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Fertility preservation in male patients with cancer

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A B S T R A C T

Advances in the treatment of cancer in young patients have led to great improvements in life expectancy, which currently approaches 80% 5-year survival rate. As a result, fertility preservation and desire for paternity have become a significant issue in this group. However, a major concern is the negative impact of chemotherapy, radiotherapy, and the malignancy itself on fertility. Thus, men about to have treatment for malignant conditions may have 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 azoospermia. 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.

Advances in the treatment of cancer in young patients have led to great improvements in life expectancy. The general expectation is that nearly 80% will achieve a long-term cure, rendering fertility preservation and the desire for paternity extremely relevant [1,2].

A major concern is the high susceptibility of spermatogenesis to the malignancy, as well as the attendant chemotherapy and radiotherapy treatments [3–6].

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Cancer and infertility risk in males

Studies investigating pretreatment semen characteristics in patients with cancer have reported an increased prevalence of oligospermia and azoospermia [7–9]. Testicular and nontesticular cancers (e.g., leukemia, lymphoma) are both considered significant risk factors for diminished semen quality [10–12].

For example, Hodgkin's lymphoma-associated fever has been reported as a potential infertility risk factor negatively affecting semen characteristics [13].

Cancer may have direct adverse effects on the testis or the endocrine system controlling testicular function [14]. Testicular cancer-associated factors such as β-human chorionic gonadotropin (βhCG) and α-fetoprotein (AFP) may both have a systemic effect through the disruption of the hypothalamic–pituitary–gonadal axis, and a local effect by impacting spermatogenesis [15,16]. Furthermore, testicular cancer may be associated with an alteration in the blood–testis barrier and local immune dysregulation, with the consequent production of antisperm antibodies [17]. Antisperm antibodies can impact sperm motility in the semen and also their ability to pass through female genital secretions and fuse with gametes and, possibly, the first step of embryo development [18,19].

In addition, deficiencies in vitamins, minerals, and trace elements are commonly associated with some cancers. These deficiencies play a significant role in the maintenance of a male's reproductive capacity, and their deficiency might negatively impact spermatogenesis [20].

Cancer-associated emotional stress can result in alterations to various hormone levels, such as catecholamines, prolactin, corticotropin-releasing factor (CRF), and endogenous opioids. These changes might also have deleterious effects on sperm production and function [12].

The effects of cancer treatments on infertility

The prepubertal testis is considered highly vulnerable to damage by chemotherapy and radiation treatment owing to the constant turnover of its undifferentiated spermatogonia [21,22].

In the postpubertal testis, too low-dose chemotherapy or irradiation can deplete the rapidly dividing and differentiating spermatogonia. However, the less sensitive slow-dividing cells survive, such as the quiescent spermatogonial stem cells, spermatocytes, and spermatids [4]. After damage due to chemotherapy or radiation, the surviving stem cells turn into mitotically active spermatogonia, and along with the supporting Sertoli cells (which are more resilient to chemotherapy and irradiation), they become the foundation of spermatogenesis regeneration.

On the other hand, when testicular damage is severe due to high-dose chemotherapy/irradiation, apoptosis is triggered in all subpopulations of spermatogonial stem cells. In a severe cytotoxic insult environment, Sertoli cells are significantly damaged and lose their ability to support spermatogenesis. The clinical outcome in such cases is permanent sterility [5].

For example, bone marrow transplantation, which requires conditioning with high-dose chemotherapy/high-dose irradiation, is associated with a high risk of future infertility [23,24]. Conditioning regimens for bone marrow transplantation involving total body irradiation (10 or 13 Gy) have been reported to be highly associated with spermatogenesis failure, with an azoospermia rate of 85% [25].

The effect of chemotherapy

The effect of chemotherapy on the pre- and postpubertal testis, and hence future fertility, varies and is mainly agent and dose dependent [26,27].

Alkylating agents and platinums seem to have the most profound reproductive effects. The reported threshold for future infertility in prepubertal patients for cyclophosphamide ranges between 7.5 g/m^2 and 9.0 g/m^2 [28,29] and 10.0 g/m^2 (300 mg/kg) in postpubertal patients [30]. Spermatogenesis recovery is believed to be unlikely with doses of 19 g/m^2 [31].

Studies of commonly used multiagent chemotherapy regimens (mechlorethamine, vincristine, procarbazine, and prednisone [MOPP] and cyclophosphamide, vincristine, procarbazine, prednisolone [COPP]) have shown high rates of long-term azoospermia (85%–100%) [32], with a clear dose-dependent effect seen in cyclophosphamide-based regimens [33].

Relative androgen deficiency and gynecomastia have been reported in patients treated with MOPP or high-dose cyclophosphamide [34,35].

The potential gonadotoxic impact is also associated with the fractionation schedule of the treatment. Treatment involving multiple administrations of low-dose chemotherapy might have more detrimental effects than exposure to higher dosages delivered in fewer administrations [36].

