Fertility after Treatment of Childhood Cancer: A Narrative Literature Review

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Abstract
Advances in the treatment of childhood cancer have markedly improved survival rates over the past decades. Consequently, there is growing concern regarding the long-term effects of the different therapeutic modalities, including the potential for impaired fertility. This literature review summarizes current evidence on fertility outcome in childhood cancer survivors (CCS), focusing on the impact of chemotherapy, radiotherapy and immunotherapy. Fertility outcome in CCS is influenced by age at diagnosis and treatment modality, with the highest infertility rates observed in patients treated with high cumulative doses of alkylating agents and/or abdominal/pelvic radiotherapy. This review also emphasizes the importance of early counselling on infertility risk and fertility preservation methods as an essential component of comprehensive cancer care.

Introduction

The outcome of childhood cancer has steadily improved over the past decades due to advances in diagnosis and treatment. Currently, the 5-year overall survival rate for childhood cancer (0-19 years) in the Belgian population exceeds 80% (1). Most paediatric cancers are treated with multimodal therapy, combining surgery, chemotherapy, radiotherapy, immunotherapy and haematopoietic stem cell transplantation (HSCT). With increasing survival, attention has shifted towards the long-term consequences of therapy, including impaired fertility.

Treatment-related infertility is primarily caused by direct gonadotoxicity, which is called primary gonadal failure. Females are born with a finite number of oocytes that naturally decline over time. Cancer treatment can accelerate this process, leading to premature ovarian insufficiency (POI) and related to this, infertility and premature menopause (2). An extreme manifestation is the so-called acute ovarian failure (AOF), defined as the loss of ovarian function occurring during or shortly after treatment with chemotherapy or radiotherapy. In the Childhood Cancer Survivor Study (CCSS), a retrospective cohort of 5-year survivors of childhood cancer diagnosed before the age of 21 years between 1970 and 1986 (n = 3390 survivors), the incidence of AOF was 6.3% (215 cases) (3). Green et al reported the likelihood of pregnancy in female childhood cancer survivors (CCS) (n = 5149) compared to female siblings (n = 1441). This showed a significantly lower likelihood of pregnancy in CCS (RR 0.81, P <0.001) (4). In males, cytotoxic therapies damage spermatogonial stem cells, sperm cells in various stages of maturity and the tubular epithelium (5). An additional study of Green et al noted that male CCS (n = 6224 survivors) were half as likely to sire a pregnancy compared to their siblings (HR 0.56, P<0.001) (6).

Fertility can also be compromised through disruption of the hypothalamic–pituitary–gonadal axis after surgery or cranial radiotherapy, resulting in secondary (central) gonadal failure. In this case, gonadal function remains intact, and reproductive potential can often be restored with hormonal replacement therapy. However, many patients undergo combined treatments, which may lead to both primary and central gonadal failure. Lastly, infertility can arise from damage to the genital tract caused by surgery or radiotherapy (7,8).

Risk factors for impaired fertility include age at diagnosis, type and cumulative dose of chemotherapeutics and radiotherapy to the hypothalamic–pituitary axis or to the ovaries or testes (5). Age at time of treatment is particularly important. The CCSS reported a higher likelihood of pregnancy in both female and male survivors diagnosed at age 0-4 years, compared with those diagnosed at age 15-20 years (relative likelihood of 1.85) (4). In females, ovarian susceptibility to gonadotoxic effects increases with advancing age, since females are born with a finite number of oocytes (3). Similarly, in males, older age at diagnosis is associated with an increased risk for impaired fertility. Some studies suggest that the prepubertal testis may be less sensitive to chemotherapy than the pubertal testis. Although complete spermatogenesis is absent before puberty, Sertoli cells, which provide structural and nutritional support for developing germ cells, and Leydig cells, which synthesize testosterone and regulate male secondary sexual characteristics, are actively proliferating. This cellular activity may contribute to the susceptibility of the prepubertal testes to chemotherapy-induced damage (6,9).

