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Male Fertility Preservation: A boon for young cancer survivors

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ABSTRACT

Diagnosis of any ailment especially cancer is found to be pivotal to evaluating the type of treatment that needs to be administered to man. It aids in subsequent prognosis and timely recovery in patients. When concerned with male cancer survivors, the emphasis on their fertility health is always an issue. As the numbers of survivors are increasing day by day due to the advanced medical and technological approaches, man could look with confidence to a life of ease from cancer. To review and compile all the feasible as well as relevant information about the preservation of male fertility from published resources. Reputed databases were searched for content based on specific keywords like “fertility preservation after cancer treatment", "methods of male gamete preservation", "methods of semen collection for preservation", "fertility preservation", "erectile dysfunction" and "testicular cancer and fertility". The year of publication for articles under study was restricted from 2016-2021 in most of the databases. It was found that oncologists generally recommended preservation of the male fertility before the commencement of the cancer treatment procedures. Preservation of fertility among young men should be considered in all patients before initiating any kind of prognosis related to the disease.

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1 Introduction

It is very important to maintain the overall reproductive potential of a cancer survivor post-treatment. The ability to sustain the quality of the same also is an essential parameter (Wollersheim et al. 2022). The increase in facilities and technologies available to cure cancer has raised the number of cancer survivors below the age of 65 years (Gordon et al. 2017). As the diagnosis is becoming easier and more effective against cancer, the magnitude of cancer survivors is also increasing (Breidenbach et al. 2022). If put in numbers, around 1-3% are diagnosed with cancer within the age group of 20 years and 9-12% by the age of 45 (Gordon et al. 2017). Statistics have provided evidence that these survivors tend to lead a normal life post-recovery if the treatment or the disease did not affect them in an adverse manner (Miller et al. 2019).

The advancement in therapeutic values has supported medical professionals to heal many cancer patients in the past 20 years (Breidenbach et al. 2022). The treatment generally consists of many harsh measures and approaches with severe side effects, especially on male fertility quality (Arafa and Elbardisi 2020). The process of spermatogenesis can be easily altered as it is sensitive to many potential toxins (Anyanwu and Orisakwe 2020). The techniques involved like radiation therapy, chemotherapy, and other surgical practices impair the normal functionality of ejaculation and could lead to erectile dysfunction (Green et al 2019). Numerous factors affect the quality of male gonads after cancer treatment. Firstly, the effect of the therapy on gametogenesis (Zapata-Restrepo et al. 2019), secondly the quantity and the quality of the sperm pre- and post-treatment, thirdly the medications administered during the prognosis, and fourthly susceptibility of the patient post-treatment and the type of cancer with its correlation with male fertility play an essential role in determining the fate of the reproductive life of a patient after recovery. The overall regime opted by the medical practitioner also influences the sperm count and quality (Byrne et al. 2018). Prediction of the same is also a challenging aspect of the cancer treatment process. Doctors predict a variety of conditions ranging from azoospermia to partial recovery of the patient after cancer therapy. Hence the Ethics Committee of the American Society for Reproductive Medicine has set some norms that need to be followed and intimated well in advance to the male patient before initiating the treatment regime (Chen et al. 2020). The options available to preserve the fertility of the patient should be discussed well in advance to take appropriate measures during the therapy (Lake et al. 2020). The adverse effects should be jotted down clearly and explained well to the recipient (Bhasin et al. 2018). For the 1% of the cases that get detected in young cancer patients hailing in their early reproductive years should consider preservation of their fertility as recommended by clinicians (Munoz et al. 2016). Especially among unmarried men and those who plan on starting a family (Newton et al. 2021). An emotional war is always evident between cancer patients with the anxieties to fight for their survival and later to lead a normal life. This is feasible by cryopreservation, which could protect their fertility status for later years (Kim et al. 2020).

