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Fertility Preservation in Cancer Patients: Review Article

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ABSTRACT

Background: Chemotherapy, radiotherapy, and surgery, which are cancer treatments, can potentially impair fertility significantly and present significant challenges to cancer patients presenting for diagnosis during their reproductive years. Chemotherapy, radiotherapy, and surgery can result in temporary or permanent infertility and undermine the reproductive potential of cancer survivors.

Aim: This in-depth review examined the current status of fertility preservation in patients with cancer, with a focus on recent advancements, ongoing challenges, and prognosis of fertility outcome.

Methods: Data were collected from online review articles and papers from the PubMed, Science direct and Google scholar for both male and female fertility preservation techniques, such as embryo and oocyte cryopreservation, sperm banking, and emerging techniques like testicular and ovarian tissue cryopreservation, were addressed in the review. Ethical concerns are also dealt with in the review, including the use of oncofertility counseling and the importance of interdisciplinarity for improved patient outcomes. The authors also reviewed references from pertinent literature, however only the most recent or comprehensive studies from 2004 to 2025 were included. Documents in languages other than English were disqualified due to lack of translation-related sources. Papers such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations that were not part of larger scientific studies were excluded.

Conclusion: Fertility preservation consists of medical and surgical interventions intended to preserve reproductive potential before, during, or after cancer treatment. Techniques of embryo and oocyte cryopreservation, sperm banking, and ovarian and testicular tissue cryopreservation showed varying success. Oncofertility counseling and multidisciplinary care enhance patient decision-making and outcomes, although difficulties regarding accessibility and ethics remain. Continued research and development of biotechnologies are necessary to optimize the effectiveness and availability of fertility preservation, bringing hope to cancer survivors for achieving reproductive goals.

Keywords: Fertility preservation**,** Cancer treatment**,** Oncofertility**,** Embryo cryopreservation**,** Oocyte cryopreservation**,** Sperm banking.

INTRODUCTION

Millions of individuals are affected by cancer every year, making it a significant global health concern. According to the World Health Organization, there were roughly 9.6 million cancer-related deaths & 18.1million new cancer diagnoses in 2018. Although progress in cancer therapies has improved survival rates, these treatments frequently come with significant side effects, including adverse effects on fertility. Chemotherapy, radiotherapy, and surgery can impair reproductive functions, leading to temporary or permanent infertility. Fertility preservation is crucial for cancer patients, particularly for those diagnosed during their reproductive years. It provides individuals with the opportunity to have biological children post-treatment. Fertility preservation methods have advanced significantly, offering various options to safeguard reproductive potential. This review explores the current state of fertility preservation in cancer patients, focusing on recent developments & ongoing challenges [1].

Ethical consideration: Approval of this literature review proposal has been obtained from the Medical Research Ethics Committee, Faculty of Medicine, Sohag University.

Cancer in children and adolescents

Cancer is relatively uncommon among children and adolescents, yet it remains a primary cause of disease-related mortality in these age groups. In 2020, about 400,000 children & adolescents aged 0-19 Years were diagnosed with cancer worldwide. The most prevalent types comprise leukemia, brain tumors, lymphomas, & solid tumors such as neuroblastoma & osteosarcoma [2]. The case distribution and survival rates, summarized in table (1), highlight age-specific patterns in childhood cancer incidence and outcomes.

Cancer treatments can severely affect the fertility of young patients. Chemotherapy and radiotherapy are particularly gonadotoxic, potentially leading to premature ovarian failure in females & impaired spermatogenesis in males [3].

Early intervention with fertility preservation strategies is critical to mitigate these effects and provide future reproductive options.

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Table (1): Case distribution (2014-2018) & five-year relative survival (2011-2017) by age & international classification of childhood cancer type, ages birth to 19 years (United States) [4].

	Birth to14		15to19	
	% of cases	5-year survival, %	% of cases	5-year survival, %
All ICCC groups combined		**85**		**86**
Myeloproliferative, myelodysplastic, and leukaemia disorders	28	87	13	75
Lymphoid leukemia	21	92	7	76
Acute myeloid leukemia	4	68	3	67
Reticuloendothelial neoplasms and lymphomas	12	95	19	94
Hodgkin lymphoma	3	99	11	97
Non-Hodgkin lymphoma (counting Burkitt)	6	91	7	89
Central nervous system neoplasms	26	74	21	76
Benign/borderline malignant tumors[a]	8	97	13	98
Neuroblastoma and other tumours of peripheral nerve cells	6	82	<1	66
Retinoblastoma	2	96	<1	
Nephroblastoma and other renal tumours that are not epithelial	4	93	<1	
Hepatic tumors	2	80	<1	56
Hepatoblastoma	1	82	<1	
Malignant bone tumors	4	73	5	68
Osteosarcoma	2	68	3	68
Bone sarcomas associated with Ewing tumours	1	76	2	59
Rhabdomyosarcoma	3	70	1	50
Gonadal and germ cell tumours	3	90	10	93
Thyroid carcinoma	2	>99	12	>99
Malignant melanoma	1	96	3	95