Fertility assessment methods vary across studies. The most definitive measure is the ability to conceive a pregnancy. However, most studies rely on surrogate markers. In females, these include gonadotropin and anti-Müllerian hormone (AMH) levels, the latter being a surrogate marker for ovarian reserve. Alternatively, antral follicle count (AFC), measured by ovarian ultrasound, can also be used to assess ovarian reserve. The prognostic value of AMH levels and AFC in female childhood cancer survivors remains, however, unknown (10). Additional studies are warranted to clarify the predictive value of these markers for fertility outcomes,

including the likelihood of achieving pregnancy and the timing of menopause in this population. For male patients, a semen analysis is considered as the gold standard. Alternatively, gonadotropin levels or inhibin B can be used, the latter being a surrogate marker for spermatogenesis (11).

In this literature review, we gather evidence on fertility outcomes after treatment for childhood cancer, focusing on the impact of chemotherapy, radiotherapy and immunotherapy. A narrative literature search was conducted using the terms childhood cancer survivors and fertility. Our objective is to highlight infertility as a potential late effect of childhood cancer treatment and emphasize the importance of counselling on infertility risk and available fertility preservation methods as an essential component of comprehensive cancer care, starting at diagnosis and continuing during follow-up, including within primary care.

Fertility after chemotherapy

Chemotherapeutic agents exert their gonadotoxic effects through diverse mechanisms. This may lead to both short- and long-term sequelae, including direct gonadotoxic effects (2). Alkylating agents and platinum compounds show the strongest association with impaired fertility. However, due to limited data, the impact of other chemotherapeutic agents on fertility remains unclear.

Alkylating agents

The risk of chemotherapy-associated infertility is particularly elevated with high cumulative doses of alkylating agents, including cyclophosphamide, ifosfamide, procarbazine, busulfan and melphalan. These agents are gonadotoxic in a dose-dependent manner (12). Quantifying exposure to alkylating agents can be done using the cyclophosphamide equivalent dose (CED).

Female patients

Alkylating agents are highly gonadotoxic and can result in POI and associated infertility (3). Risk factors for POI include high cumulative dose of alkylating agents and older age at time of treatment (12).

Exposure to alkylating agents is independently associated with reduced risk of pregnancy in a dose-dependent manner in female survivors. No significant increase in infertility was observed below a CED of 6000-8000 mg/m² (4).

High doses of alkylating agents used as conditioning prior to HSCT, especially busulfan and cyclophosphamide, are strongly associated with gonadotoxicity (5). Borgmann-Staudt et al reported a significantly increased risk for infertility in female CCS after conditioning with busulfan. High dose of cyclophosphamide (120-200 mg/kg) prior to HSCT was associated with elevated FSH levels, with an even greater risk when combined with busulfan (13).

Surrogate markers for ovarian reserve, such as AMH, have been investigated in female CCS, who generally show lower serum AMH levels compared with healthy controls. Higher CED correlated with lower AMH levels, suggesting the potential use in identifying patients at risk for future infertility to guide fertility counselling. Ovarian ultrasound in female CCS showed that higher exposure to alkylating agents was a predictor for lower AFC (14).

Male patients

Alkylating agents are also directly gonadotoxic in male patients, ranging from impaired spermatogenesis to azoospermia, depending on the treatment intensity and age at diagnosis. In the St. Jude Lifetime Cohort Study, azoospermia was significantly associated with CEDs above 4000 mg/m², whereas CEDs below this threshold were generally linked to preserved spermatogenesis (15). In a related analysis within the CCSS, Green et al. examined the ability to sire a pregnancy in male survivors (n = 6224) and found that survivors were half as likely to father a child compared to their siblings (HR 0.56, P < 0.001) (6,7,11). Impaired spermatogenesis was more likely at cumulative doses exceeding 7500 to 9500 mg/m², with only 10% recovering to normospermia when doses exceeded 7500 mg/m² (2,6,15).

High-dose busulfan- or cyclophosphamide-based conditioning prior to HSCT is associated with high rates of gonadotoxicity, evidenced by elevated FSH, decreased testosterone or delayed puberty in 50% to 68% of adult survivors (5).

Inhibin B, a surrogate marker for spermatogenesis, correlates with sperm concentration and testicular volume. Van Casteren et al reported a negative correlation between inhibin B levels and CED (11).

Platinum drugs

In both female and male CCS, cisplatin and carboplatin have been associated with an increased risk of gonadotoxicity. However, the current evidence is limited and further studies are needed to define the risk of individual platinum derivatives and toxic doses (2).