2 Cryopreservation and assisted reproductive technology

The male reproductive potential majorly depends on sperm health and count, so preservation of the same can help in the effective management of male reproductive quality (Colaco and Modi 2018). Cryopreservation is the most sought-after technique in the medical field to preserve sperm. A cancer survivor can opt for the cryopreservation technique before the treatment regime and later utilize assisted reproductive technologies (ART) if needed in the future to lead a normal life (Appiah 2020). Even if the patient has a previous or current medical condition of low sperm motility, abnormality, and other adverse characteristics, still cryopreservation is found to be the best solution to conserve a man's reproductive capability (Hezavehei et al. 2018). Amidst the numerous developments and success scenarios related to ART, only a handful of patients utilize the cryopreserved samples post recovery to attain parenthood (Morgan et al. 2020). The main goal of this freeze preservation was to utilize the samples after treatment to have patients' progeny if demanded in the future. Around 12% of the stored samples available in ART centers are used to have children by post-cancer survivors (Asafu-Adjei and Jenkins 2020). The low utilization of the conserved and preserved samples might be due to the retaining of the reproductive capability of the cancer survivor, stress, lack of interest in parenthood, or the expensive nature of the ART sample retrieval procedures. Even the success rate of the samples stored through ART also plays an important role while preferring to use these cryo sperms for fatherhood (Klipstein et al. 2020). Of the small number of patients who prefer ART post-recovery, around 65% of them do achieve fatherhood (Paoli et al. 2018). Some suggested that the efficiency can go up to 77% in certain cases. Few patients found the whole process for cryopreservation irrelevant and unnecessary as the reutilization percentage was seen to be very low by the cancer survivors before them (Medrano et al. 2018). But, the surety and prediction as to who would retain their fertility and who would restore the same after treatment cannot be easily pointed out by clinicians and doctors. Hence, the most effective and safest way to father a child post-recovery would be cryopreservation.

The mutation load on the semen due to radiation therapy and chemotherapy is a potential hazard faced by many male cancer patients (Nahata et al. 2019). This will in still doubt about genetically defective progeny born to many cancer survivors. Similarly, the same doubtful scenario is seen around samples stored in ART. The genetic normalcy of the progeny and associated

ailments that might occur due to cryopreservation of sperms do haunt the cancer survivors to a large extent (Grin et al. 2021). The process involved with freezing the sample and then thawing it before use could cause unwanted alternations in the genes that lead to progeny with birth and genetic defects (Gianaroli et al. 2019). Boys in their pre-puberty years are not recommended for cryopreservation before their cancer therapies as the active spermatogenesis process wouldn't have reached its maximum potential at this young age (Lei et al. 2020). Testicular tissue could be a better alternative for these patients instead of for living sperms. Later transplantation can be opted to have effective spermatogenesis in these young cancer survivors (Ibtisham et al. 2017). But the experimental complexity of the process is a major drawback of the whole process. The impending urge to have their biological progeny becomes feasible for pre-pubertal cancer survivors after a certain age post-recovery (Lei et al. 2020). Hence, the SickKids fertility preservation program was organized to counsel pre-puberty patients about testicular cryopreservation (Ibtisham et al. 2017). The tram addresses the risks and other effects associated with infertility induced due to radiation and chemotherapy to the family members of the patients. Later motivating them to opt for this cryo method to conserve the fertility state of young boys (Nagirnaja et al. 2018). Testicular tissue [TT] could be collected from the patient before the therapy and a biopsy should be performed for samples from patients with a previous history of cancer onset in them. This uncertainty related to cancer therapy could primarily lead to gonad damage (Jain 2018).

3 Mechanism of DNA damage for testicular cancer patients

Researchers have previously reported that cancer patients have shown more instances of DNA damage when compared to normal patients. But the difference is not found to be too vast among testicular cancer patients and normal infertile men. The conditions of the sperms are found to be quite similar in both scenarios (Cheng et al. 2018; Moody et al. 2019, Panner Selvam et al. 2021). But these reports are limited to the patients who were yet to start therapy and treatment. Hence, suggesting pre-therapy may cause sperm DNA damage. The damage is found to be evident for 2-3 years in the DNA and chromatin among the cancer survivors' post-treatment, especially for testicular cancer. So, the best option is to go for cryobanks before the commencement of the treatment regime. The post-treatment phase has been found to result in damages varying based on the type, dosage of radiation, etc. (Arda et al. 2020). The actual relationship between testicular cancer and the reproductive potential of the patient is still unclear (Arda et al. 2020).

