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REVIEW

Medical techniques of fertility preservation in the male and female

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Summary Therapeutic advances in many medical fields have led to the need to consider patient quality of life after curative medico-surgical treatments for malignancy. Thus, it has become a major issue for young patients to preserve the ability to become ''genetic'' parents, with their own gametes.

While the preservation of male fertility has been an established technique for more than 30 years, it is only in the last decade that progress in cryopreservation techniques has allowed surgeons to offer successful oocyte and ovarian tissue cryobanking. However, in addition to the still experimental nature of some fertility preservation techniques, this practice also raises many ethical and moral questions.

The progress made in recent years in the treatment of cancers in young patients has allowed a marked increase in cure rates and the life expectancy of men and women who present with malignant disease. However, the oncologic treatments employed often have gonadotoxicity that will negatively impact the survivors' fertility. Recent advances in cryopreservation now make it possible to consider fertility preservation (FP) techniques for both men and women. These aim to offer the best possible quality of life following treatment for cancer, in particular by giving patients the maximum chance of achieving ''genetic'' parenthood with their own gametes.

FP is governed by the Bioethics Law of 2004. Article L. 2141-11 of the Public Health Code, amended by Law 2011-814 of July 7, 2011. This provides that ''any person may benefit from the collection and the preservation of their gametes or germinal tissue, with a view to subsequent provision of assisted reproductive technology (ART), or for the preservation and restoration of their fertility, when care is likely to impair fertility, or when fertility is likely to be prematurely altered.''

Thus, all patients who are scheduled to undergo treatment or surgery that may entail a risk of infertility, should be referred to a specialized center to receive information on the risks of treatment-related gonadotoxicity, on the possibilities of FP, and on the possibilities of employing FP techniques. For both men and women, these steps

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are carried out in the CECOS (Centers for the Study and Conservation of ova and spermatazoa).

Male fertility preservation

Male FP has been practiced for more than three decades, thanks to the efficiency of sperm freezing. Advances in ART, including *In Vitro* Fertilization (IVF), particularly using Intracytoplasmic Sperm Injection (ICSI), have enabled the use of frozen spermatozoa even when *in vivo* spermatic parameters are highly impaired.

Spermatogenesis takes place in the testicles in the seminiferous tubules and allows the formation of spermatozoa from germinal stem cells. This process begins at puberty, continues throughout life, and depends on hormonal production and a specific intratesticular microenvironment.

Indications of male fertility preservation

Indications:
- Medical treatment that may temporarily or permanently alter spermatogenesis (chemotherapy, radiotherapy);
- Surgery that can alter normal ejaculation (prostatic surgery, urethral surgery, proctectomy, some lymph node dissections);
- Before vasectomy;
- In the course of IVF, when the availability of frozen spermatozoa optimizes the management and increases the chances of success.

Male fertility preservation in adult and pubertal adolescent males

Male FP relies on the freezing of ejaculated spermatozoa, collected after masturbation at the laboratory. Compliance with three to five days of ejaculatory abstinence is recommended, but not essential, and should not delay FP, especially in urgent indications of gonadotoxic treatment. Sperm freezing must be done before the initiation of any treatment to avoid genetic alterations and a decrease in both quantity, and quality of spermatozoa.

The semen parameters are analyzed on a sample of ejaculate according to the criteria of the World Health Organization (WHO) [1]. Sperm is diluted in a cryoprotective medium and then conditioned in vials that will be frozen and stored in liquid nitrogen at −196 °C. Ideally, two or three sperm collections are proposed in order to accumulate a sufficient number of vials (15—20 on average). It has been well established that frozen sperm can be preserved for more than 20 years without impairing the sperm fertilization potential [2].

The freezing of spermatozoa is possible with good results from the onset of puberty, *i.e.*, from 11 to 14 years depending on the degree of psychosexual maturation [3]. Sperm production remains continuous throughout life with no theoretical upper age limit. Nevertheless, this raises a certain number of ethical problems, since recent data have revealed particular psychological consequences in children conceived by men over the age of 60 [4,5], and this situation may lead to the birth of children who will become prematurely orphaned by the death of their father.

In certain situations, the freezing of ejaculated spermatozoa can be difficult or impossible. Collection failures occur in about 5% of cases, favored by poor general health and/or stress [6]. If time permits, another effort at sperm collection is proposed before the start of treatment. Spermatic parameters can be extremely poor in some patients with severe oligoasthenoteratozoospermia or azoospermia, making any attempt of sperm autopreservation useless. These situations are often due to the primary pathology requiring FP. In patients with retrograde ejaculation refractory to medical treatment, spermatozoa can be recovered from the previously alkalinized urine [7] and then frozen. In case of neurological erectile disorders, some teams propose the use of vibratory penile stimulation. Endorectal electrostimulation under general anesthesia or spinal anesthesia is another more invasive possibility, reserved for certain specialized centers; its results are not very convincing in terms of the quality of sperm obtained [8]. As a last resort, when collection is impossible or when the patient has azoospermia, surgical harvesting of a sample of epididymal or testicular spermatozoa may be considered for freezing [9].

Preserving fertility in the prepubertal boy

In the particular case of the prepubertal child, who does not yet have spermatozoa, but whose seminiferous tubules contain spermatogonia stem cells, it is possible to consider freezing testicular tissue [10,11]. Although still experimental, several promising strategies for reusing these frozen cells have been considered, *including in vitro* maturation or transplantation.

Female fertility preservation

Female FP is an area of recent medical innovation, which owes its rapid growth to the emergence of new oocyte collection techniques, as well as to the improvement of techniques of egg cryopreservation. Initially developed to preserve the subsequent fertility of women with cancer who would receive gonadotoxic treatment such as chemotherapy, pelvic radiotherapy, or ovarian surgery, the indications have more recently been extended to all medical or surgical situations that may lead to premature decrease of the ovarian reserve. Various techniques have therefore been developed to try to respond to a possible desire for subsequent ''genetic'' maternity for these patients. The choice of technique must take into account the patient age, pubertal status, ovarian reserve, the underlying pathology, the possible gonadotoxicity of the treatments, and the amount of time available before starting treatment.

Oocyte or embryo freezing

Embryo cryopreservation has been feasible for 30 years and is routinely used in IVF centers. This technique has long been the only one considered as non-experimental for female FP. Since January 2013, oocyte freezing can also be proposed as a technique of choice [12], because of steadily improving results [13]. The vitrification technique has recently supplanted slow freezing for both embryos and oocytes. It consists of a very rapid lowering of temperature thanks to the use of cryoprotective agents at high concentrations, thus avoiding the formation of ice crystals. This makes it possible to obtain excellent survival rates during thawing [14]. Outside the context of oncofertility, and when the oocyte freezing was carried out before the age of 38, the vitrification of eight oocytes would lead to a 46% chance of initiating a pregnancy [15] and cryopreservation of between 15 and

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