Preservation of Fertility in Patients with Cancer

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ABSTRACT
Survival rates in oncological patients are steadily increasing in recent years due to the greater effectiveness of the new oncological treatments. However, these treatments impair the reproductive ability, causing premature ovarian failure in women and azoospermia in men. The main objective of this review is to describe the different existing options of fertility preservation in patients undergoing gonadotoxic treatments as well as the differences in success rates that may appear in the evaluated different techniques. The conclusion of this work is that oocyte vitrification for female patients and sperm banking for male patients are considered the first line fertility preservation option at the moment.

Keywords: Fertility Preservation; Women; Male; Prepuberal; Gonadotoxic Treatment; Oncological Treatment; Oncofertility

INTRODUCTION
More than 70,000 Adolescent and Young Adult (AYA) patients, which comprise ages between 15 and 39 years old, are diagnosed with cancer every year just in the United States. The incidence of cancer in children younger than 15 is also around 10,000 cases per year (1).

In Europe, more than 15,000 AYA are diagnosed with cancer every year, according to the International Association of Oncology Pediatrics. In 2004, the Spanish database of children tumours - RETI-SEHOP - concluded that around 1,100 children in Spain are diagnosed with cancer every year. The incidence of children cancer in Spain is similar to other European countries, around 160 new cases per million children every year, aged between zero and fourteen, according to the Spanish Federation Of Parents With Kids With Cancer (F.E.P.N.C) (2). Survival rates in these patients are steadily increasing in recent years due to the greater effectiveness of the new oncological treatments. In fact, 5-years-survival rate for pediatric cancer patients approaches 80% (3). However, treatments entailing chemotherapy or radiotherapy, often result in impaired or absent reproductive ability. Besides, only about half of them report, having previously been informed about the therapeutic options of Fertility Preservation (FP), which has been identified as the second most important aspect among young patients, after survival. In order to improve the quality of life of the surviving patients, improvement of fertility preservation techniques has become of great effort in the field of research in the last years. In fact, the concept of Oncofertility has recently appeared: an interdisciplinary integrated network, based on medical methods which is designed to maximize the reproductive future of oncological patients by offering various fertility preservation techniques. Furthermore, a standardization of the fertility preservation healthcare for oncological patients is needed. Currently, two major international networks have been created for this aim: International Network on Cancer, Infertility and Pregnancy (INCIP) and the European Society of Gynecological Oncology (ESGO)(3).

METHODS
A literature review has been conducted by searching for publications in PubMed between September 2017 and May 2018 with the following keywords and their combinations: “fertility”, “preservation”, “women”, “male”, “prepuberal” “young adults”, “gonadotoxic treatment”, “cancer treatment”, and “oncofertility”.

RESULTS
Fertility Preservation Techniques in Women and Men

At the 20th week of embryogenesis, women reach the maximal number of germ cells in the genital ridges, around 6-7 million potential oocytes, known as the primordial follicles. However, just 1 million of them will remain at birth and just around 400,000 oocytes will arrive to puberty. This number, known as ovarian reserve, will decrease, reaching 1,000 oocytes at the time of menopause, due to the approx. 450 monthly ovulatory cycles, when most of them undergo atresia (degeneration and reabsorption) (4). Preservation of the ovarian reserve is necessary to maintain overall women’s health, as they play a role not only in oocyte development and fertility but also in other systems, such as the cardiovascular system and osseous system. (5)

Women who are willing to preserve their fertility prior to or during chemo- and radiotherapy have the following techniques available: embryo cryopreservation; immature or mature oocyte cryopreservation; ovarian tissue cryopreservation and ovarian transposition. We will specially focus on the oocyte and ovarian tissue cryopreservation. Other experimental techniques, such as activation of ovarian follicles, in vitro follicle culture, artificial ovaries and new fertoprotective agents may appear to be very promising, although further research is still required (7).

