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SPECIAL ARTICLE

FIGO statement: Fertility preservation

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Abstract

Fertility preservation is a growing field in reproductive medicine that may raise ethical questions. Preservation of fertility must be discussed with the patient if gonadotoxic treatment is required, whether in the case of benign or malignant pathology, or in the management of transgender identity. As a result, surgery or chemotherapy that has fewer adverse impacts on fertility should be proposed if this does not alter the prognosis of the disease. If the risk of infertility persists, then fertility cryopreservation should be proposed for children and adults of reproductive age. Sperm, oocytes, and gonadal tissue can be cryopreserved for many years. FIGO wishes to emphasize the importance of fertility preservation in the medical and surgical management of patients, and the importance of a specialized, multidisciplinary approach.

KEYWORDS
female, fertility preservation, male, oocytes, ovarian tissue, sperm, testicular tissue

1 | INTRODUCTION

Different techniques for fertility preservation have been developed over the past decades. Fertility preservation is a growing sector of reproductive health, owing to improved technology and an increasing number of clinical indications beyond those related to oncology.

The choice of the most appropriate technique for a given patient depends on multiple parameters, including the age of the patient and pubertal status, type of pathology, treatment required and its urgency to be started, and the presence or absence of a partner. Among the different fertility preservation techniques, it is necessary to differentiate between procedures that limit the impact of treatments and those that cryopreserve reproductive cells, whether in the form of mature gametes, embryos, ovarian tissue, testicular tissue, or immature gametes.

In adult males, the primary means of gamete preservation is sperm cryopreservation, which is a relatively simple procedure. This is not the case in females, for whom there are multiple choices, but all of which are invasive with some risk, substantial cost, and less certainty of success.

Furthermore, it is necessary to distinguish interventions aimed at limiting the impact of a disease from those aimed at cryopreserving reproductive cells. Among surgery, radiotherapy, and chemotherapy, the choice of the most appropriate technique for fertility preservation can be complex. Surgical management of underlying malignancies may disrupt the hormonal axis, the neurological pathway leading to reproductive function, or directly impact the gametes or genital organs. Chemotherapy or gonadotoxic radiation may also disrupt the endocrine pathway or damage stem cells or differentiating gametogenic cells. Fertility preservation may allow patients with cancer and other patients to build families with their own genetic makeup.

2 | FIGO POSITION

2.1 | Ethical viewpoint

In the field of reproductive medicine, cryobiology is used to cryopreserve sperm, eggs, embryos, and gonadal tissues. Fertility preservation with oocyte or embryo cryopreservation has become increasingly common in the last decade. The indications for this type of treatment are diverse in nature including personal health and social indications such as delayed childbearing, infertility diagnosis, medical conditions such as diminished ovarian reserve and gender dysphoria, or for newly diagnosed oncologic diseases requiring gonadotoxic therapies. Biotechnology has improved cryoprotective media, storage systems, and freezing protocols, making possible adequate oocyte and embryo survival upon thawing and pregnancy rates similar to fresh (non-frozen) embryo transfer.

Finally, the utilization of gametes and vitrified embryos is a practice that has been considered ethical for decades in many countries. The American Society for Reproductive Medicine and the European Society of Human Reproduction and Embryology recognize cryopreservation of gametes as safe and effective medical treatment.[1]

2.2 | Male fertility preservation

For the postpubertal male, the primary method of fertility preservation is sperm cryopreservation. This should be undertaken prior to any gonadotoxic therapy.

For postpubertal males that are unable or unwilling to provide a semen sample for cryopreservation, testicular sperm aspiration (TESA) and testicular sperm extraction (TESE) can be performed under local anesthesia. In patients with azoospermia, controlled sedation or general anesthesia with testicular sperm extraction by microdissection (microTESE) are recommended.

For azoospermic men with testicular cancer, testicular tissue may be harvested at the time of orchiectomy or excisional biopsy (oncoTESE). Ipsilateral harvesting may be considered in instances where access to healthy tissue is possible. If such tissue is unavailable to be safely accessed, extraction of the contralateral testis by microTESE can be performed. Male patients are advised to actively avoid pregnancy for at least 1 year after chemotherapy or radiation therapy due to the potential induction of germ cell mutations.

