Fertility preservation in men: Perspective

Fertility preservation, in the era of assisted reproduction techniques (ARTs), is an important issue in a number of situations. The most common indication is for cancer survivors and another important indication is posthumous or cadaveric sperm retrieval in patients who are brain dead. The estimated number of people living with cancer in India is about 2.5 million. In an Indian Council of Medical Research (ICMR) projection, the total number of newly diagnosed cancer cases will reach nearly 1.73 million by 2020. Moreover, the incidence of cancer in adolescent and young adults (AYA) is increasing, considering the large number of young people in developing, cancer of AYA will constitute a significant burden. Paralleling this, the 5-year survival rates have markedly improved due to development of better chemotherapeutic agents, oncological surgeries, and radiotherapy. These gains in survival, especially in peripubertal male population, call for attention to fertility preservation. Oncofertility, a branch of medicine which balances lifesaving treatments against the fertility preserving options, has become popular. Posthumous sperm retrieval and gamete utilization is another aspect of fertility preservation which is discussed in detail.

FERTILITY PRESERVATION STRATEGIES

Improvements in surgical technique such as testis-sparing surgeries and nerve-sparing modifications for retroperitoneal lymph node dissection, are fertility preservation strategies for testicular tumor. Modification of chemotherapy regimens has been found to be of great value in preserving fertility. For example, in patients with lymphoma, transition from Mustargen, Oncovin, Procarbazine and Prednisone (MOPP) regimen to Adriamycin, Bleomycin, Vinblastine and Dacarbazine (ABVD) has increased the fertility gain in these patients. Gonadoprotection in the form of mechanical and chemical shielding can be used for protection of fertility in patients exposed to radiotherapy. In spite of the availability of varying strategies, semen cryopreservation remains the cornerstone of fertility preservation in male cancer survivors. However, there is underutilization of sperms which are banked and the reported rates of use range from 10% to 15%. Post treatment, some patients may achieve near normal levels of spermatogenesis sufficient for normal fertility. Other reasons for low utilization rates could be limited follow-up or utilization of the banked sperm after completion of the study. Limited follow-up and utilization of the cryopreserved sperm much later after the study end date may have resulted in underreporting of utilization rates. Death of the patient also contributes to underutilization of the cryopreserved sperm.

Although semen parameters are decreased upon thawing, advances in in vitro fertilization/intracytoplasmic sperm injection (ICSI) require a low number of viable sperms for fertilization. Reported rates of fertilization from cryopreserved sperms range from 26% to 55%. How long the cryopreserved sperms remain viable is not known. However, Feldschuh et have reported successful paternity with cryopreserved sperm after up to 28 years. Menon et al. reported no difference in ICSI rates from cryopreserved semen of patients with testicular cancer, lymphomas, and other tumors, thereby implying that fertility rates remain the same irrespective of the type of cancer.

ROLE OF UROLOGIST

During cryopreservation, the number of vials preserved depends on the quality of semen. Typically, 2–3 samples are collected before cancer treatment. In case of anejaculation or a low-volume ejaculate, postejaculatory urinalysis is ordered to rule out retrograde ejaculation. If sperms are found in postejaculatory urine, retrograde ejaculation is confirmed, and initially, alpha-agonist such as pseudoephedrine or imipramine is tried to convert retrograde to antegrade ejaculation. In case of persistent retrograde ejaculation, a catheter is placed in the bladder before ejaculation for bladder drainage and washed with sperm media. The catheter is removed and then reinserted to collect urine, after ejaculation. The ejaculated sperms are centrifuged from the solution and resuspended in fresh media with cryoprotectant. In case of confirmed anejaculation, vibratory stimulation or electroejaculation (EEJ) is performed to retrieve semen for cryopreservation. In case of aspermia, sperm retrieval techniques such as percutaneous epididymal sperm aspiration, microsurgical epididymal sperm aspiration, testicular sperm aspiration, or micro-testicular sperm extraction are used and the retrieved sperms are cryopreserved.