The effect of radiation

The extent of DNA damage to testicular germ cells and somatic cells is field, dose, and fractionation dependent [37,38].

Radiation exposure to testes can be direct or a result of scatter when treatment is delivered to other organs. Spermatogenesis is highly sensitive to radiation doses as low as 0.1 Gy. Reversible short-term azoospermia has been identified at the dose of 0.35 Gy, whereas doses of 2–3 Gy may cause a long-term effect with the potential for recovery. Doses of more than 6 Gy are able to cause total depletion of spermatogonial stem cells and permanent sterility [39,40]. Pubertal development is impaired with irradiation doses as high as 12 Gy, and hypogonadism is caused by doses of 20–30 Gy, requiring androgen replacement [37,41,42].

Options for fertility preservation in pubertal boys, adolescents, and young adults

Given the potential harmful effects of chemotherapy and/or radiation therapy on future fertility, preservation options should be discussed with patients and their families before the initiation of any treatment. This is because, provided a semen sample can be produced, the fertility capacity of adolescents and young adults facing chemotherapy/radiotherapy can be preserved with a similar success rate to that achieved in adults. Pubertal boys with a testicular volume of 10–12 mL should be encouraged to produce a sample [13,43]. Boys at the onset of puberty may have a small number of sperm cryopreserved after testicular biopsy or aspiration under anesthesia. In vitro fertilization using intracytoplasmic sperm injection (ICSI) may then result in their ability to father a child.

Several samples are usually required to facilitate the cryopreservation of an appropriate number of vials. Sperm production can be accomplished at a fertility clinic facility. Alternatively, it can be produced at home or in the patient's hospital room with immediate transport of the specimen to the fertility clinic.

Men should be advised of the potentially higher risk of genetic damage in sperm collected after commencement of chemotherapy [44].

Sample production may be hindered by the fact that some patients may be unfamiliar with masturbation before their cancer diagnosis, which might place them in a difficult situation. In such cases, they may benefit from parental involvement [45].

Furthermore, the perception of sperm production, reproductive health, and fertility treatment varies across different cultural and religious backgrounds and involves complicated views. Therefore, although masturbation for sperm banking is the preferred approach, some patients are unable to ejaculate for various reasons (social, religious, cultural, or medical). In such cases, sperm can be retrieved by other methods such as penile vibratory stimulation (PVS), electroejaculation (EEJ), or surgically from the epididymis or the testis.

PVS is considered to be the least invasive technique, as it can be used in the privacy of a patient's home and does not require general anesthesia. EEJ does involve general anesthesia, and hence, it requires coordination with theatre and laboratory staff. Finally, surgical sperm extraction is used when patients are unable to produce a specimen or present with azoospermia (as discussed above). This can be performed concurrently with other procedures such as central line placement. The use of an operating microscope with microsurgical testicular sperm extraction (micro-TESE) can assist in the identification of focal areas with active spermatogenesis. With this procedure, the risks for testicular damage (such as scrotal hematoma and skin discoloration, infection, persistent pain, and swelling) are minimal. For these reasons, TESE has become an emerging option for azoospermic patients with cancer and has been termed “onco-TESE.” [46,47].

Fertility preservation counseling

Patients should be assessed based on their cancer type and planned gonadotoxic treatment, and the effects of cancer and its treatment on fertility should be discussed early in the diagnostic process to allow for proper decision making and enable the completion of required procedures before treatment initiation. Although future fertility is not their main concern at the time of initial diagnosis, this issue causes significant stress for both parent and patients once treatment is complete.

Research shows that survivors of childhood and young adult cancer are interested in discussing fertility preservation options and that most parents are willing to consider and consent to fertility preservation despite the often limited and stressful time before treatment commencement. Furthermore, when fertility preservation counseling was performed, patients indicated more satisfaction and less decisional regret regardless of whether they chose to pursue fertility preservation [48,49].

The main difficulty is that for the majority of patients and their families, the time of diagnosis is accompanied by emotional distress. Often, urgency to commence treatment might prevent patients from receiving appropriate fertility preservation counseling. Limited resources and time, perceived high costs, and lack of knowledge of the medical provider are also considered as barriers to counseling [50,51].

Therefore, it is crucial to provide sufficient support for patients and families during the time-critical period of extreme emotional strain at diagnosis. Because the involvement of multiple providers may, at times, lead to confusion [52], a patient navigator or coordinator can assist with information processing and facilitate decision making [53].

Fertility preservation in prepubertal boys

Sperm cryopreservation or sperm banking is a routinely used, highly reliable, and well-established approach applicable in adolescents but unfortunately not in prepubertal boys [43,54,55]. Indeed, fertility preservation in prepubertal boys presents a great challenge, as mature sperm do not exist. This eliminates the possibility of sperm banking.