Other chemotherapeutic treatments

Van den Berg et al reported an association between high cumulative doses of dactinomycin and primary amenorrhea (16). Another study of this group found an association between high-dose dactinomycin and reduced AMH levels (17). However, evidence regarding the gonadotoxic effects of other chemotherapeutic agents remains limited, and no definitive conclusions can yet be drawn.

Fertility after radiotherapy

Abdominal/pelvic radiotherapy

The risk of infertility following localized radiotherapy (RT) to the gonads (ovaries or testes) or the female genital tract is well established (4).

Female patients

In female patients radiation to the abdomen, pelvis and spine is associated with an increased risk of gonadotoxicity, particularly when the ovaries are in the radiation field (5).

There is a dose-dependent risk for infertility. The CCSS cohort showed an association between exposure to higher doses of pelvic radiation (especially doses >10 Gy) and POI. The cumulative incidence of POI approached 30% in survivors treated with both alkylating agents and ovarian irradiation (5). Green et al demonstrated a dose-dependent association between ovarian radiotherapy and decreased likelihood of achieving pregnancy. Survivors exposed to ovarian radiation doses >5 Gy had a significantly lower likelihood of achieving pregnancy, with a relative likelihood of 0.56 (95% CI, 0.37 to 0.85) for doses of 5-10 Gy and 0.18 (95% CI, 0.13 to 0.26) for doses >10 Gy (4).

Additionally, studies showed an association between ovarian irradiation and adverse pregnancy outcomes such as miscarriage, preterm birth and/or low birthweight (18).

Male patients

Radiation exposure to the testes is associated with impaired spermatogenesis. The testicular tissue is radiosensitive, and even low doses can impair its function. Immature spermatogonia are more radiosensitive than spermatocytes and spermatids.

The potential for recovery depends on the number of surviving stem cells and the radiation dose (19).

Radiation exposure to the testes results in dose-dependent damage (5). Green et al demonstrated an association between testicular radiation doses >7.5 Gy and a decreased ability to sire a pregnancy (6). Testosterone production may remain within the normal range at testicular doses <12 Gy, however elevated LH may suggest subclinical Leydig cell dysfunction. Leydig cells are more resistant to radiation damage than Sertoli cells, and their function is generally preserved at exposure levels <20–30 Gy (6,12). Radiosensitivity is greater in prepubertal than pubertal males, with Leydig cell dysfunction observed at doses >20 Gy in prepubertal boys compared to higher doses in postpubertal boys (12,16).

Total body irradiation

Total body irradiation (TBI) is commonly used as conditioning prior to HSCT and can lead to gonadal dysfunction and infertility in female and male CCS.

Bresters et al reported POI in 68% of female CCS treated with TBI after a median follow-up of 7.2 years (20). Sanders et al noted that female CCS exposed to TBI at doses of 10-15 Gy have a significantly higher risk of miscarriage, whereas no miscarriages were noted following exposure to 5-8 Gy (21). This could however not be confirmed in the study of Carter et al (22). Older age at treatment is a known risk factor for POI. When TBI is administered before puberty, there is a higher chance of ovarian recovery with spontaneous onset of puberty occurring in 40-60% of girls. The protective effect of a younger age might be related to different factors, including higher number of nongrowing follicles, higher resistance of primordial follicles, vascular phenomena and fibrosis or paracrine factors (23).

Among male CCS, Borgmann-Staudt et al showed that boys who received TBI (median dose of 12.3 Gy, range 2.0-14.4 Gy) had a significantly higher risk of infertility (84%) compared with CCS who did not undergo TBI (56%) (P<.001) (13). Van Casteren et al reported extremely low inhibin B levels in male CCS after TBI (11).

Cranial radiotherapy

Radiation-induced disruption of gonadotropin secretion can lead to hypogonadotropic hypogonadism. The risk for fertility impairment following cranial radiotherapy, and more specifically radiation exposure to the hypothalamus and pituitary, depends on the irradiated region, total dose, fractionation schedule and age. Doses >30 Gy at the pituitary are associated with LH/FSH deficiency (12). The CCSS data showed a lower likelihood of pregnancy in female CCS with radiation dose to the hypothalamus/pituitary >20-30 Gy (4,24). Importantly, hypogonadotropic hypogonadism can be treated with hormone replacement therapy, enabling fertility in affected survivors. However, many patients receive combined radiotherapy and alkylating agents treatment, which also frequently result in primary gonadal failure.

