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Fertility Preservation

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Fertility preservation is a process of saving reproductive cells (spermatozoa/ oocytes/ embryo) or tissue (testicular and ovarian tissue in prepubertal boys and girls respectively) for future reproduction in individuals who are at risk of infertility due to diseases, medical interventions, genetics, age or other circumstances.[1]

The need for Fertility preservation

Fertility preservation helps a wider range of individuals. It primarily benefits patients who have reproductive potential and may be keen to preserve it while undergoing chemotherapy or radiation for malignant conditions or some non-malignant conditions, which are gonadotoxic.[1] Among the patients undergoing treatment for malignancies, 15% face a risk of infertility.[2] It is also influenced by the age and type of treatment provided. (Box1)

Box 1:

The risk of infertility depends on:

- Cancer - Type
- Age of patient
- Relevant infertility treatment history
- Chemotherapy – Regimen, type and dosage
- Drug administration methods
- Radiation – Size and location of the field
- Need for adjuvant endocrine therapy

It is also beneficial for patients with medical interventions involving the prescription of medications or surgery that can affect their fertility.

Currently, fertility preservation is offered for non-medical reasons like postponement of childbearing especially in women, as fertility declines with age.[3]

Indications

Malignancies:[1]

- Breast cancer
- Childhood cancers
- Endometrial cancer
- Cancer cervix

Autoimmune diseases requiring chemotherapy:[4]

- Systemic Lupus Erythematosus (SLE)
- Crohn's disease
- Nephropathies
- Multiple sclerosis
- Wegener's granulomatosis

Family history of premature ovarian failure/ chromosomal abnormalities (Turner mosaic).[5]

Clinic requirements to offer Fertility preservation

Clinics offering fertility preservation should have the expertise and infrastructure to provide Assisted Reproductive Technology (ART) procedures and cryopreservation without delay. In India, fertility preservation can be offered only in registered Level 2 ART clinics.

Since a multidisciplinary approach is required, along with a Reproductive Endocrinologist and reproductive surgeon trained in fertility preservation techniques, the team also requires Oncologists and Urologists. Additionally, genetic counsellors, mental health professionals, and financial counsellors should be involved in providing quality care for the patient undergoing fertility preservation.[6]

Fertility preservation in patients undergoing treatment for malignancies

Counselling and evaluating the patient are of prime importance as they will guide the physician in deciding on fertility preservation modalities and future implications. The patients are evaluated in the following regard:

- Cancer – Type, stage, treatment available and life expectancy
- Time that can be taken before beginning the treatment
- Age
- Pubertal/ menarcheal status
- Partner status
- Chemotherapy – Type and dosage employed

Patients undergoing fertility preservation should be counselled on the methods of fertility preservation techniques in practice along with available alternative methods. They should also be counseled about the advantages and disadvantages of all available modalities along with their success rates. It is imperative to discuss the choice of using donor gametes/ embryos in the future or adoption if they are not keen on fertility preservation

Some patients in the advanced stages of cancer may not be medically fit to undergo fertility preservation procedures. Hence, it is important to elicit the patient's current status of health. Addressing women's safety in undergoing future pregnancy should be in conjugation with the type of cancer, severity and type of treatment proposed. Therefore, treatment decisions should involve active participation from the reproductive medicine specialist and the oncologist, along with the informed consent obtained from the patient.

In patients who are willing to undergo fertility preservation by cryopreservation of gametes, embryos or reproductive tissues, written consent should be obtained prior, to the future disposition methods in case of their death.[7]

Available treatment procedures and associated risk for infertility

Haematopoietic Stem Cell Transplant (HSCT): Fertility in individuals undergoing HSCT is impaired significantly. The overall conception rate that is documented is less than 1%. Approximately, 80% of the women subjected to HSCT with cyclophosphamide/ Total body irradiation (TBI) or cyclophosphamide/busulfan possess a risk of permanent amenorrhea.[8]

Alkylating chemotherapy: The major concern among long-term surviving men and women treated for Hodgkin's lymphoma is the risk of developing azoospermia and premature ovarian failure, respectively. Under the age of 30, when treated with procarbazine alone or in combination with cyclophosphamide, 90 – 100% of men possess the risk of developing azoospermia and 5–25% of women possess the risk of developing premature ovarian failure. Infertility risk increases with cumulative dosage of alkylating agents. In patients receiving salvage therapy including conditioning and autologous or allogeneic transplantation, the risk is even higher.[9]

Doxorubicin-bleomycin-vinblastine-dacarbazine (ABVD) regimen: The risk of

infertility and gonadal damage is lesser and is reported to be less than 10% in patients treated with this regimen. In women, the risk of premature ovarian failure is also reduced.[9]

Radiotherapy: Based on the patient's age and dose of radiation, gonadal damage is evident in both men and women.