Childhood Cancer International Classification., The survival rates are based on patient follow-up through 2018 & are adjusted for normal life expectancy, a Although they were included in the denominator for case distribution, benign & borderline brain tumors were not included in the survival estimates for total central nervous system tumors & all cancers combined. The survival rate's standard error ranges from five to ten% points, Because there were less than twenty-five instances from 2011 to 2017, statistics could not be computed.

Cancer survivors

Due to advancements in early detection, treatment, and supportive care, the number of cancer survivors has been on the rise. According to the American Cancer Society, there are now over 17 million cancer survivors in the United States alone [5].

Cancer survivors often face significant fertility challenges. Treatment-induced gonadotoxicity can result in reduced ovarian reserve, decreased sperm count, and compromised hormonal function [6]. These effects can complicate natural conception and necessitate the use of assisted reproductive technologies.

Pregnancy rates and factors affecting fertility in cancer survivors

With advancements in cancer treatment, the number of cancer survivors has increased significantly. However, cancer treatments, involving chemotherapy, radiotherapy, & surgery, can have deleterious effects on fertility. Understanding pregnancy rates and the factors affecting fertility in cancer survivors is crucial for providing comprehensive care and counseling. Figure (1) illustrated that female cancer survivors are forty percent less likely to become pregnant compared to the general population. The likelihood of subsequent pregnancy varies by cancer type. This analysis accounts for age, prior parity, & educational level. The data were derived from a population-based study in Norway, involving 16,105 female cancer survivors & 85,500 controls.

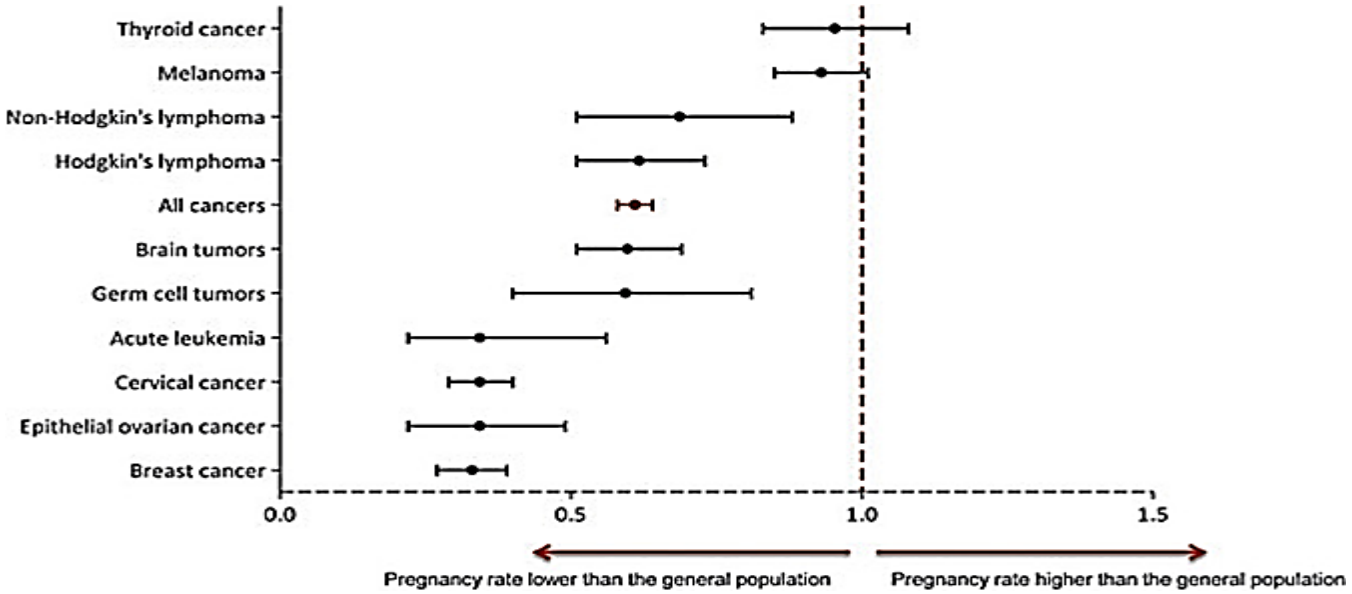

Figure (1): Reduced pregnancy likelihood among female cancer survivors [7].