Fertility after immunotherapy

Over the past decade, immunotherapy has become increasingly used in the treatment of childhood cancers. However, little is known about its long-term side effects. One concern is that immunotherapy may cause endocrine complications and potentially affect fertility, although the underlying mechanisms remain poorly understood (2).

Data on the impact of immunotherapy on gonadal function and fertility are scarce. What is known is that immune cells, such as T-cells and macrophages, are present in the ovaries, where they play a key role in follicular growth, ovulation, clearance of atretic follicles, and formation of the corpus luteum after ovulation. Further prospective multicentric studies are necessary to address this knowledge gap.

Monoclonal antibodies

Examples of monoclonal antibodies frequently used in the treatment of childhood cancer include rituximab (anti-CD20), blinatumomab (anti-CD19) and bevacizumab (anti-VEGF).

Rituximab

In female patients with primary mediastinal B-cell lymphoma, the addition of rituximab to EPOCH chemotherapy (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) was not associated with an increased risk of impaired ovarian function, particularly in women younger than 40 years. However this study did not include paediatric patients (25). The impact on gonadal function and fertility in male survivors has not yet been established.

Blinatumomab

In mouse models, administration of blinatumomab did not demonstrate adverse effects on reproductive organs (26). Its effect on fertility in humans remains unknown.

Bevacizumab

Lorenzi et al reported ovarian failure, defined as transient amenorrhea for more than three months and elevated FSH levels (>30 mIU/ml), in patients with stage II or III colorectal cancer treated with adjuvant FOLFOX-6 combined with bevacizumab. The incidence of ovarian failure was 2.6% of patients receiving FOLFOX-6 alone, compared to 39% in those receiving the combination regimen. In only 22% of the women ovarian function recovered after treatment discontinuation. However, the long-term effects of bevacizumab on gonadal function remain unclear (27).

Immune checkpoint inhibitors

Immune checkpoint inhibitors (ICI), a class of immunotherapeutic agents that enhance the host immune response by targeting regulatory pathways in T-cells, have become important components in the treatment of several paediatric cancers. Examples of ICI are ipilimumab (CTLA4-inhibitor), nivolumab (PD1-inhibitor) and pembrolizumab (PD1-inhibitor). While their efficacy is increasingly recognized, evidence on long-term effects, particularly on reproductive health, is limited. ICIs can trigger immune-related hypophysitis, which may indirectly impair fertility. The rate of hypophysitis in female patients is 5.6% for ipilimumab, 0.5% for nivolumab, 1.1% for pembrolizumab and 8.8–10.5% for the combination of ICI (ipilimumab and nivolumab 8.8%, ipilimumab and pembrolizumab 10.5%) (28). These endocrine side effects are mostly permanent. Direct effects on gonadal function remain largely unexplored. In female patients there is no evidence for primary hypogonadism. In male patients orchitis with primary hypogonadism has been reported in case studies (29).

Fertility after HSCT

The number of HSCT's performed has increased over recent decades. Most pre-transplant conditioning regimens include alkylating agents, radiotherapy, or both, which are known to cause gonadal damage and subsequent infertility. The risk of gonadal failure depends on several factors including age at diagnosis,

TABLE 1: Fertility preservation options in female and male patients

PATIENT GROUP		FERTILITY PRESERVATION OPTIONS
Female	Prepubertal	Ovarian tissue cryopreservation (OTC) Ovarian transposition or oophoropexy
	Postpubertal	Oocyte cryopreservation
Male	Prepubertal	Testicular tissue cryopreservation (experimental)
	Postpubertal	Sperm cryopreservation Testicular sperm extraction (TESE)

the specific agents used, cumulative dose, and the use of TBI prior to HSCT. Rotz et al studied the impact of reduced-intensity conditioning regimens and found no significant reduction in gonadotoxicity in either male or female CCS (34).