INTERNATIONAL GUIDELINES

Both the American Society of Reproductive Medicine (ASRM) and American Society of Clinical Oncology (ASCO) recommend informing patients suffering from cancer about their potential risks of malignancy, treatment, and available
fertility preservation options (sperm cryopreservation in males and embryo cryopreservation in females).[16,17]

The only approved fertility preserving method in men with malignancy is sperm cryopreservation.[16,17] ASCO strongly recommends “that sperm should be collected before initiation of treatment because of anticipated adverse effect of cytotoxic treatment on sperm DNA integrity”.[16] However, there may be situations such as urgent need for initiation of chemotherapy or poor sperm quality (counts, motility and morphology) even before initiation of any treatment. This should not deter the individual from getting sperm cryopreserved because with availability of IVF/ICSI even small number of sperms suffice for conception. It must be emphasized that methods, such as testicular tissue cryopreservation and tissue harvesting and auto implantation after treatment, are experimental and should only be a part of clinical trial.[16,17]

Position statements provided by these societies deal with the nitty-gritty of fertility preservation including medicolegal problems which may arise thereof.[16,17] These include the use and disposal of sperms in case of demise of the patient or nonpayment of storage fees. Posthumous use of these gametes is yet another set of legal and ethical dilemmas discussed later in this article. The third major issue is the legal rights of the child arising out of such an arrangement.[17] The position statement directs that “programs storing gametes, embryos, or gonadal tissue for cancer patients should request clear instructions about what should be done with stored materials in the event of the patient’s death, unavailability, nonpayment of storage fees, or other contingency. Spouses or family members with legal rights to dispose of a deceased patient’s stored gametes or other material could use them for posthumous reproduction only if the deceased had previously consented to such posthumous use”.[17]

**TECHNIQUE OF SPERM CRYOPRESERVATION**

The principle behind sperm cryopreservation is to prevent dehydration due to ice crystal formation, stabilization of intracellular ions, and maintaining integrity of plasma membrane. Cryoprotectants and semen extenders are used for these purposes. Egg yolk and glycerol is the most common used cryoprotectant. There are three techniques of sperm cryopreservation: slow freeze (SF), rapid freeze (RF), and ultra-RF (URF). Superior postthaw motility and survival have been shown with RF techniques, although no differences in morphology and DNA integrity has been reported.[18] Similarly, URF and SF protocols have shown similar decrease in postthaw motility. In the RF protocol, Sperm Freeze medium is used and the sample is mixed with it in equal volumes. Similarly, free sperms aspirated from the testicular tissue are added to the medium in case of tissue harvest. The mixture is loaded into 0.25 ml straws and the end is sealed with cement. The straws are incubated at 4°C for 10 minutes and are then placed over liquid nitrogen at a temperature of ~80°C over a period of 15 minutes. All the straws are then immersed into liquid nitrogen to achieve a storage temperature of ~196°C. For looking at post thaw motility one straw can be thawed and motility is examined to look for number of motile sperms, viable sperms. If found insufficient further tissue can be examined and the relatives are counseled about the poor prognosis.[18]

**POSTHUMOUS SPERM RETRIEVAL-AN ETHICAL DILEMMA**

Posthumous sperm retrieval is a delicate and controversial aspect of fertility preservation. Although an old concept, it came into light recently in our country. A 22-year-old unmarried male patient was admitted at a tertiary care trauma center. He was declared brain dead. Upon counseling regarding organ donation, the family members agreed but requested for sperm harvesting and cryopreservation to maintain the legacy of the family.[19] This gave rise to pertinent questions. Could this request be honored? What are the ethical and legal issues involved? Who is the rightful owner of these sperms? What technique can be used for retrieval?