4 Sperm cryopreservation

The safest method to non-invasively collect samples for cryopreservation would be through masturbation or any other technique. These techniques are especially preferred for post-pubertal cancer patients (Machneva et al. 2020). The rate of success was nearly 92% in most of the freshly ejaculated samples for cryopreservation (Vickram et al. 2015a, Parameswari et al. 2017, Pathy et al. 2017, Kumar and Sridharan 2020). The most important requirement would be that the puberty of the patient lies between the age groups of 12 to 15 years and the testis volume around 10 cm^3 or more. For young patients, their last nocturnal seminal emission is very vital (Hoffmann et al. 2021).

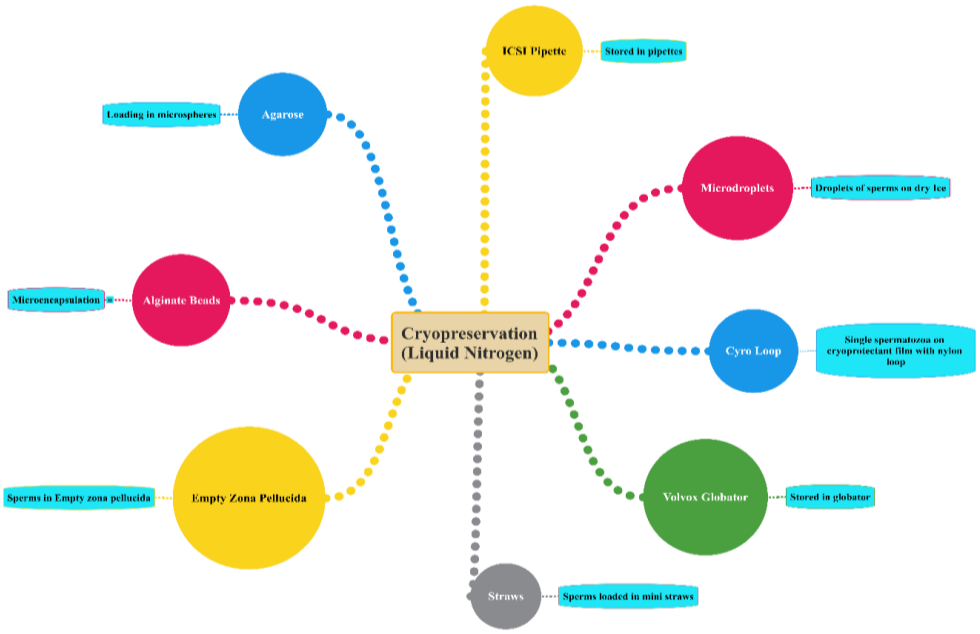

Figure 1 Feasible cryopreservation techniques for human sperm preservation

Cryopreservation of sperms is also possible in azoospermia. This is generally a condition when there is officially nil count of sperms, but pellet assay would show evidence of sperm cells (Pathy et al. 2017). Intracytoplasmic sperm injection can also be opted to transfer a single sperm cell for reproductive purposes (Vickram et al. 2015b). Previously many oncologists weren't suggesting cryopreservation procedures before cancer therapy. If emphasized by the clinicians, around 60% of the patients do agree to deposit their sperm for preservation in banks. Out of these, 70% of them utilize ART to achieve parenthood. This technique is also gaining popularity among patients through mutual contacts and friends (Iannarino and Palmer-Wackerly 2022). Figure 1 gives an outlook on the various feasible techniques for cryopreservation of human sperms.

4.1 Surgery for cryopreservation

The retrieval methods that use surgery as a mode for sperm collection and preservation is mostly considered the last resort (Alouf et al. 2020). This procedure is performed when patients show medical indications of azoospermia, failed ejaculations, and peri-pubertal situations (Talebi et al. 2021). Semen collection is much more effectively done by surgical methods in special cases like non-obstructive and obstructive azoospermia conditions (Hua et al. 2021).

