FERTILITY PRESERVATION

The field of reproductive medicine, that focuses on helping reproductive-age men and women to prevent infertility and birth defects.

About Fertility preservation

Fertility preservation procedures are indicated when it's predicted that there will be exposure to a cause of infertility. Mainly cancer treatment, such as chemotherapy, radiation, and surgery, may destroy a person's ability to have children later in life, and oncosterility research focuses on increasing fertility preservation options. Oncosterility is a subfield that bridges oncology and reproductive research to explore and expand options for the reproductive future of cancer survivors. It is scientifically proven that the number and quality of sex cells decreases with age. That is why this procedure (known as Social freezing) is also used by healthy men and women who want to postpone their parenting on later for any reason. They want to have the certainty of a young and healthy sperm and oocytes at a later age.

The main methods of fertility preservation are ovarian protection by GnRH agonists, cryopreservation of ovarian tissue, eggs or sperm, or of embryos after in vitro fertilization. The patient may also choose to use egg or sperm from a donor by third party reproduction rather than having biological children.

1. Options for females

**Ovarian Suppression by GnRH during Chemotherapy**

Chemotherapeutic agents have high levels of ovarian toxicity. Oocytes are contained in ovarian primordial follicles, which are very susceptible to the gonadotoxic effects of chemotherapy. Suppression of ovarian function through manipulation of GnRH has been evaluated as a mechanism to decrease the loss of primordial follicles. This has been studied in animal models with promising results but data regarding effectiveness in humans is limited to small retrospective reports. Unfortunately, it cannot be determined from these studies that the administration of GnRH agonists provided definitive ovarian protection.

**Ovarian tissue cryopreservation**

The basic principle of cryopreservation is to store cells or tissue for future use. Ovarian tissue cryopreservation involves surgically removing all or a part of the ovary, which contains thousands of primordial follicles. The resected tissue is cut into strips, cryopreserved and transplanted back to the pelvis, or other location (arm or abdominal wall) after cancer treatment. This procedure is usually performed by laparoscopy, can be planned immediately after the diagnosis of malignant disease and does not require hormonal stimulation. The advantage is that this is the only fertility preservation technique that is available to pre-pubertal girls or females in whom initiation of treatment cannot be delayed. It is also recommended to healthy women fearing the loss of their fertility.

On the other hand there is a risk of graft failure or reactivation of cancerous cells, particularly in hematologic malignancies after the return of ovarian tissue into the body.

**Oocyte and embryo cryopreservation**

Embryo and oocyte cryopreservation are both considered non-experimental options for fertility preservation in post pubertal females. Oocyte cryopreservation is the most commonly used for women who want to postpone their motherhood for the time being. Both interventions involve controlled two-week period of ovarian stimulation to produce multiple mature oocytes. Because of hormonal stimulation, this procedure is not optimal for patients with hormone-sensitive cancers (such as breast cancer or ovarian cancer) or those who
cannot delay cancer treatment. Cryopreservation is typically performed by incubation in a low concentration of cryoprotectant to minimize ice crystal formation during freezing; however, cells with a high osmotic content such as oocytes are particularly vulnerable to damage. Embryos are composed of multiple blastomere cells and are more stable for cryopreservation. Due to the difficulties with oocyte cryopreservation, embryo cryopreservation has been the primary modality for fertility preservation.

In embryo cryopreservation the mature follicles are fertilized in vitro with partner or donor sperm and then cryopreserved. In oocyte cryopreservation the oocytes are cryopreserved following their extraction. When the woman is ready to initiate pregnancy, the embryo is thawed and implanted into the uterus for maturation and birth. While this option is the most common fertility preservation method in women, it is not available to pre-pubescent girls, who do not have mature eggs that can be fertilized.

Protection of Ovarian Function

Oophoropexy, the relocation of the ovaries outside of the radiation field, may mitigate ovarian damage, although radiation scatter can still cause follicle depletion. Shielding of the ovaries during radiation therapy should be considered standard of care, when ovaries are not in the treatment field.