Pregnancy rates among cancer survivors vary widely based on several factors, including the type of cancer, treatment modalities, age at diagnosis, & the use of fertility preservation methods. Studies have shown that women who undergo fertility preservation procedures before treatment have higher pregnancy rates compared to those who do not [8]. For instance, research by **Simms-Cendan *et al.*** [6] described that the pregnancy rate among female cancer survivors who had undergone fertility preservation was around 40%, whereas it was significantly lower in those who did not utilize these services [6].

Factors affecting fertility in cancer survivors

The type of cancer & its treatment play a significant role in determining the impact on fertility. For example, Hodgkin's lymphoma & breast cancer treatments often involve high-dose chemotherapy and radiotherapy, which are highly gonadotoxic [1]. Conversely, treatment for cancers like thyroid cancer, which typically involves less aggressive therapies, may have a less profound impact on fertility.Age is a crucial factor influencing fertility outcomes in cancer survivors. Younger patients generally have a better chance of retaining their fertility post-treatment. The ovarian reserve, which is the pool of available eggs, declines with age, making younger women more resilient to gonadotoxic treatments [2]. Similarly, prepubertal boys are less likely to experience permanent infertility from chemotherapy compared to older adolescents and adults, as their spermatogonial stem cells can be more resilient [3].

The time elapsed since treatment completion also affects fertility outcomes. Some patients may experience a temporary decline in fertility, with potential for recovery over time. However, prolonged gonadotoxic treatment effects can result in permanent infertility [9].

Long-term follow-up studies are essential to understand the full effect of cancer treatments on fertility & the potential for recovery.

The use of fertility preservation methods significantly influences pregnancy rates among cancer survivors. Techniques such as embryo & oocyte cryopreservation, sperm banking, & ovarian tissue cryopreservation provide options for patients to have biological children post-treatment. A study by **Torkashvand *et al.*** [5] highlighted that cancer survivors who utilized fertility preservation methods had a higher likelihood of achieving pregnancy compared to those who did not.

Psychological and socioeconomic factors also play a role in fertility outcomes. Cancer survivors may face emotional and financial challenges that impact their decisions and ability to pursue fertility treatments. Support systems, counseling, and financial assistance programs are essential to help survivors navigate these challenges [9].

A comprehensive study by **Zheng *et al.*** [8] examined fertility outcomes in young women with breast cancer who underwent fertility preservation. The study found that the pregnancy rate among these women was approximately 35%, with many achieving natural conception or successful outcomes through assisted reproductive technologies. The use of fertility preservation methods prior to chemotherapy significantly improved their chances of pregnancy.

Research conducted by **Asadi-Azarbaijani *et al.*** [2] focused on fertility outcomes in childhood cancer survivors in Nordic countries. The study reported a

pregnancy rate of 25% among female survivors who had undergone ovarian tissue cryopreservation. The success rates were higher in those who received fertility preservation counseling and interventions before treatment.

A study by **Huang *et al.*** [3] analyzed fertility outcomes in male cancer survivors who utilized sperm banking. The findings indicated that the overall pregnancy rate was around 30%, with higher rates observed in younger patients and those who banked sperm prior to starting chemotherapy. The study emphasized the importance of early referral to fertility preservation services for male studied cases.

Fertility preservation

Fertility preservation encompasses medical and surgical interventions aimed at safeguarding reproductive potential before, throughout, or after cancer treatment. It is a critical component of comprehensive cancer care, offering hope for future parenthood to survivors. Fertility preservation has evolved significantly over the past few decades. Initial procedures, like sperm banking & embryo cryopreservation, have been complemented by newer techniques as oocyte & ovarian tissue cryopreservation [10]. Advances in biotechnologies, including in vitro maturation (IVM) and artificial ovaries, hold promise for further expanding fertility preservation options.Fertility preservation raises several ethical considerations, including issues of consent, especially for pediatric patients, and the potential for posthumous reproduction [11]. Ethical guidelines emphasize patient autonomy and the importance of informed decision-making.