5 Parenthood post testicular cancer therapy

Cancer associated with the testicles is very prevalent and can occur at the peak of the reproductive age man. After successful therapy and treatment of the disease, it is very essential to restore the reproductive status of the individual (Wyns and Kanbar 2021). The ability to father children is an important social and instinctive need of a human male (Ohan et al. 2020). It leads to the overall well-being of the man. The relationship between testicular cancer and its impact on male fertility seems to have a positive correlation that eventually leads to the loss of reproductive traits in men. During the initial stages of diagnosis of testicular cancer, several patients have shown signs of reduced and failed spermatogenesis (Sineath et al. 2021). In these cases, oncologists suggest and prescribe fertility preservation for restoring the existing reproductive status of the cancer patient. In exceptional conditions spermatogenesis has been seen to revive post-therapy. This again purely depends on the amount of radiation being exposed and the extent of therapy based on the severity of cancer (Wyns and Kanbar 2021). If chemotherapy alone is used to cure and treat testicular cancer, 71% of the survivors were able to father children with any ART (Okada and Fujisawa 2019). But the combinational treatment with cisplatin has shown to bring down the conception rate by 54%. This shows that the rate of conception is very much influenced by the protocol utilized for the treatment of testicular cancer. Germ cell testicular cancer is seen on the rise among men in their reproductive years (Goldberg et al. 2019). The efficiency of treating testicular cancer increases to 95% when cisplatin is administered in combination with radiotherapy, but the fate of the sperms becomes a big question mark. Still, it is a known fact that one out of three testicular cancer patients do show defects in their spermatogenesis processes during diagnosis. Hence, it would be wise for oncologists and andrologists to counsel young cancer patients to opt for fertility preservation before undergoing the therapy regime. At least temporarily impaired has been reported due to chemo and radiotherapy on the process of spermatogenesis (McGowan et al. 2017). Dry ejaculation might be very common among post-testicular cancer survivors (Parekh et al. 2020). A longer duration of chemotherapy often leads to this condition in men, which is commonly known as retroperitoneal lymph node disease or failure.

Sympathetic nerves tend to get damaged during the therapy which might lead to hindrance in seminal emission. This phenomenon is also called retrograde ejaculation (Meng et al. 2005). Seminal plasma is very essential for the movement of the sperms in the female reproductive tract. So, ejaculation with seminal plasma will not aid in fertilization (Schoeller et al. 2020). Other possible ways to preserve sperm count and quality naturally in the patient would be limited exposure to the para-aortic area, restricted dosage and duration of radiation therapy for each cycle, dose limitations of chemotherapeutants, etc. (Hamano et al. 2017). The patients feel that attaining parenthood gave a purpose and fulfilment to their life's goals and wishes (Rondhianto et al. 2020). Hence, it is essential to preserve semen before the treatment of testicular cancer (De Roo et al. 2016). It should be a mandatory protocol for patients of their reproductive ages and with no children to perform preservation of their semen and sperm before the commencement of the therapy for cancer (Kyweluk et al. 2018).

6 Neurogenic anejaculation patients

Damage to the spinal cord through injury could be a possible cause of the neurogenic version of anejaculation (Stoffel et al. 2018). These injuries could be related to injuries caused due to accidents or due to an onset of cancer (Brackett et al. 2020). It would create reflex erections usually when oral agents or penile injections which have erectogenic properties are administered (Yafi et al. 2016). A plan for treating testicular cancer would be the categorization of retroperitoneal lymph nodes. This would increase the rate of survival of the patient and then treat infertility (Vaz et al. 2019). The procedure involves the removal of sympathetic chains surgically, that directly leads to seminal emission rectification of normal ejaculation (Butcher and Brannigan 2016). The easiest way among all these techniques would be nerve-sparing protocol. Ejaculation in retroperitoneal lymph node disease is considered to be retrograde ejaculation by many clinicians and researchers (Agha et al. 2017). Failure in the seminal plasma emission is very evident

among the patients while exhibiting dry ejaculation (Andrade-Rocha 2017). If the patient agrees to fertility preservation, then the sperm cells are retrieved through a needle and standard cryopreservation methodologies are followed (Martins et al. 2019).

