertility and the options of fertility preservation. The knowledge and attitudes of physicians regarding fertility preservation significantly influence management practices. A multidisciplinary team including cancer specialists, surgeons, nurses, and reproductive experts is essential to accelerate fertility preservation options for cancer patients. Involvement of specialists from many fields is essential for maintaining treatment standards.

C. Development of patient navigation system

Clinicians have an obligation to inform patients about both the known and unknown risks of treatment on future fertility. Current guidelines emphasize the importance of early referral to reproductive specialists and psychosocial providers for patients at risk of infertility.[72-77] Referrals should occur as soon as possible. Social workers and psychologists, play a critical role in supporting patients as they cope with the distress associated with potential infertility an especially important consideration given the heightened psychological burden among individuals with cancer[78] Evidence shows that addressing fertility concerns early reduces long-term emotional distress, whereas many survivors who were not adequately informed report regret about missed opportunities [79]. For patients who are unable to pursue biological parenthood after treatment, alternative family-building options such as gestational surrogacy, gamete or embryo donation, and adoption remain available. Psychosocial providers are integral in guiding patients and families through decision-making about fertility preservation and stored gamete disposition, ensuring choices align with legal, ethical, and personal values.

Oncofertility patient navigation is essential for assisting cancer patients in accessing fertility preservation by bridging the gap in information, coordination, and accessibility, hence enhancing reproductive outcomes. Their role should be

- Close collaboration between oncology and fertility centers
- Selection of representatives from oncology, infertility (includes urology/andrology), and psychology departments
- Development of a patient navigator in an oncology center- either clinical or non-clinical
- Patient education: Patient should be well informed regarding i) the impact of cancer treatment on fertility, ii) the duration for preservation for males and females, iii) the long-term cost of preservation, shipping, and storage, and iv) for future use. iv) assistance for FP decision-making, vi) the effects of cancer and its therapies on sexual health, together with information regarding self-image and relevant sexual health resources.
- Resources: Navigators can assess patients' eligibility for financial assistance for FP and assist patients with applying for external grants.
- Access: The navigator reviews the medical record and refers directly (If doctor) or by a health care provider (If non-medical) to the fertility center. If needed, the navigator coordinates consultation with an in-house fertility center or other fertility centers. The navigator communicates with all individuals involved in the patient's care to understand the treatment timeline and assist with scheduling and FP consultation, ensuring consistency with this timeline (ASAP of referral).
- Support: If more decisional or psychological support is needed, the navigator refers the patient to a clinical psychologist, psychiatrist, and sex therapist.

Conclusion:

Currently, several individuals are achieving disease-free states in oncological healthcare. Given the enhanced prospects for recovery and prolonged living, it is imperative to explore several strategies for

preserving patient fertility at the time of diagnosis and during survivorship. The optimal technique must be selected from the available options according to the patient's characteristics: male, female, prepubertal, or post-pubertal. Cryopreservation of sperm and embryos is regarded as a standard procedure and is frequently performed. Alternative methodologies should be regarded as experimental and conducted in facilities possessing the requisite expertise. Despite an increase in the availability of FP for cancer patients undergoing gonadotoxic therapies, only a minority of patients pursue FP. One important barrier in low-resource setups is economic constraints. The lack of a standard setup and skilled personnel is a barrier to offering the services. Besides those, the lack of knowledge regarding FP and the awareness of providers is also a significant factor. The navigator's participation in patient care might alleviate provider workload by providing patients with fertility education. Facilitate prompt and convenient access to fertility centres. To assist patients in making value-based decisions regarding parenthood and comprehending family-building alternatives.

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