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EMAS position statement: Fertility preservation

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ABSTRACT

Introduction: The increasing incidence of malignant diseases that often require gonadotoxic treatment and the tendency to become a parent later in life result in an increased need for fertility preservation.
Aims: The aim of this position statement is to provide and critically appraise evidence on available options for fertility preservation in both pre-pubertal and post-pubertal men and women.
Materials and methods: Literature review and consensus of expert opinion.
Results and conclusions: Fertility preservation should be a priority when treating children or adults of reproductive age with agents that may have hazardous effects on the reproductive system. Gonadotoxicity should be kept at a minimum. If gonadotoxic treatment has to be used, methods of fertility preservation should be discussed, as early as possible.

1. Introduction

Fertility preservation is defined as the use of available technologies to help individuals retain their fertility or ability to procreate. These technologies have been developing in recent years, as the need for their use has been growing. The increased incidence of malignant diseases that often require gonadotoxic treatment and the tendency to become a parent later in life are two of the main causes of the increased need for fertility preservation. The techniques were initially designed for patients who are at increased risk of developing infertility due to medical conditions or treatments. However, the use of fertility preservation to counter the normal age-related decline in fertility is also becoming a topic of interest for many healthy women.

The American Society of Clinical Oncology (ASCO) and the American Society for Reproductive Medicine (ASRM) have recommended that the impact of cancer treatments on fertility be addressed with all cancer patients of reproductive age, and that options for fertility preservation, such as embryo cryopreservation, be discussed routinely [1]. Special guidelines have been designed for specific populations, such as children, adolescents and young adult cancer patients [2,3], and patients with a specific malignant disease [4,5]. However, as far as age-related decline in fertility is concerned, there are no clear recommendations for fertility preservation [1,6].

This position statement from the European Menopause and Andropause Society (EMAS) aims to provide and critically appraise

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evidence on available options for fertility preservation in both pre-pubertal and post-pubertal males and females.

2. Conditions that may result in reproductive failure

Gonadotoxic treatments (chemotherapy or radiotherapy), used in patients with cancer, autoimmune or hematological conditions that require hematopoietic stem cell transplants [7], are a common cause of reproductive failure in young adults. Autoimmune diseases, such as systemic lupus erythematosus, can be accompanied by infertility or premature ovarian insufficiency (POI) [8], either due to the autoimmunity itself or due to the drugs used to treat it (Table 1).

Chemotherapy and radiotherapy may result in permanent damage of steroid – producing cells and gametes, thus causing hormonal deficiencies, abnormal pubertal development and infertility. These sequelae are important, especially when managing children and adolescents.

Drug type and dose, total body irradiation (TBI) and patient characteristics, such as sex and age, are the main determinants of the degree of impairment to the patient's reproductive potential. Table 1 categorizes the main chemotherapy drugs according to their level of gonadotoxicity.

Radiation therapy delivered to the pelvis/abdomen or TBI causes dose-related damage to the gonads. A radiation dose of 2 Gy is estimated to irreversibly damage 50% of ovarian follicles, and doses between 5 and 20 Gy may cause sterility [9].

Recurrent ovarian surgery for benign disease and prophylactic oophorectomy in women with *BRCA* mutations are two conditions that also result in reproductive failure. Others include POI and genetic syndromes that affect the reproductive system, such as Klinefelter syndrome in men and Turner syndrome in women. Klinefelter syndrome is a genetic disorder in which there is at least one extra X chromosome to a normal male karyotype (47,XXY), characterized by hypogonadism and reduced fertility. Turner syndrome, on the other hand, is a genetic disorder in which one sex chromosome is missing (45,X) and is characterized by ovarian dysfunction.

Age is a well-recognized infertility risk factor for both women and men. In women, the ovarian reserve diminishes with age, the hormonal environment is altered and the quality of oocytes deteriorates (specifically, there are more chromosomal, morphologic and functional abnormalities). In men, increasing age has been associated with an increasing rate of sperm DNA fragmentation, possibly due to oxidative stress, with deterioration in semen quality [10–12].