6.1 Dysfunction in iatrogenic ejaculation

This dysfunction is different from the neurogenic type of failure. It exists due to the intake and administration of a few specific medications like antidepressants and serotonin (Sadowski et al. 2016). These are prescribed for cancer patients who have symptoms of depression, which in turn leads to iatrogenic ejaculation (Shindel et al. 2022). This dysfunction is seen to be irreversible in most cases with a permanent failure in proper ejaculation. Hence, this worsens the situation of cancer survivors as they are unable to initiate a family. Furthermore, drugs administered for genitourinary complications and hypertension also tend to block the sections about prostatic emissions. Therefore, these types are also classified under retrograde ejaculation (Amsterdam et al. 2019).

7 Retrograde ejaculation

At times in some patients, there is a medical condition where the neck of the bladder doesn't close, but other components of the ejaculatory functions are normal (Tanabalan and Ballaro 2019). This is due to the high pressure developed in the bladder. Subsequently leading to adverse anatomic or physiologic abnormality, this is resulting in retrograde ejaculation (Althof and McMahon 2016). The resistance caused due to the high pressure and lack of closure makes the semen flow backward into the bladder (Steuer and Guertin 2019). Their urine exhibits a characteristic cloudy hue due to the presence of semen indicating retrograde ejaculation (Parnham and Serefoglu 2016). Cancer patients might exhibit high pressure and any subsequent surgery-based therapy can affect the closure of the bladder, leading to retrograde ejaculation (Shoshany et al. 2017).

8 Approaches for semen collection for preservation

For an average normal cancer patient, the collection is feasible through masturbation (Kumar et al. 2020). A seven days abstinence is essential before the collection protocol at ART centers (Manna et al 2020). The patient will be provided with a wide container to ejaculate the semen samples after masturbation. Analysis of the sample will be performed to ensure the quality of the sperm. Later cryopreservation techniques will be employed using proper extenders (Skidmore et al. 2018).

9 Penile vibratory simulation

In certain cases of ejaculatory conditions, a penile vibrator will be used to collect semen for fertility preservation (Liu et al 2018). The vibrator will create a stimulus on the tissue when placed on the penis, leading to antegrade ejaculation (Ibrahim et al. 2022). Men with a history of injury or antidepressant medications can opt for this technique for collecting samples for cryopreservation (Chong et al. 2017). The parameters of the vibrator along with continuous adjustment as per the patient's need make this technique very apt for semen collection. 2.7 amplitude at 100 Hz is found to be the optimal parameter to yield maximum semen for collection (Meng et al. 2018). It is advised to keep the vibrator on the frenulum with adequate settings set for ejaculation to occur (Cong et al. 2019). A sterile toxic free wide-mouthed plastic container should be used for collecting the ejaculate. The vibrator should be stopped once ejaculation occurs as continuous usage would lead to dysreflexia (Eldahan and Rabchevsky 2018). Blood pressure should be monitored throughout the process. It generally takes 3 minutes for the entire process to take place. An extra minute is allowed if no ejaculation is seen in the first 3 minutes (Flack and Mellon 2018). Dysreflexia and changes in penile tissues could be one of the main drawbacks that one could face while using this technique. The collection is feasible at the patient's own home if the procedure is clearly explained by the clinicians (Cong et al. 2019). The collected sample will be immediately processed for preservation (Cong et al. 2019).

10 Electroejaculation method - paediatric cancer patients

Patients who failed in collecting semen through vibrators can use rectal probes for the same. These approaches could have improvised results when compared to penile vibrators (Skott et al. 2018). Swagger electro ejaculator is a well-recognized and approved device by the United States Food and drug administration department. Before the procedure nifedipine is given sublingually to avoid any instances of dysreflexia. Around 10mg of the drug is administered at a time (Eldahan and Rabchevsky 2018). The catheter is inserted before the bladder gets stimulated, which aids in emptying the bladder. This is clearing the path for a sperm-friendly environment during this procedure (Furthner et al. 2018). Pre and post-the technique it would be necessary to perform rectoscopy procedure to avoid complications (Barnard et al. 2019). To derive the stimulation a wave pattern seems apt. The rectal probe is inserted into the dorsal lithotomy position to collect anterograde ejaculations effectively (Halpern et al. 2020). A wide-mouthed nontoxic container made of plastic is placed to collect the ejaculate. The container should be proven to be sperm friendly. The initial voltage from r stimulation would be 5V for 5 seconds then discontinued for the 20s. This cycle is repeated until ejaculations occur (Lorenzo et al. 2020). The next cycle commences when the contraction stops. The gradual increase in voltage is done to continue the technique with great efficacy (Anazodo and Ledger 2019). It can go up to 30V if needed. Paediatric cancer patients are administered this technique to