Fertility preservation

An overview of available modalities for fertility preservation is discussed below and summarized in Table 1. Given the risk of infertility, timely counselling of patients and their parents, along with early referral to a specialized fertility centre, is essential. However, not all patients are eligible for fertility preservation. Fertility preservation prior to the start of gonadotoxic therapy may be challenging due to the young age at diagnosis, acute illness at presentation, or urgency to initiate treatment. The PanCareLIFE consortium has provided recommendations on eligibility for fertility preservation in childhood cancer patients (9,30).

Female patients

Ovarian tissue cryopreservation

Ovarian tissue cryopreservation (OTC) is the only option for fertility preservation in prepubertal girls. In OTC, (part of) the ovarian cortex containing primordial follicles is surgically removed, usually via laparoscopy, and frozen for potential future use. When the patient reaches reproductive age, the tissue can be thawed and autotransplanted. This approach has been shown to reestablish both fertility and endocrine function. For general paediatricians involved in the longitudinal care of children with cancer, it is important to understand that despite the benefits of OTC, a major concern is the potential reintroduction of malignant cells during autotransplantation. Because the ovarian cortex is harvested before oncologic treatment, there is a risk that microscopic malignant cells may be present within the tissue, especially in cancers with known ovarian or hematogenous dissemination. If such cells survive cryopreservation and are returned to the patient during transplantation, they could theoretically lead to disease recurrence. This concern is particularly relevant in survivors of leukaemia, non-Hodgkin lymphoma and metastasized solid tumours (30).

Oocyte cryopreservation

Oocyte cryopreservation requires hormonal stimulation before oocyte collection can take place. This stimulation phase typically takes 2-3 weeks, which can delays the initiation of cancer treatment, what can be an important limitation when therapy must begin urgently. Moreover, this procedure can only be performed in postpubertal girls (30).

Ovarian transposition

Ovarian transposition or oophoropexy is a surgical technique in which the ovaries are repositioned outside the radiation field in female patients undergoing pelvic or abdominal irradiation. The primary goal is to reduce the radiation dose to the ovaries and thereby preserve ovarian endocrine function and future fertility. This approach is particularly relevant in paediatric and adolescent patients, as their long-term reproductive potential is highly sensitive to cumulative gonadotoxic exposure. However, available evidence – though limited and of low methodological quality – indicates no significant difference in live birth before age of 40 years between patients who underwent ovarian transposition and those who did not. The procedure itself carries several risks, including fallopian tube infarction due to compromised blood supply, intraoperative or postoperative bleeding, and postoperative pain. Furthermore, the need for general anaesthesia poses additional concerns, particularly in children who may be acutely ill from their underlying malignancy. Despite theoretical concerns that surgical manipulation or radiation scatter could contribute to premature ovarian insufficiency, existing studies have not been able to confirm an increased risk (31).

Male patients

Sperm cryopreservation

Sperm collection, obtained through masturbation, is the standard method of most effective method for fertility preservation for pubertal and postpubertal male patients. However, psychological barriers such as stress or embarrassment can pose challenges for adolescents. From a medical perspective, sperm collection via masturbation is considered a safe procedure and no procedure-related complications have been reported in the literature (9).

Testicular sperm extraction

Testicular sperm extraction (TESE) is a surgical procedure in which sperm cells are retrieved directly from testicular tissue. It is considered an alternative fertility preservation strategy for pubertal or postpubertal male patients who are at high risk of infertility and are unable to provide an ejaculate through masturbation. TESE allows for the collection of viable sperm that can subsequently be cryopreserved for future assisted reproductive techniques. The procedure carries potential risks, including hematoma formation, infection, and complications related to general anaesthesia (9).

Testicular tissue preservation

Cryopreservation of testicular tissue containing spermatogonial stem cells is still experimental, but is currently the only available option for fertility preservation in prepubertal patients. In this procedure, a small portion of testicular tissue is surgically harvested and cryopreserved for potential future autotransplantation. The procedure is invasive, requiring surgery under anaesthesia, and carries the standard risks associated with tissue retrieval. A major oncologic concern is the possibility that malignant cells could be present in the harvested tissue. During future autotransplantation, these cells could theoretically be reintroduced, posing a risk of disease recurrence (9). Although still experimental, recent advances suggest promising future applications. Notably, the first autotransplantation of cryopreserved immature testicular

tissue was recently performed in a Belgian CSS, marking an important milestone in the field (32). Several ongoing studies continue to investigate the safety, feasibility and efficacy of testicular tissue preservation.