3. Fertility preservation in pre-pubertal boys and girls

3.1. Pre-treatment counseling

As more than 80% of children diagnosed with cancer will survive the disease [13], the potential harmful effects of the treatment to reproduction should be discussed beforehand, together with the parents; long-term reproductive potential should be taken into consideration in the construction of the therapeutic plan.

Children diagnosed with genetic conditions that impair their reproductive function should be referred, as early as possible, to a reproductive endocrinologist.

3.2. Options for fertility preservation

Reduction of treatment-related gonadotoxicity should be a priority when treating pre-pubertal girls and boys. As there are no easy-to-apply technologies that can preserve fertility, all efforts should be made to include in the therapeutic plan agents with minimum gonadotoxicity (Table 1).

Table 1
Chemotherapeutic drugs according to gonadotoxicity level.

High	Moderate	Mild or none
Cyclophosphamide	Cisplatin	Bleomycin
Chlorambucil	Carboplatin	Actinomycin D
Melphalan	Doxorubicin	Vincristine
Busulfan	Etoposide	Methotrexate
Nitrogen mustard		5-Fluoro-uracil
Procarbazine		Mercaptopurine
Dacarbazine		Prednisone
Ifosfamide		Interferon-alpha
Thiotepa		
Carmustine		
Lomustine		

Source: Modified from [44].

Preservation of gonadal tissue and transplantation of germ stem cells could be applied for fertility preservation in pre-pubertal boys and girls; indeed, at present it is the only option. Testicular tissue or spermatogonial cryopreservation and transplantation are still considered experimental. Ovarian tissue cryopreservation is also largely experimental, but it could be used in pre-pubertal girls who require gonadotoxic treatment, in the absence of other available options. After treatment, ovarian tissue is thawed and re-implanted either orthotopically, in the ovarian fossa, or heterotopically [14]. Both testicular or ovarian tissue preservation and re-implantation should be considered only in specialized research centers, following clear protocols. The main concern about these techniques, apart from their experimental nature, is that they may carry additional risks, such as cancer recurrence.

Ovarian transposition could be considered in pre-pubertal girls whose treatment plan involves pelvic irradiation. However, this method is not always practical.

Other experimental options that may in the future become options for fertility preservation include production of germ cells by embryonic stem cells and in vitro spermatogenesis [15].

Retrieval and subsequent freezing of immature germ cells should be considered in pre-pubertal boys diagnosed with Klinefelter syndrome [16]. Similarly, ovarian tissue cryopreservation can be performed in pre-pubertal girls diagnosed with Turner syndrome or other genetic conditions that are known to impair ovarian function, but only in specialized centers following specific protocols [17].

Gonadal shielding during radiotherapy should be considered in both pre-pubertal boys and girls who are going to be irradiated in the pelvic area. Testicular protection was reported to be followed by puberty in 30 boys, but only one fathered a child [18].

4. Fertility preservation in women

4.1. Pre-treatment counseling

All women of reproductive age or younger should be thoroughly informed before the initiation of any gonadotoxic treatment about the risks of treatment and all available options for fertility preservation. The therapeutic plan should be the result of close communication between the patient and the medical team, taking into consideration issues such as the patient's age and wishes, as well as the timing and possible need for urgent initiation of treatment. For women with gynecological malignancies, conservative surgery, such as cervical dissection for early-stage cervical cancer, should be considered, when appropriate [19].

4.2. Fertility preservation options

New options for fertility preservation for women of reproductive age have been introduced in the last few years. They include embryo cryopreservation, cryopreservation of unfertilized oocytes, ovarian transposition and conservative gynecologic surgery. There is limited evidence that ovarian suppression can be also helpful.

Embryo cryopreservation is a well-established technology and should be applied whenever possible. The technique may give a satisfactory live birth rate for cancer patients. Emergency in vitro fertilization (IVF) before gonadotoxic treatment has a reasonable chance of leading to pregnancy [20]. Random-start ovarian stimulation is an option to produce oocytes than can subsequently be fertilized and cryopreserved. Aromatase inhibitors, such as letrozole, or selective estrogen-receptor modulators (SERMs) such as tamoxifen, can be used for ovarian stimulation in patients with estrogen-sensitive cancers [21] to avoid estrogen stimulation. Individualized assessment is required for the design of a personalized, optimum ovarian stimulation protocol. The main concerns about ovarian stimulation, followed by embryo cryopreservation, are its cost-effectiveness and a probable two-week delay in treatment, required for follicular development [21,22].