Table 1 Comparison of various cryopreservation techniques used with its pros and cons (Di Santo et al. 2012)

Technique	Mechanism	Merits	Demerits	References
Microdroplets	Droplets of sperms frozen in liquid nitrogen on dry ice	No adhesion to the walls	Cross contamination, difficulty in storage and transportation	Bouamama et al. 2003
Cryoloop	Single spermatozoa on cryoprotectant film with nylon loop frozen in liquid nitrogen	Vitrification, no sample preparation	Cross contamination	Desai et al. 2004; Arraztoa et al. 2022
Straws	Sperms loaded in mini straws	Convenient and simple	Adhesion and loss of sperms	Koscinski et al. 2007; Kaneko et al. 2021
Volvox globator spheres	Stored in globator	Easy thawing	Frequent algae growth	Just et al. 2004
Empty zona pellucida	Sperms in Empty zona pellucida	Less time consuming, easy loading	Cross Contamination	Hassa et al. 2006; Lee et al. 2021
Alginate beads	Microencapsulation	Inert	Less motility	Herrler et al. 2006; AbdelHafez et al. 2009
Agarose microspheres	Loading in microspheres	Non biological carrier	Clinical effect not evaluated	Isaev et al. 2007; Kurihara et al. 2021
Intracytoplasmic Sperm Injection pipette	Stored in pipettes	Simple, convenient	Cross contamination, no long term storage, set up is fragile	Sohn et al. 2003; Baldini et al. 2021

preserve their fertility. Patients with spinal cord injury, spina bifida, multiple sclerosis, situational anejaculation scenarios, retroperitoneal disease, and senile anejac conditions use the electroejaculation technique to collect semen for preservation (Anazodo and Ledger 2019).

11 Collection procedure for idiopathic anejaculation

Infertility due to unknown conditions is referred to as idiopathic infertility. The cause of the existence of the physiological aliment cannot be specifically identified (Perry et al. 2021). 30% of the cases of male infertility fall under this category. Most of the reasons might be due to undiagnosed neurogenic or iatrogenic conditions. But the psychological condition seems to influence this situation the most. Patients with the above-mentioned conditions masturbate normally, but fail to ejaculate during intercourse (Plante et al. 2019). So to preserve semen in these patients' masturbation is the most preferred technique. Cancer patients having similar fertility conditions should opt for masturbation and later cryopreservation. If masturbation doesn't work electroejaculation can be performed (Çayan et al.2017).

12 Methods for preservation

The essential requirement for the preservation of semen is mature spermatozoa. This can be used in *in-vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) (Sarasa et al. 2020). The most regular method used is masturbation. But in the case of peri-pubertal conditions, immature testicular tissue can be preserved for later. Retrieval of spermatozoa is an issue in these patients (Braye et al. 2019). In recent years, there has been an increase in the preservation of testicular tissue because of continuous counselling and monitoring (Goossens et al. 2020). Hence, 90% of the families of cancer patients agree to preserve mature and immature testicular tissues before starting cancer treatment. After the treatment is completed, a fertility check-up is performed to analyze the status of the patient. If the gonads and the related components and parameters report being normal for conception, then ART is not preferred (Çayan et al. 2017). In case of adverse effects on the male reproductive system are detected, then preserved semen or immature/ mature testicular tissues are utilized. Xenotransplant of the immature tissue to mature spermatozoa is recommended by current clinicians for ART (Zarandi et al. 2018). Problems and hindrances may arise while transferring malignant cells into a cancer survivor. Clinical trials for the xenotransplant of mature spermatozoa from immature testicular tissues are still a long way to go. Still developed countries perform the procedure of preserving immature testicular tissues from cancer patients who are peri-pubertal (Zhang et al. 2009) Table 1 provides a summation of the various cryopreservation techniques used to preserve sperms.