Cryopreservation of sperm or mature oocytes after the initiation of gonadotoxic treatment is not recommended, due to the risk of DNA damage in developing gametes, which may increase the likelihood of congenital abnormalities in subsequent offspring (33). Further long-term studies are needed to establish the safety, efficacy and reproductive outcomes of available and emerging fertility preservation strategies.

In Belgium, the cryopreservation and long-term storage of gametes or gonadal tissue for fertility preservation is fully reimbursed by the national health insurance system for up to 20 years in patients younger than 16 years and for up to 10 years in patients aged 16 years and older. Eligible patients include those undergoing gonadotoxic cancer treatment for solid tumours, leukaemia, lymphoma, testicular cancer, borderline ovarian tumours, genetic mutations requiring prophylactic oophorectomy (e.g., high risk of breast or ovarian cancer) and hematologic conditions necessitating stem cell transplantation (36).

Discussion and Conclusion

Fertility impairment remains a significant long-term consequence of childhood cancer treatment. The strongest risk factors for reduced fertility are exposure to alkylating agents and gonadal irradiation with dose-dependent effects observed in both male and female CCS. However, clear dose-response relationships have not been established for all chemotherapeutic agents. This is likely due to the frequent use of multi-agent chemotherapy in combination with radiotherapy, which complicates the attribution of effects to individual drugs.

Gonadotoxicity is further determined by multiple factors, including known variables such as treatment type, cumulative dose, timing and patient-specific characteristics such as age and sex, while other risk factors remain unidentified. Moreover, paediatric oncology is a rapidly evolving field in which new treatments are continually being developed, including immunotherapies, for which data on fertility risk are even more limited. This uncertainty should be explicitly addressed during patient counselling to better characterize the potential gonadotoxic effects of these treatments. Moreover, many patients receive combined therapies, resulting in concurrent primary and secondary gonadal failure, complicating the identification of patients who may benefit from hormone replacement therapy.

Age at diagnosis is a critical risk factor for fertility outcomes, reflecting a relation between developmental stage and sensitivity to gonadotoxic effects. Although gonadal damage is often irreversible, partial or complete recovery may occur in younger patients. In female CCS, recovery of the menstrual cycle and normalization of gonadotropins have been reported. However, POI is a common long-term consequences. In male CCS, recovery of spermatogenesis is described if spermatogonial stem cells survive initial treatment (6,35).

As discussed above, several options for fertility preservation exist. Considering that not all patients are eligible, the PanCareLIFE made recommendations to guide eligibility for fertility preservation (9,30). Options remain limited in prepubertal male patients, where testicular tissue preservation is still experimental and requires further research. It is important to recognize that some preservation procedures, such as oocyte cryopreservation, may delay initiation of treatment and this consideration should be integrated into the counselling process.

Early and repeated counselling at diagnosis, during treatment and follow-up is essential to inform patients and their families about the fertility risk and available, although limited, preservation strategies. Because counselling is a continuous process, long-term follow-up in adolescence and adulthood remains essential. Integrating multidisciplinary collaboration and individualized fertility counselling into routine oncologic care is essential to optimizing long-term reproductive health outcomes in survivorship. Early discussion of fertility risks allows families to make informed decisions regarding fertility preservation strategies prior to treatment initiation and promotes psychological preparedness, thereby supporting future reproductive goals and long-term quality of life.

Fertility counselling should be initiated as soon as a treatment plan is being established, discussing potential reproductive risks and available fertility preservation options, including their feasibility and possible impact on treatment timing. This counselling must be conducted by specialized fertility centres, ensuring expert guidance and individualized care. Paediatricians play a supportive role by identifying patients who may benefit counselling, facilitating timely referrals and addressing concerns in those at low risk of infertility who may be unaware of potential reproductive effects.

Future studies with long-term follow-up are needed to better elucidate the associations between different treatment modalities and fertility risks, and to foster the development of innovative fertility preservation strategies.

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