2. Options for males

Semen cryopreservation

Preservation of fertility in post pubertal males is reliably accomplished by cryopreserving sperm prior to the onset of gonadotoxic therapy which may lead to testicular failure or ejaculatory dysfunction. Semen can be used successfully indefinitely after cryopreservation. The most common method to obtain sperm is through masturbation, which can be done in the in-patient or out-patient setting, or via referral to a sperm bank. Optimal procedures for the collection of sperm include abstinence 48 h prior to collection and the collection of multiple specimens, at least 24 h apart. The semen sample is evaluated for sperm count, morphology and motility prior to cryopreservation. Limitations to this form of cryopreservation are related primarily to an inability to masturbate, whether secondary to age, illness or cultural mores that prohibit masturbation. Emotional and practical issues may also be present that limit success. Alternative approaches exist when masturbation is not possible. Electroejaculation involves the placement of a transrectal probe while the patient is under general anesthesia. Electrical stimulation is applied until ejaculation occurs and sperm is collected.

After cryopreservation can potentially increase the risk of mutations in offspring DNA. In long-term follow-up studies, no evidence has been found either of an increase in birth defects or chromosomal abnormalities in people conceived from cryopreserved sperm compared with the general population.

Testicular Tissue Cryopreservation

Sperm banking is not possible for pre-pubertal boys as they cannot yet produce mature spermatozoa. However cryopreservation of gonadal tissue offers hope to childhood cancer survivors and also post-pubertal males who cannot produce a sperm sample. Immature boys at risk of losing their spermatozoa, mostly cancer patients, are the main target group that may benefit from testicular tissue cryopreservation and spermatozoa autotransplantation.

Procedure is similar to ovarian tissue cryopreservation - testicular tissue is surgically removed and frozen. Success has been reported in cryopreservation methods of testicular tissue but more research is still needed in how to use the frozen-thawed tissue and obtain mature spermatozoa in vitro.

Protection of the Testes during Treatment

The testes should be shielded during radiation therapy to try to minimize the exposure to scatter radiation. Consideration can also be given to moving the testes out of the radiation field.

3. Options for both

Third-party reproduction

Many patients diagnosed with a malignancy or another disease requiring treatment that may impair their fertility consider alternatives to bearing biological children, such as assisted reproductive technology (ART) using in vitro fertilization (IVF) with donor eggs or donor sperm. The resulting embryo can be implanted into the woman's uterus after her endometrium (the lining of the uterus) is stimulated with hormones to prepare for the
Success or failure factors

Therapy is effective only when it is meant to it ahead of time - before the start of cancer treatment or before reaching the age when they are no longer sufficiently viable sex cells. Ideal age for social freezing is 25 years. Many healthy women undergoing this therapy are aged over 35 years. With increasing age, decreases the likelihood of success – women under age 35 have the probability about 40%, in the age 35 – 39 is about 10% lower.

Complications

There are risks, which can destroy the process. In the preparatory time is the compliance of patient, wrong answer to a given treatment (for example ovarian stimulation) or bad timing of therapy. In the course of treatment some complications may occur during the collection of the tissues. Compared with the general population, people with cancer have a higher risk of arterial thrombotic events such as stroke, myocardial infarction and peripheral arterial embolism. This risk has a potential to be further increased in women undergoing controlled ovarian hyperstimulation for fertility preservation, but is usually only associated with cases of ovarian hyperstimulation syndrome (OHSS). On the other hand, venous thromboembolism rarely occurs unless a pregnancy is achieved, and is therefore usually not particularly relevant in the stage of oocyte retrieval. Therefore, the recommended controlled ovarian hyperstimulation protocol for in women with cancer is an antagonist protocol using a GnRH agonist for final maturation induction, in order to decrease the risk of OHSS. Anticoagulant prophylaxis is recommended to be administered only to selected subgroups of women such as those with other risk factors of hypercoagulability or those who do develop early OHSS.