13 Cancer and the sperm characteristics

The correlation between malignancy and baseline sperm characteristics has been discussed well by many researchers previously. The negative effect of cancer on parameters of sperm has been successfully elucidated in various reputed articles (Rives et al. 2017). Most of the patient's sought cryopreservation who had sperm specifications that represented normalcy or intermediate to some extent (Barbaroșie et al. 2021). Table 2 represents the various

Table 2 Comparison of various techniques used before cryopreservation

Age of the patient	Condition	Procedure	Reference
14 years	Hodgkins disease	Transrectal electroejaculation	Skott et al. 2018
peripubertal	Any cancer	masturbation	Tran et al. 2022
	severe necrozoospermia, oligozoospermia, azoospermia	testicular biopsy with testicular sperm extraction	Daudin et al. 2015
Prepubertal or peripubertal with treatment in the process	Azoospermia	spermatogonia stem cells with testicular cell or tissue freezing	Picton et al. 2015
Prepubertal	Tissue banking	vitrification	Poels et al. 2013

techniques that could be opted on a patient before cryopreservation. Patients with testicular cancer exclusively exhibit a reduction in sperm parameters when compared with standard values from the world health organization (Panner et al. 2019). The stage of cancer does not seem to have a proper correlation with semen quality that considers the motility, morphology, and count of the sperm (Ghasemi et al. 2020). The volume of ejaculation was also found to decline in patients suffering from hematopoietic malignancy and testicular cancer. 20% of the cases reported for the previously mentioned conditions had azoospermia irrespective of the presence of obstruction or not (Pelloni et al. 2017). But this group of individuals was not found to be in their reproductive age groups. Chromatin integrity and DNA fragmentation seemed to get worsened in testicular cancer patients (Dave et al. 2021). Aneuploidy was at higher rates in sperms from testicular cancer gonads when compared to healthy control individuals. But the actual mechanism behind cancer and its manipulating effects on sperm characteristics has not been understood well, making the mechanism unclear (Baldi et al. 2021).

14 Nanotechnology and sperm life

The use of nanoparticles to preserve sperms has been of great interest in the past few decades. Through their success in animal models for sperm preservation, utilization of the same is making its way to human clinical trials for sperm conservation. These particles have limited applications for *in vivo* preservations of sperms, but their potential has no bounds when it comes to *in-vitro* based conservation aids. They always act as additional supporting material to the already established system of cryopreservation. The encapsulation of the chemotherapeutic agents within a nanoparticle gives functional features like targeted drug delivery and reduces the potency of the chemo drugs (Ahn et al. 2010, 2013). The lack of free drugs in the plasma decreases the toxicity of these medications on the non-target tissues like sperms and ovaries. The gonads can be well protected while having targeted and specific cancer treatment.

They generally address and rectify the drawbacks found in cryopreservation and thrive to make the whole procedure as efficient as possible. Some nanoparticles are designed to maintain sperm quality for both purification and preservation purposes in cattle. When experimented in boars nano-magnetic iron oxide pods showed results that were compatible and functional with both fresh ejaculates as well as frozen-thawed semen. These particles seemed to increase the rate of conception in cattle too (Huang and Juang 2011; Odhiambo et al. 2014; Ajinkya et al. 2020). High antioxidant features of a few nanoparticles like selenium, zinc, and cerium have been reported to protect semen from reactive oxygen species generated using the cryopreservation procedure (Jahanbin et al. 2015; Falchi et al. 2016; Khalil et al. 2019). But these effects have been seen in animal models to date. Clinical trials on human sperm and nanoparticles still have a long way to travel. Cryopreservation is known to create undesired oxidative stress on the spermatozoa that impair the integrity of spermatozoon membranes. Even mitochondrial and nuclear DNA content gets reduced to a large extent. Hence decreases the aptitude of fertilization in the frozen sperms compared to fresh ejaculates (Falchi et al. 2018a). During the process of freeze preservation, synthetic extenders are used to collect semen samples that provide a nutritional medium and support to the spermatozoa from freeze shock and microbial infestation. If further innovative changes are made to the extenders the negative effects of the cryopreservation procedure can be handled effectively. Nano water as a synthetic extender has promised novel properties of low viscosity, low density, antimicrobial property, high diffusivity, low dielectric constant, and nil thermal coefficients. Thus, claims to be a promising platform to dissolve lipids and a better nutrient and inorganic compound carrier than normal water. Media containing nano water exhibited better fertilization ability in frozen-thawed semen of ram. The ewes impregnated with the same also produced healthy lambs. Nano minerals tend to improve the quality parameters of semen while freezing and thawing. Among animal models' cerium oxide is quite well known for semen storing applications at 4 C for up to four days. This nanoparticle is reported to improve the motility of sperms (ram) after 2 days and maintain the DNA and plasma integrity throughout the 4 days (Falchi et al. 2018b). Selenium nanoparticles also tend to have ROS scavenging activity against sperm cells. 1mg/L of selenium nanoparticles in Holstein bull's frozen sperms manifested improved quality of the same towards fertilization. They reduced apoptosis, damage, and lipid