Cryopreservation of unfertilized oocytes is the most suitable option for young women who wish to preserve their fertility as it is possible to preserve oocytes of good quality, without the need for sperm. The concept of 'reproductive banking' is of great interest to all women undergoing gonadotoxic therapy, as well as to many women of advancing reproductive age [23]. Cryopreservation of unfertilized oocytes requires ovarian stimulation and can take place before gonadotoxic treatment. The technique is best used with women with malignant diseases who are younger than 35 years. Women with malignant disease should expect to have fewer oocytes retrieved after ovarian stimulation for fertility preservation than will healthy, age-matched women [24].

Oocyte slow freezing and vitrification are the two main methods of oocyte cryopreservation. Oocyte slow freezing was the first to be applied, but it failed to be established in everyday clinical practice. In contrast, oocyte vitrification is considered to be an everyday option for fertility preservation; that is, it is no longer an experimental procedure [6]. Vitrification protocols use very fast cooling in combination with a high concentration of cryoprotectants, to avoid the formation of ice crystals [25]. In cases of malignant disease, collection of immature oocytes can be followed by cryopreservation and subsequent in vitro maturation (IVM) after mild ovarian stimulation. A major concern about oocyte vitrification is its potential effect on the genetic material, such as increased rates of chromosome misalignment [26]. When cryopreservation procedures, slow freezing and vitrification are studied in relation to the gene expression profile of human metaphase II (MII) oocytes, it seems that, in vitrified oocytes, many genes of the ubiquitination pathway are down-regulated, including members of the ubiquitin-specific peptidase family and subunits of the 26S proteasome. This inhibition of the degradation procedure could stabilize the maternal protein content that is necessary for oocyte developmental competence [27].

Where there is permanent ovarian damage, oocytes from donors could be used. The live birth rate has been estimated to reach 55% with fresh and 34% with thawed donor oocytes [28]. For women in whom pregnancy is associated with high morbidity or in those with uterine pathology, a gestational carrier could be sought. In these cases, a variety of legal and medical regulations should be applied.

For women of reproductive age with a malignant disease, ovarian tissue cryopreservation is considered to be a promising procedure [29,30] but is an option only in specialized centers. Ovarian tissue cryopreservation does not need any hormonal preparation and does not delay the initiation of gonadotoxic oncological treatment, unlike embryo or oocyte cryopreservation, although pregnancy rates with those techniques seem to be higher. When ovarian tissue of a cancer patient is cryopreserved, the risk of reintroducing malignancy should be taken into consideration [31,32]. The risk of ovarian metastasis is higher for leukemia than for other malignant diseases (lymphoma, breast cancer, gynecological cancers) [31,33]. It is extremely important to identify minimal residual disease before ovarian tissue transplantation in patients with hematological malignancy [32]. New technologies are being developed to detect the presence of malignant cells in the ovaries. As an example, multicolor flow cytometry (FCM) can evaluate the presence of leukemic cells in the ovarian cortex [34].

Gonadal shielding during radiotherapy should be considered and ovarian transposition (oophoropexy) could be considered in women undergoing pelvic irradiation. Ovarian suppression during chemotherapy has been used in an attempt to decrease the loss of primordial follicles. Though there seems to be limited evidence of pregnancies after ovarian suppression, a recent Cochrane systematic review concluded that the use of GnRH-analogues should be considered in women of reproductive age receiving chemotherapy [35]. According to this meta-analysis, intramuscular or subcutaneous GnRH-analogues seem to be effective in protecting the ovaries during chemotherapy, although no significant difference in pregnancy rates was seen between the use of GnRH-analogues or not. Two other meta-analyses that assessed ovarian suppression in pre-menopausal patients with breast cancer also showed a probable protective effect of GnRH-analogues during chemotherapy [35,36].