Alternative strategies have been studied, but all are currently experimental. These strategies are based on immature testicular tissue (ITT) cryopreservation as cell suspensions or the whole testicular tissue for future fertility restoration by autografting, xenografting, or in vitro spermatogenesis [56]. To date, resumption of spermatogenesis from grafted ITT has been achieved in animals [57,58] but not in humans.

Furthermore, additional research is required regarding the optimization of cryopreservation protocols and strategies to minimize the risk of disease recurrence from the reintroduction of cancerous cells in the ITT [59].

Ethical concerns

Prepubertal fertility preservation options involve the surgical removal and freezing of the testicular tissue with the hope that future technology will allow the use of this tissue [56]. Although testicular biopsy involves some minor risks such as bleeding, infection, scarring, and risks associated with general anesthesia, it is generally considered to be safe [60].

While limited evidence for the value of prepubertal tissue collection raises ethical concerns with regard to the justification of such procedures, failing to offer a potentially beneficial and low-risk fertility preservation procedure in an area of rapidly progressing research is equally concerning [61]. Although the chance of success is remote, it is still greater if the fertility preservation procedure was not undertaken. Furthermore, as mentioned above, discussions about fertility and fertility preservation are highly valued by patients with cancer [44].

An additional ethical concern worth mentioning is that offering fertility preservation may create false hope with regard to the patient's chances of survival and the likelihood of future paternity [62].

Given the above, testicular tissue cryopreservation should be recommended in prepubertal boys even though fertility restoration strategies based on future grafting are experimental and have not yet been successfully tested in humans. Although the potential risks and benefits are not totally known, unless the procedure is offered, the opportunity to evaluate it and assess its clinical benefit will be missed.

Efforts to preserve fertility in prepubertal children using experimental methods should be attempted under institutional review board-approved protocols.

Postchemotherapy sperm recovery

There may be various barriers to sperm banking, such as prepubertal age, under-referral, inadequate understanding of the sterilizing effect of chemotherapy, or defective spermatogenesis before the treatment [63,64]. In these patients, an approach similar to that used for men with severe primary spermatogenic disorders can be used, as successful recovery of spermatogenesis after gonadotoxic treatments is highly variable. Men with persistent azoospermia following chemotherapy or radiotherapy can be offered micro-TESE and ICSI, as there is some chance of success [65,66].

Summary

Cancer may impact current and future fertility due to the disease itself and to gonadotoxic treatment. The potential harmful effect of chemotherapy and radiotherapy on spermatogenesis, along with the significant improvement in the life expectancy of patient with cancer, requires adequate fertility preservation counseling before commencement of treatment. Sufficient emotional and logistical support for patients and families in this time-critical period of extreme emotional strain is vital.

Fertility preservation options should be provided as early as possible to allow proper decision-making process and to enable the completion of required procedures, and men should be advised of the potentially higher risk of genetic damage in sperm collected after the commencement of chemotherapy.

Although masturbation for sperm banking is the preferred approach, some patients are unable to ejaculate for various reasons. In such cases, sperm can be retrieved by PVS, EEJ, or surgically from the epididymis or the testis. Surgical sperm extraction is also indicated when patients present with azoospermia.

Testicular tissue cryopreservation should be recommended in prepubertal boys, although fertility restoration strategies based on future grafting are experimental and have not yet been successfully tested in humans. While the potential risks and benefits are not totally known, unless the procedure is offered, the opportunity to evaluate it and assess its clinical benefit will be missed.

Efforts to preserve fertility in prepubertal children using experimental methods should be attempted under institutional review board-approved protocols.

Additional research is required with regard to the optimization of cryopreservation protocols, the genetic and epigenetic stability of cells originated from prepubertal testicular tissue, and strategies to minimize the risk of disease recurrence from the reintroduction of graft-associated cancerous cells.

Practice points

- The potential harmful effect of chemotherapy and radiotherapy on fertility requires adequate fertility preservation counseling before the commencement of treatment
- Fertility preservation options should be provided as early as possible to allow proper decision-making process and to enable the completion of required procedures
- Masturbation for sperm banking is the preferred fertility preservation approach
- Surgical sperm extraction is indicated when masturbation is not possible or when patients present with azoospermia
- Men should be advised of the potentially higher risk of genetic damage in sperm collected after the commencement of chemotherapy
- Testicular tissue cryopreservation should be recommended in prepubertal boys
- Efforts to preserve fertility in prepubertal boys should be attempted under institutional review board–approved protocols

Research agenda

- Optimizing the current protocols for immature testicular tissue cryopreservation
- Improving detection techniques for malignant cells in the cryopreserved testicular tissue
- Understanding the use of fertility preservation options among patients with cancer from various ethnic and socioeconomic groups

Conflicts of interest

The author has no conflict of interest.

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