Prognosis

Infertility due to gonadal failure is one of the major consequences of cancer therapy, particularly in patients who receive aggressive chemotherapy and/or radiotherapy treatment. Many surveys of cancer survivors have found that those patients are at increased risk of emotional distress if they become infertile as a result of their treatment. Evidence suggests that long-term survival after treatment for cancer during childhood is associated with increased risk of impaired quality of life and higher frequency of psychosocial problems often related to infertility issues. Adolescent cancer survivors have increased anxieties about body image and dating, and pediatric cancer survivors are less likely to marry than matched controls. Although cancer survivors can become parents by adoption or gamete donation, most would prefer to have biological parenthood and biologically related children. Patients interested in fertility preservation should be promptly referred to a reproductive medicine expert to offer timely and appropriate counseling and improve success of fertility preservation.

Find more about related issues

Diagnoses

Endometrial cancer
Cancer that arises from the endometrium, the lining of the uterus.
Learn more at: www.fertilypedia.org/therapy/diag/endometrial-cancer

Menopause
The time in most women’s lives when menstrual periods stop permanently, and the woman is no longer able to have children.
Learn more at: www.fertilypedia.org/therapy/diag/menopause
Ovarian cancer
A type of cancer in which abnormal cells begin to grow in one or both of a woman’s ovaries.
Learn more at: www.fertilypedia.org/therapy/diag/ovarian-cancer

Ovarian tissue cryopreservation
Putting ovarian tissue strips into the preserving solution.

Testicular tissue cryopreservation
Schematic diagram showing testicular tissue cryopreservation and future spermatogonial stem cell autotransplantation to restore male fertility in high-risk patients.

Algorithm of fertility preservation options for females

Algorithm of fertility preservation options for males

Strategies for fertility preservation in males and females
Strategies for fertility preservation in males and females

Radiation therapy to pelvic organs and gonads
Shielding aiming at reducing damage of reproductive organs. Ovarian transposition in females

Fertility-sparing oncologic surgery
Fertility-sparing surgery preserving gonads. Preservation of the uterus in females

Cytoprotective treatment with high risk of gonadal damage
Sperm banking for males. Freezing of embryos and oocytes for females (established methods)
Gonadal tissue freezing (experimental stage)
Radiotherapy protocols with high or intermediate impact on ovarian and testicular function

<table>
<thead>
<tr>
<th>High risk of prolonged azoospermia in men or amenorrhea in women</th>
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<tbody>
<tr>
<td><strong>Total Body Irradiation (TBI) for bone marrow transplant/stem cell transplant</strong> (9,15,16)</td>
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<tr>
<td><strong>Testicular radiation dose &gt;2.5 Gy in adult men</strong> (9,17)</td>
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<tr>
<td><strong>Testicular radiation dose ≥ 6 Gy in pre-pubertal boys</strong> (18,19)</td>
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<tr>
<td><strong>Pelvic or whole abdominal radiation dose ≥ 6 Gy in adult women</strong> (20,21,22)</td>
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<tr>
<td><strong>Pelvic or whole abdominal radiation dose ≥ 10 Gy in post-pubertal girls</strong> (21,22,23,24)</td>
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<tr>
<td><strong>Pelvic or whole abdominal radiation dose ≥ 15 Gy in pre-pubertal girls</strong> (21,22,23,24)</td>
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<td><strong>Intermediate risk</strong></td>
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<tr>
<td><strong>Testicular radiation dose 1-6 Gy from scattered pelvic or abdominal radiation</strong> (13,16)</td>
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<tr>
<td><strong>Testicular radiation dose 5-10 Gy in post-pubertal girls</strong> (21,24)</td>
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<tr>
<td><strong>Testicular radiation dose ≥ 10 Gy in pre-pubertal girls</strong> (21,22,24)</td>
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<tr>
<td><strong>Craniospinal radiotherapy dose ≥ 25 Gy</strong> (14)</td>
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