4.3. Other experimental procedures

Recent advances in the field of female fertility preservation include the use of existing germ stem cells in the adult ovary, bone marrow transplantation, and oocyte and zygote micro-manipulations, such as cytoplasmic (mitochondria), germinal vesicle and pronuclear transfer. Ethical matters remain to be solved. Kawamura et al. [37] have recently reported the delivery of a healthy baby after disruption of Hippo signaling, by fragmenting the ovaries of a woman with POI, followed by Akt stimulator treatment and auto-grafting. The ovarian fragmentation – in vitro activation approach, if proved efficient and safe, could be a valuable option for women whose fertility is challenged by diminished ovarian reserve, because of advancing age, POI, cancer or other conditions.

5. Fertility preservation in men

5.1. Pre-treatment counseling

All males of reproductive age or younger should be thoroughly informed before the initiation of any gonadotoxic treatment about the possible risks. Fertility preservation should be always undertaken in accordance with the patient's wishes.

5.2. Fertility preservation options

Sperm cryopreservation (sperm banking) is an established fertility preservation method that should be always the first-line option for men of reproductive age. With the development of intracytoplasmic sperm injection (ICSI), even patients with subnormal or seriously impaired sperm parameters should be encouraged to cryopreserve their sperm prior to treatment. Sperm should be retrieved by masturbation; when this is not possible, other techniques could be considered, such as penile vibratory stimulation,

electro-ejaculation and testicular sperm aspiration [38]. Sperm should ideally be collected prior to treatment, as chemotherapy may cause genetic damage.

When the pelvis or malignancies of the proximal thigh are being irradiated, a scrotal shield may protect the gonads [39,40].

5.3. Other experimental procedures

Hormonal gonadal protection in men is not considered an effective method of fertility preservation. Testicular tissue cryopreservation is of limited use in adults, although it is the only fertility preservation option for pre-pubertal males [41]. Testicular tissue or spermatogonial cryopreservation and transplantation or testis xenografting are still considered experimental, with scarce information about their efficacy and risks [42,43].

6. Conclusions

As the number of cancer survivors is increasing, the need for fertility preservation is emerging. Fertility preservation should be a priority when treating children or adults of reproductive age with agents that may have hazardous effects on the reproductive system. Gonadotoxicity should be kept to a minimum. If gonadotoxic treatment has to be used, methods of fertility preservation should be discussed, as early as possible. Fertility preservation may also be used with adults who wish to postpone parenthood. Decisions always have to be taken after careful consideration of all relevant ethical and social aspects.

7. Recommendations

7.1. Pre-pubertal boys and girls

- Children diagnosed with genetic conditions that impair reproductive function should be referred to a reproductive endocrinologist. Retrieval and subsequent freezing of immature germ cells in pre-pubertal boys and ovarian tissue cryopreservation in girls are options to be considered.
- Potential harmful effects of cancer treatment on reproduction should be discussed; long-term reproductive potential should be taken into consideration, when constructing the treatment plan.
- Ovarian transposition could be considered for pre-pubertal girls whenever pelvic irradiation is involved in the treatment plan. Preservation of gonadal tissue and transplantation of germ stem cells remains an experimental procedure and should be considered only in specialized research centers, following clear protocols.

7.2. Women of reproductive age

- All women of reproductive age or younger should be thoroughly informed before the initiation of any gonadotoxic treatment about the possible risks and all available options for fertility preservation.
- Options for fertility preservation include embryo cryopreservation, cryopreservation of unfertilized oocytes and conservative gynecologic surgery. Gonadal shielding during radiotherapy should be considered and ovarian transposition could be considered in women who are going to be irradiated in the pelvic area. There is limited evidence that ovarian suppression can be helpful. Ovarian tissue cryopreservation is still considered an experimental procedure.

7.3. Men of reproductive age

- All men of reproductive age or younger should be thoroughly informed before the initiation of any gonadotoxic treatment about the possible risks and all available options for fertility preservation.
- Sperm cryopreservation (sperm banking) is an established fertility preservation method that should be always the first-line option for men of reproductive age.
- Hormonal gonadal protection in men is not considered an effective method of fertility preservation.
- Testicular tissue or spermatogonial cryopreservation and transplantation and testis xenografting are still considered experimental.

Contributors

G.M., I.L. and D.G. prepared the initial draft, which was circulated to E.M.A.S. board members for comment and approval; production was coordinated by M.R. and D.G.

Competing interests

The authors have no conflicting interests to declare.

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