Cancer therapy and fertility

Cancer treatments can have varying impacts on fertility, depending on the modality and dosage. Surgical procedures for cancer can directly affect reproductive organs. For example, orchiectomy (removal of one or both testicles) can lead to male infertility, while oophorectomy (removal of the ovaries) can cause female infertility [12]. Chemotherapy drugs are known to be gonadotoxic, with agents like alkylating agents posing the highest risk. They can damage ovarian follicles in females & disrupt spermatogenesis in males, leading to reduced fertility [13]. The degree of the impact of cytotoxic agents on spermatogenesis were summarized in table (2).

Table (2): Effect of cytotoxic agents on spermatogenesis

Agent	Known effect on testis
Cyclophosphamide	Severe
Nitrogen mustard	Severe
Procarbazine	Severe
Bleomycin	Moderate
Carboplatin	Moderate
Cisplatin	Moderate
Cytarabine	Moderate
Doxorubicin	Moderate
Etoposide	Moderate
Ifosfamide	Moderate
Thioguanine	Moderate
Vinblastine	Moderate
Vincristine	Moderate
Methotrexate	Minimal

Endocrine therapies, used primarily in hormone-sensitive cancers, can impair fertility by altering hormonal balance. For instance, treatments for breast cancer, such as tamoxifen, can induce temporary amenorrhea and impact ovarian function [14].

The effect of targeted therapies & immunotherapies on fertility is less well-documented compared to traditional treatments. However, emerging evidence suggests that these therapies can also affect reproductive health, warranting further research [15].

Radiotherapy, particularly when targeting the pelvic region, can severely damage reproductive organs and reduce fertility. Shielding techniques and ovarian transposition are strategies used to mitigate these effects [16].

Oncofertility Counseling

Oncofertility counseling plays a vital role in educating studied cases about the potential effects of cancer treatments on fertility & the available preservation methods. It enables studied cases to make informed decisions regarding their reproductive futures [17]. Effective oncofertility counseling requires interdisciplinary collaboration between oncologists, reproductive specialists, & mental health professionals. Comprehensive patient education ensures that individuals understand the risks & benefits of different fertility preservation methods [18].

Medical considerations for fertility preservation include the patient's age, type of cancer, treatment regimen, & overall health. Obtaining informed consent is vital, especially for procedures that may have experimental aspects or long-term implications [19]. Fertility preservation encompasses a range of medical and surgical interventions designed to protect reproductive potential in patients undergoing treatments that threaten fertility, such as cancer therapy. The patient's age, the type of cancer, the treatment plan, & personal preferences all influence the procedure selection. The main methods for preserving fertility in both males & females are described in detail below.

Fertility preservation techniques in females

Embryo cryopreservation is the most established and commonly utilized method of fertility preservation. In this process, the ovaries are stimulated to generate a large number of eggs, which are subsequently collected & fertilised in a lab with sperm. For later usage, the resultant embryos are frozen & kept in storage. Depending on the woman's age & the embryos' quality, this technique has a high success rate, with live birth rates ranging from thirty percent to fifty percent every transfer cycle [20]. Embryo cryopreservation is advantageous because it is a well-established technique with proven efficacy, and it allows for the use of pre-implantation genetic testing to ensure healthy embryos. However, it requires hormonal stimulation, which may not be suitable for all cancer patients, and necessitates having a partner or sperm donor at the time of preservation.

Oocyte cryopreservation, or egg freezing, is another option for women who do not have a partner or prefer not to use donor sperm at the time of preservation. This process involves hormonal stimulation of the ovaries, followed by the retrieval and freezing of mature eggs. The eggs are preserved using vitrification, a rapid freezing method that prevents ice crystal formation. The success of oocyte cryopreservation depends largely on the age of the woman at the time of freezing, with younger women typically experiencing higher success rates. Live birth rates per thawed egg range from 4% to 12% [21]. This method offers the advantage of autonomy over reproductive decisions and the flexibility to fertilize the eggs with sperm at a later date. However, it has lower success rates compared to embryo cryopreservation and still needs ovarian stimulation & egg retrieval.

A new procedure called ovarian tissue cryopreservation is beneficial for prepubescent girls or women who are unable to postpone ovarian stimulation for cancer therapy. Ovarian tissue is surgically removed during this surgery, frozen, & kept for a potential donation. The tissue can later be re-implanted to restore ovarian function and fertility. This method has shown promising results, with several successful births reported worldwide [19]. The main advantage of ovarian tissue cryopreservation is that it does not need ovarian stimulation and may be performed immediately. It also preserves hormonal function along with fertility. However, it is still considered experimental, and long-term outcomes regarding the safety & efficacy of the procedure are still being studied.