In men, there is a significant reduction of semen volume with a dose of 0.15 Gy and with a dose of 0.3–0.5 Gy temporary oligozoospermia is noted. Post radiotherapy, the severity of spermatozoa damage is noted between 4 and 6 months. Permanent oligozoospermia and azoospermia are seen in patients requiring higher doses of radiation. Post radiation, during the recovery phase, survived spermatogonial stem cells undergo proliferation to form mature spermatozoa resulting in a return of fertility. Time taken for normal semen volume and spermatozoa concentration to return after a single exposure dose below 1Gy is 9–18 months, for a dose of 2–3 Gy is 30 months and for a dose of 4–6 Gy it is 5 or more years. In men exposed to a dose of more than 4 Gy, irreversible azoospermia is seen. Testosterone is produced by Leydig cells that are less sensitive to radiation. Thus, testosterone levels are reduced only after exposure to a radiation of 20 Gy.[10]

The Effective Sterilizing Dose (ESD) is the dose of fractionated radiotherapy [Gy] at which premature ovarian failure occurs immediately after treatment in 97.5% of patients. In women with increasing age at treatment, ESD decreases. At birth, ESD is 20.3 Gy, at 10 years ESD is 18.4 Gy, at 20 years ESD is 16.5 Gy, and at 30 years ESD is 14.3 Gy.[11]

When women undergoing radiation for Hodgkin's disease are given radiation of 35 Gy involving the ovaries, irreversible damage to ovarian cells is noted. Similarly, a radiation dose of 25–50 Gy results in infertility in women over 40 years of age.[12]

Fertility Sparing Treatments in Gynaecological Cancers

Cervical cancer: In women with microscopic tumours (stage 1A1), nodal metastasis and parametrial disease incidence are lesser and thus performing a simple cone biopsy will preserve future fertility.

Radical trachelectomy is yet another fertility-sparing surgery, but it is essential to explain the associated obstetric risks in these women.

In patients with squamous cell cervical carcinoma, involvement of ovaries is extremely rare. In cases of adenocarcinoma and adenosquamous carcinoma of the cervix, up to 12% ovarian involvement is seen. Pelvic radiotherapy is offered to treat cervical cancer, and, in these women, ovarian transposition is commonly considered to preserve fertility. The outcome and success rates tend to vary with this procedure.

In women with cervical cancer, even if there is adequate time for controlled ovarian stimulation, some physicians consider it unsafe to perform transvaginal oocyte aspiration as the risk of profuse bleeding is higher.[13]

Endometrial cancer: In a higher group of young women with endometrial carcinoma, the lesion is well differentiated and confined to the endometrium and these women generally have associated polycystic ovarian syndrome. In stage IA endometroid endometrial cancer without myometrial invasion, progesterone treatment is well established. Histopathological staging of endometrial cancer is performed after hysterectomy and in cases where no hysterectomy

is performed, other modalities like ultrasound and MRI should be employed to diagnose myometrial involvement. In the majority of cases, MRI is used and it provides 90% accuracy. Various progestogenic regimens have been used, with the most common being Medroxyprogesterone acetate 400–800 mg in divided daily doses or megestrol 160 mg daily. The levonorgestrel-containing intrauterine system has been used in recent series and may be useful for maintenance therapy. Appropriate duration of treatment is not formulated and most authors performed endometrial sampling at an interval of 3 months and the time to response varies between 3 and 12 months.[14]

Ovarian cancer: In women confirmed to have stage I disease, fertility-sparing surgeries can be done by preserving the uterus and the contralateral ovary. The risk of recurrence is high as microscopic metastatic disease is not recognized. Yet, the European Society of Gynecologic Oncology recommendations [15]by its fertility taskforce published in 2011 states that,

- Stage IA grade 1 and possibly grade 2 tumours of mucinous, endometrioid or serous types were suitable for fertility-sparing surgery and
- Grade 1 stage IC could also be considered.
- Recently published NICE guidelines have recommended that information and help should be made available to patients with ovarian cancer to preserve their fertility in appropriate cases.

Fertility preservation in women

Oocyte and Embryo cryopreservation:

In women, the principal established modalities are oocyte and embryo cryopreservation.

In post-pubertal girls or adolescent girls who are peripubertal but still premenarchal, ovarian stimulation can be performed to retrieve mature oocytes and cryopreserve them. In women who have a partner, ovarian stimulation followed by oocyte retrieval and intracytoplasmic sperm injection (ICSI) may be done to create embryos for cryopreservation. Embryo cryopreservation offers the best success rates among all other ART procedures done for fertility preservation.