For prepubertal males, cryopreservation of testicular tissue may be considered under approved clinical trials. Informed consent requires explaining that there are no current clinical care pathways for the use of prepubertal testicular tissue.[2–4]

2.3 | Female fertility preservation

Benign gynecologic pathologies

Surgery that preserves the most fertility is recommended whenever possible. In the case of ovarian cyst removal, for patients who wish to preserve their fertility, the impact of ovarian surgery on ovarian reserve and function must be considered. During surgical treatment it is essential to avoid inadvertent removal or damage to healthy ovarian tissue through excessive use of electrosurgery.[5] The key surgical principles are: identify the plane between the cyst and ovarian stroma; dissect the cyst wall away from the overlying ovarian tissue in a straightforward manner with traction/countertraction; use electrosurgery judiciously, and obtain hemostasis with sutures, if necessary. Laparoscopy also reduces postoperative adhesions and inadvertent removal of normal ovarian tissue. Endometriosis and endometriomas are associated with infertility in one in three women and have a negative impact on fertility potential. Endometriosis surgery that reduces ovarian reserve reduces the success of assisted reproduction technology. Removal of peritoneal endometriosis has no impact on ovarian reserve.[6] However, regardless of ovarian reserve,

laparoscopic treatment of endometriosis would improve viable intrauterine pregnancy rates.[7]

Due to the possibility of decreased ovarian reserve or even ovarian failure, laparoscopic ovarian drilling for women with polycystic ovary syndrome should be used with caution.[8]

In patients who require myomectomy, care must be taken to minimize uterine damage and avoid intrauterine adhesions. Removal of FIGO type 0, 1 or 2 submucous myomas and uterine cavity-distorting intramural myoma increases the pregnancy rate.[9] Similar to uterine myoma, focal adenomyoma could be safely removed.[10,11] However, removal of diffuse adenomyosis has been associated with uterine rupture. Other methods including the use of gonadotropin-releasing hormone agonists or antagonists before fertility treatment have been successful.[12]

Gynecologic cancers

Surgical techniques for fertility preservation depend on the site and type of malignancy.

- *Ovarian cancer*: there is no unanimous consensus on criteria for conservative approaches; treatment options are primarily determined by histology and stage of disease.[13–18]
  - Malignant ovarian germ cell tumors (MOGCT): As a tumor with high chemoresponsiveness, commonly diagnosed in the young age group (10–30 years of age), every stage of MOGCT should be surgically treated conservatively, which includes unilateral salpingo-oophorectomy (USO) and comprehensive surgical staging.
  - Sex cord stromal tumors (SCSTs): Due to their good prognosis, the option of fertility preservation is supported and includes USO and complete surgical staging for FIGO Stage IA and IC disease.
  - Epithelial ovarian cancers (EOC): Fertility-sparing surgery for Stage IA or unilateral and Stage IC EOC.
- *Endometrial cancer*: The approach to preserve fertility by hysteroscopic resection requires a series of fulfilled criteria:[19–24]
  - Well-differentiated tumors with less than 50% myometrial invasion based on magnetic resonance imaging.
  - No evidence of pathologic lymph nodes.
  - No evidence of synchronous or metachronous ovarian tumors.
  - No family history or hereditary cancer syndromes, proved by mutation testing primarily for Lynch syndrome with immunohistochemical staining of the tumor specimens for mismatch repair (MMR) proteins.
- *Cervical cancer*: Criteria for fertility-preserving treatments are as follows:[25–27]
  - Histologic type: squamous cell carcinoma, adenocarcinoma, or adenosquamous.
  - Tumor size: lesion ≤2 cm.
  - No deep stromal invasion.
  - No evidence of lymph node involvement.
  - No distant metastatic disease.

In cancers treated with radiation therapy, especially in young patients, ovarian transposition could be proposed to limit the effect of radiation on ovarian reserve by removing the ovary from the radiation field.[28]

In women with breast cancer treated with chemotherapy, medical protection using GnRH agonists could be proposed but should not be considered as an equivalent or alternative option for fertility preservation.[29,30]

All patients who opt for conservative treatments must be thoroughly evaluated and counseled regarding every detail of the treatments and outcomes, especially the potential effect upon survival. Rigorous post-treatment surveillance and subsequent standard treatments are compulsory, once the family is completed.

Cryopreservation techniques

When optimal protection of the ovary cannot be assured, cryopreservation of oocytes, embryos, or ovarian tissue may be necessary.