First, the deceased has no spouse or legal partner who is party to the request. The deceased cannot rear the child himself. Whether he had an interest in reproducing, even though he cannot raise the child, is not known. Another ethical consideration is the unforeseen interests of the surviving family members (parents in the indexed case or spouse/partner) who wish to utilize the deceased’s gametes. How these vested interests are weighed against the will of the deceased remains a conjecture. Furthermore, jurisdictions vary on the status of children arising out of such a coalition; of their legal recognition as rightful heir of the deceased and also whether they are entitled to any property or social rights based on their legal status. The ICMR has no formal guidelines on posthumous sperm retrieval.[19] There is country-wise variation on this controversial topic.[20] Various countries have also formulated legislations which limits the utilization of sperm posthumously and have also defined the the inheritance rights of children conceived thereafter.[20] Canada, France, Germany, and Sweden have legislation forbidding posthumous reproduction. In Israel, UK, and Western Australia, the state registers such a child as legal son/daughter of the deceased. However, such registration does not entail any rights of inheritance or succession.[21,22] ASRM, in its recently published committee opinion, has stated that “posthumous gamete (sperm or oocyte) retrieval or use for reproductive purposes is ethically justifiable only if written documentation from the deceased, authorizing the procedure, is available.”[23] Moreover, retrieval of sperm or eggs does not commit their later use for reproduction but may be permissible under certain circumstances. In the absence of written documentation from the decedent,
programs open to considering requests for posthumous use of embryos or gametes should only do so when such requests are initiated by the surviving spouse or partner. Hence, in the index case, the request by the parents cannot be honored due to the reasons mentioned above. However, further ethical and legal dilemmas are bound to arise necessitating formulation of guidelines to help the treating physicians, reproductive biologists, ART specialists, and urologists in deciding the further course of action during such requests. In another situation where the gametes are cryopreserved and the patient dies due to ongoing illness or otherwise, the following is recommended. In case of a formal written directive or declaration given by the deceased, the rightful legal owner of the gametes is the spouse or lawful partner. If there is no dying declaration available, the mere act of getting sperm cryopreserved (after marriage) can be seen as a sign of willingness to reproduce and bear children in the future. However, the desire for a joint reproduction still remains a matter of conjecture. In such situations, the guidelines state “that decisions to retrieve the gametes must be made quickly, whereas decisions about their use in reproduction may occur at a later time. Clinics should be aware that the decision to retrieve does not commit them to later reproductive use of the gametes which should take place after adequate time for grieving and counseling has occurred.” The retrieval as suggested by animal studies is up to 48 h.

The ASRM further guides the clinicians and programs regarding the technicalities and state that “Regardless of the actual policy, physicians, and programs should develop written guidelines to address all such scenarios before they arise to avoid emergency appeals for guidance to entities such as hospital ethics committees.” In addition, programs should familiarize themselves with laws in their state, if any, regarding the retrieval and/or use of tissue for posthumous reproduction.” In case the request is made by the parents or family members, the ethics committee opinion by ASRM clearly states that “in the absence of written instructions from the decedent, programs that are open to considering requests for posthumous gamete procurement or reproduction from surviving spouses or life partners should decline requests for such services from other individuals.”

If the deceased was married and the decision is made to harvest the sperm, then the technique of retrieval is varied in literature. In the series published by Shefi et al. from Israel who harvested sperms in 14 deceased subjects, methods used for sperm harvesting included en block orchidectomy with epididymectomy with or without vasal sperm aspiration and epididymectomy alone. EEJ was used in patients who were still perimortem and were unresponsive due to neurological cause and were on ventilatory support. The time of sperm harvestation from the time of death varied from 7.5 to 36 h in this study.

Jequier et al. removed the testicular contents in the autopsy room and placed them in Quinn’s Advantage Sperm Freeze medium (Sage Media Australia). Microscopic examination was then performed at a magnification of 400X to look for sperm tails and free spermatozoa with the seminiferous tubule. After confirmation of the sperm, the tissue was cryopreserved.

**THE FUTURE**

Fertility preservation in prepubertal males is hampered by lack of mature sperm and knowledge of spermarche. Testicular tissue cryopreservation provides the greatest potential for these children. Investigational protocols include pretreatment harvesting of testicular tissue with spermatogonial stem cell and providing them a microenvironment to dedifferentiate into mature sperm. Creation of complicated testicular microenvironment is difficult and induction of meiosis is another difficult part in the induction of spermatogenesis. Animal studies with tissue harvesting and replantation have met with limited success, however, similar study with human testicular tissue showed poor results and short survival time for the testicular tissue. Reintroduction of malignancy from a malignant testis is another concern which limits the use of this technique.

**CONCLUSIONS**

To summarize, the awareness of patients and treating clinicians regarding fertility preservation is increasing. Cancer patients who are candidates for fertility preservation must be offered all the available information regarding these. Overcoming the barriers to utilization of the existing facilities and encouraging research to develop newer modalities for fertility preservation is the need of the hour. Posthumous sperm retrieval, which is an ethical and legal dilemma, needs formulation of indigenous guidelines based on recent international recommendations.
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