Fertility Preservation Techniques in males

Sperm banking is the most common & straightforward technique of fertility preservation for males. It involves collecting and freezing sperm before starting cancer treatment. The sperm can be used later for intrauterine insemination or in vitro fertilization. This method is highly effective and relatively simple. It requires minimal time and has high success rates, with the ability to maintain viable sperm for many years [22].

The primary advantage of sperm banking is its established reliability and ease of use. However, it may not be an option for prepubertal boys who are not yet producing mature sperm. The fertility preservation options presented in table (3) provide an overview of strategies suited to boys at different developmental stages undergoing gonadotoxic cancer therapy.

Table (3): Fertility preservation options for boys undergoing gonadotoxic cancer therapy: Pre-pubertal and pubertal considerations [23].

Fertility restoration strategy	Current state	Advantages	Disadvantages
Testicular tissue engraftment	Experimental	Simple; no culture manipulation; possible testosterone production	Risk of reintroducing cancer cells; tissue ischaemia; spermatozoa must be surgically removed in order to do ICSI
SSC propagation & transplantation	Experimental	Possibility of restoring sperm cell excretion naturally; natural conception	Risk of genetic and epigenetic changes; risk of reintroducing cancer cells; inapplicable non cases when the testicular microenvironment is compromised
In vitro spermatogenesis	Experimental	Patient-friendly; little chance of reintroducing malignant cells	Unpredictable genetic & epigenetic stability; no spermatogenesis restoration
Frozen–thawed sperm from masturbation	Clinical	Simple; non-invasive	Boys find it challenging & embarrassing.
Frozen–thawed sperm from PVS	Clinical	Simple; non-invasive	Difficult & embarrassing for boys
Frozen–thawed sperm from EEJ	Clinical	Given that the child is anaesthetized, ejaculation is less embarrassing and may have a greater success rate than PVS.	requires specialised equipment and general anaesthesia.
Frozen–thawed sperm from TESA	Clinical	Simple procedure	Risk of infection & bleeding; general anaesthesia is necessary
Frozen–thawed sperm from TESE	Clinical	Potential tissue recovery beyond TESA	Risk of bleeding & infection; requires general anaesthesia

EEJ: Electroejaculation, **ICSI:** intracytoplasmic sperm injection, **PVS:** penile vibratory stimulation, **SSC:** spermatogonial stem cell, TESA**:** testicular sperm aspiration, TESE, testicular sperm extraction.

Testicular tissue cryopreservation is an experimental technique intended for prepubertal boys who cannot provide a sperm sample. The procedure involves surgically removing and freezing small pieces of testicular tissue, which contain spermatogonial stem cells. The hope is that, in the future, these cells can be matured into sperm either in vitro or through transplantation back into the patient. While, still in the experimental stages, this technique holds significant promise for preserving fertility in young boys undergoing gonadotoxic treatments **[24]**. The main advantage is its applicability to prepubertal boys, but the technique's long-term success and safety are not yet fully established.

Emerging methods in fertility preservation for both males & females include advances in in vitro maturation (IVM) of oocytes, artificial ovaries, & testicular tissue engineering. These innovative approaches aim to improve the effectiveness and accessibility of fertility preservation. For example, IVM involves maturing oocytes outside the body, which can be particularly useful for cancer patients who cannot undergo traditional ovarian stimulation. Artificial ovaries are being developed to provide a scaffold for the growth & maturation of ovarian follicles outside the body, potentially offering a new avenue for preserving and restoring fertility **[25]**.

Similarly, testicular tissue engineering is exploring ways to cultivate sperm-producing cells outside the body, which could revolutionize fertility preservation for young boys & men.

CONCLUSION

Fertility preservation is an essential aspect of comprehensive cancer care, offering hope for future parenthood to survivors. With advancements in cancer treatments, the number of survivors has increased significantly, highlighting the importance of addressing fertility challenges resulting from these treatments. Techniques such as embryo & oocyte cryopreservation, sperm banking, & ovarian tissue cryopreservation provide viable options for safeguarding reproductive potential. However, the success of these methods may vary based on factors like age, type of cancer, & treatment modalities. Continuous research and interdisciplinary collaboration are crucial for improving fertility

preservation strategies and outcomes, ensuring that cancer survivors can achieve their reproductive goals.

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