Oocyte cryopreservation by vitrification is the method of choice for women undergoing treatment for age-related fertility loss and for most women undergoing fertility preservation for medical indications.[30] However, it is only available for women who have reached puberty and requires ovarian stimulation followed by transvaginal ovarian oocyte retrieval.[30,31] This technique is increasingly being proposed for medical diseases and conditions other than oncologic disease. Examples include endometriosis[32,33] and other conditions predisposing to premature depletion of the ovarian reserve, but also transgender men before starting hormonal treatments.[34]

Embryo cryopreservation has similar advantages to oocyte vitrification. It is more widely available worldwide but can only be offered to women in stable relationships and must consider the need for joint legal ownership with the male partner.[30] This important requirement can potentially lead to difficulties regarding use of the embryos if the parties are not in agreement.

Oocyte vitrification is a less cumbersome and less intrusive procedure than ovarian tissue cryopreservation. However, ovarian tissue banking is an important fertility preservation technique that remains the only method to preserve fertility in prepubertal girls or if there is insufficient time for ovarian stimulation in patients undergoing moderate or high-risk gonadotoxic therapy.[30,35–37] However, it does carry the potential risk of cancer cell transmission because currently the only option to restore fertility after ovarian tissue freezing is to transplant the ovarian tissue back into the woman.[38] Pregnancy without medical intervention can frequently be achieved after ovarian transplantation so that assisted reproductive technology (ART) is not necessary.

In vitro oocyte maturation, which is not yet widely used, involves the culture of immature cumulus-oocyte complexes recovered from small antral follicles, after possible mild stimulation with follicle-stimulating hormone. Although the overall success rate of these oocytes is lower compared with matured ones, there is no increase in congenital anomalies when compared with IVF children.[30,39] In vitro maturation (IVM)

has also been used as an adjunct with cryopreservation of ovarian tissue, referred to as ex vivo IVM. However, success rates are unknown, and limited to a small number of live births to date.[40]

2.4 | Transgender

Fertility preservation is an important aspect of reproductive health for transgender individuals, including both transgender men and women. Transgender people often face unique challenges related to fertility preservation due to medical and social factors associated with their gender transition.

For transgender men who were assigned female at birth but identify as male, fertility preservation options typically involve freezing of oocytes or embryos before undergoing surgical procedures such as removal of the uterus, ovaries, or both. This allows transgender men to preserve their fertility and have the option to become biological parents in the future. The ART process is based on using their preserved eggs or embryos or through gestational surrogacy.

Transgender women who were assigned male at birth but identify as female may face challenges related to the irreversible effects of hormonal therapy on sperm production. However, fertility preservation options for transgender women may still be based on sperm cryopreservation prior to hormone therapy, allowing them to have the option to become biological parents through ART intrauterine insemination (IUI) with a partner or gestational carrier. Fertility preservation in transgender individuals not only addresses their reproductive autonomy and family planning desires but also has important psychological and emotional benefits as it provides a sense of control and peace of mind concerning future reproductive options.[34]

It is important that transgender patients are managed in a multidisciplinary manner by a specialized team so that they can make an informed decision in relation to fertility preservation.

3 | FIGO RECOMMENDATIONS

FIGO recognizes fertility preservation as an important area of reproductive medicine for both women and men.

FIGO recommends:

- It is important to recognize that fertility can be compromised by both benign or malignant pathologies and also by the treatment required to manage them.
- Fertility preservation should be discussed with each patient whose fertility may be compromised by any medical treatment or disease. Cancer patients should be consistently informed of:
  - the standard of care
  - the possibility of fertility-sparing treatments and their probability of success
  - the risk of compromised oncologic outcomes and survivals
- The patient, ideally, should be referred to a multidisciplinary team experienced in fertility preservation procedures.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception or design of the work; drafting the work or reviewing it critically for important intellectual content; and gave final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

Laurie Henry reports consultancy fees and personal fees for lectures or presentations from Merck N.V.-S.A. Craig Niederberger reports participation on committees and advisory boards for the American Board of Urology, the American Urological Association, Contraline, COMMIT, COMMA, Posterity Health and ReproNovo; he is Chief Technology Officer at NexHand, and Nursing Educator at Letters and Sciences LLC; he hold stocks or stock options in NexHand and Posterity Health; he contributed to a scientific trial for Ferring Pharmaceuticals. Edgar Mocanu reports a leadership or fiduciary role at IFFS (President), and participation on a data safety monitoring board or advisory board at CRYOS International. Togas Tulandi reports travel expenses from McGill University. All other authors report no conflicts of interest.

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