peroxidation caused due to cryopreservation (Khalil et al. 2019). Similarly, zinc nanoparticles decrease lipid peroxidation and enhance mitochondrial activity. The overall sperm functionality is maintained by optimizing the dosage of the nanoparticle (Afifi 2015). Cryopreservation could also re-localize the phospholipids of the cell membrane of frozen sperms. Stabilizing the membrane using nanoparticles can compensate for the free fatty acids and phospholipids that get altered or removed from the membrane of the spermatozoa during the freezing process (Nadri et al. 2019). Extenders containing nano lecithin (2%) used for diluting goat semen showed traces of improving sperm cryo survival. It lowered the chances of apoptosis and enhanced membrane functionality and motility of the sperm when compared with extenders containing egg yolk (Nadri et al. 2019). The general morphology of the sperm and semen is quite similar in most higher mammals. These particles can also be employed along with cryopreservation on cancer patients to effectively preserve their samples for the future.

15 Futuristic options for fertility revival

Spermatogonial stem cells (SSC) accompanied by autotransplantation can be considered the most effective method to restore fertility in cancer patients. Cryopreserved testicular tissue can be transplanted into the rete testis. SSC can proliferate and colonize by spermatogenesis and provide optimum sperm population to the cancer survivor (Brinster 2007). Xenotransplantation has reported excellent results in *in-vitro* studies (Sadri et al. 2011). A major risk still lurking around this promising technique is the uncertainty of reintroducing the host's cancerous cells again into the recovered patient body. Patients with leukaemia or metastasis of the blood are at high risk of relapse under the given conditions (Sadri et al. 2014). Currently, there are not many references that exclude the possibility of reoccurrence of cancer by autotransplantation, thus re-implantation strategies for real-time clinical application are still under study. SSC cells are maintained in their natural niche and can only be proposed if the presence of tumor cells is excluded (Liu et al. 2020). Xenografts have shown full spermatogenesis in several animal species but never in humans (Goossens et al. 2008). Human testis grafts were found to have better survival and initial differentiation rates in rats when compared to human models (Van Saen et al. 2011). Hence, extensive research is needed to understand the relationship between autotransplantation and the reoccurrence of cancer to put this promising technology into mainstream clinical practice.

Conclusion

Collecting semen samples from cancer patients is a non-invasive and easy procedure that doesn't tend to delay the cancer therapy process in any way. Oncologists recommend and prefer cryopreservation of sperms, especially for post-pubertal patients without much hesitation. The range of azoospermia conditions after chemotherapy or radiation therapy varies from 0 to 65%. Hence it is advisable to preserve the sperms for future progeny and to attain fatherhood. The recent development and improvisation in ART technologies have helped patients to preserve their samples well for childbirth later in life. As the number of cancer survivors is increasing, the desire to attain a normal life makes man hopeful about fatherhood. In our opinion, the preservation of fertility should be made mandatory before starting any cancer-related treatments and therapies.

Conflict of interest

The authors declare no conflicts for this article.

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