The ovarian tissue cryopreservation technique is not considered experimental anymore and it is employed clinically. This technique is beneficial in preserving fertility for prepubertal patients or in cases where there is not adequate time for ovarian stimulation.[16]

To prevent ovarian insufficiency in women affected by breast or any other cancers, undergoing Chemotherapy or Radiotherapy GnRH agonists may be offered. However, GnRH analogue administration is not an option to replace oocyte or embryo cryopreservation as these methods are very well established providing successful outcomes.

In women undergoing pelvic irradiation, ovarian transposition can be performed during the initial oncology surgery or at a later time. In future, when IVF is required, transvaginal oocyte retrieval is difficult and hence transabdominal oocyte retrieval may be accomplished.[17]

Ovarian tissue cryopreservation:

For cryopreservation of ovarian tissue, laparoscopy or laparotomy is performed to obtain ovarian cortical tissue before oncotherapy. Dissection of the obtained tissue into small fragments is done and cryopreservation is carried out. Either orthotopic transplantation can be done later or immature oocytes can be retrieved from

the dissected tissue and in vitro maturation (IVM) performed to obtain mature oocytes or embryos, that can be subsequently cryopreserved.

Orthotopic transplantation of thawed tissue in humans is considered the most successful technique. The transplanted tissue becomes functional between 60 and 240 days and it remains functional for up to 7 years.[18] In women older than 40 years, this is not feasible due to the relatively low follicular survival rate following ovarian transplantation.

Bilateral oophorectomy for cryopreservation is not justified at this point. It can be done only when there is a high likelihood of inducing complete ovarian failure by the choice of chemotherapeutic regimen employed.

Since malignancies like leukaemias are systemic, it poses a significant risk for reseeding tumour cells. Also, in conditions where cancer cells may present in the cryopreserved tissue, autologous transplantation is contraindicated.

Fertility preservation in men

The principle established modality is to perform cryopreservation of ejaculated spermatozoa. In men who cannot provide an ejaculated sample or in those with azoospermia, a surgically retrieved sample may be cryopreserved.

Men undergoing spermatozoa cryopreservation should be counseled about the quality of sample cryopreserved and its potential for future use. To provide an adequate number of spermatozoa for future treatment procedures, at least two to three ejaculated samples should be cryopreserved in multiple vials.[19]

In the absence of other modalities of fertility preservation in prepubertal males, testicular tissue cryopreservation can be considered. This technique is still considered experimental and adequate counseling should be provided to the patient regarding the experimental nature of the procedure. Moreover, in patients with blood-borne cancers or testicular cancers, autologous transplantation of cryopreserved testicular cells or tissues may not be appropriate due to the risk of re-seeding tumor cells.[20]

In men, GnRH agonist therapy is not recommended as it is not effective in preserving fertility.[21]

Men with difficulty in semen collection:

In men who have difficulty in semen collection, providing adequate counseling and a comfortable environment for semen collection may be beneficial. Associated medical conditions, drug intake, comorbidities, pubertal status, anxiety, pain, or the underlying disease itself can cause difficulty in semen collection. These men may be evaluated and depending on the requirement, they can be prescribed Phosphodiesterase type 5 (PDE-5) inhibitors or some may even require vibratory stimulation or electroejaculation.

In men with retrograde ejaculation, resulting from prior surgery (autonomic or pelvic nerve injury, bladder neck injury, etc.), **alpha-agonists** such as pseudoephedrine can be used with care in some of these men to restore antegrade ejaculation. Spermatozoa can be retrieved from bladder by processing the post masturbatory/ ejaculatory urine.[22] Alkalization of urine with or without administration of sperm wash media into the bladder before ejaculation can be performed.

Surgical sperm retrieval:

Surgical sperm retrieval is an alternative method in men who cannot produce an ejaculate via the aforementioned techniques or in those

who have azoospermia. Epididymal aspiration provides adequate spermatozoa for cryopreservation in men who have obstructive azoospermia. Testicular sperm retrieval for fertility preservation yields better outcomes in men with non-obstructive azoospermia. Spermatozoa from retrieved tissue are processed and cryopreservation is carried out. Alternatively testicular tissue may be cryopreserved and spermatozoa retrieved later when required. This will yield more motile spermatozoa.[23]

The sample can be subsequently thawed, and spermatozoa can be isolated and utilized for intracytoplasmic sperm injection (ICSI).

Conclusion

Fertility preservation is a potent technique enabling individuals to safeguard their reproductive potential and make informed decisions about their reproduction. It provides reassurance on future reproduction to individuals undergoing medical treatments affecting fertility like chemotherapy and radiotherapy. Recently, it is also being used for non-medical indications like preserving oocytes to overcome age-related decline in fertility. Although these techniques have challenges and ethical considerations, the increasing availability and success of these techniques represent an important advancement in reproductive technologies that benefit patients. As fertility preservation continues to evolve, it is important that physicians counsel and provide these options to the patients in need, especially to the ones who undergo treatment for malignancies as life expectancies post-treatment have improved to a great extent.

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