In males, the onset of production of spermatozoa starts in puberty and it is known as sperm Arche. Unlike women, from the moment of the sperm Arche, spermatogenesis is maintained during the entire duration of a man’s life, on account of the spermatogonia type A, among others (8). Testicular stem cells differentiate into spermatogonia, which will eventually become spermatozoa under the process of spermatogenesis. Spermatogonia in the testis are extremely sensitive to radiation, regardless of age. Leydig cells, on the other hand, are more sensitive to radiation before puberty onset, whereas in adulthood they become more resistant to it (9). Consequently, adult patients may preserve Leydig cell function and testosterone production after radiotherapy despite being azoospermia. Furthermore, if a population of spermatogonia stem cells (SSC) remains after cancer treatment – as the effect is dose-dependent – regeneration of spermatozoa may continue for years (10). Those at the highest risk of developing permanent sterility are children and adolescent with testicular cancer, leukemia and Ewing sarcomas.
Sperm banking is the recommended fertility preservation's technique, although cryopreservation of spermatogonial stem cells is also available.

Fertility Preservation Techniques in Woman

Embryo cryopreservation

This technique has established success rates and is the most widely used and reliable method of all. It is like an In Vitro Fertilization (IVF) protocol, which has been performed for over 30 years. Women undergo Controlled Ovarian Stimulation (COS) with gonadotropin injections to promote multifollicular growth. Ten to fourteen days later, oocyte retrieval is performed, normally under conscious sedation and with transvaginal ultrasound-guided needle aspiration (11). The oocytes are then fertilized in the laboratory and will be cryopreserved for future use, commonly in their blastocyst phase (4).

The disadvantages of this technique are mainly three: the need of a stable male partner, ethical issues regarding embryo disposition and the time required for ovarian stimulation. COS normally starts in the early follicular phase. When a patient is diagnosed in her early follicular phase, ovarian stimulation with GnRH antagonist starts immediately. However, if the patient is in any other phase, the IVF standard protocols require to wait up to 3 weeks before start (11). Therefore, this method is not a viable option for women whose aggressive cancers’ treatment is of highest priority, as the IVF standard protocols require to wait up to 3 weeks before start (11). It is also not recommended in women with hormone-sensitive cancers and not possible for prepubertal girls. It is also not recommended in women with hormone-sensitive cancers and not possible for prepubertal girls.

There are three main cryopreservation techniques: slow-freezing, ultra-rapid and vitrification. Slow-freezing involves a step-wise programmed decrease in temperature (12), achieving an equilibrium freezing due to the exchange of the extra- and intracellular fluids without causing meaningful osmotic and deformation cellular effects. However, ice crystals can be formed within the cells, which could result in extremely harmful effects for the cell (13). The procedure lasts long (about 1 or 2 hours) and requires expensive instrumentation, large quantities of liquid nitrogen, among others. Vitrification converts water into solid glass-like cells, avoiding ice crystal formation, both intracellular and extracellular (14). Expensive instrumentation it is not needed, and it requires only several minutes. Furthermore, a meta-analysis in 2013 showed that the rates of oocyte survival, fertilization and implantation where higher in vitrification than in slow-freezing methods (15). For these reasons, vitrification is nowadays the preferred technique.

Data on pregnancy and live births in cancer patients after frozen embryo transfer are limited. Live birth rates in non-oncological patients <35 years of age amounted to 38.7% per frozen embryo transfer and to 34.8% for oocyte donor cycles (16).

Oocyte Cryopreservation

As an alternative to embryo cryopreservation, this technique is the preferred option for postpuberal and adolescent females, women without a stable couple and for those who do not want to use a sperm donor. It overcomes the ethical and religious issues that emerge from the embryo preservation. Clinical outcomes in oocyte vitrification’s strategy is superior to slow-freezing and thawing (17). With oocyte vitrification, women are able to conceive in the future and maintain their reproductive autonomy. However, it is not appropriate for patients in urgent need of treatment or patients with hormone-sensitive cancers, as the procedure also includes COS. The oocytes can be cryopreserved as mature eggs or as immature germinal vesicle oocytes. Mature oocyte cryopreservation is performed with the oocytes stopped in Metaphase II. Nowadays, this is the preferred method for postpuberal patients and for patients whose chemotherapy and radiotherapy can be delayed. Immature oocytes obtained by aspiration and followed by in Vitro Matura tion Techniques (IVM) is a suitable option for prepubertal girls and women with hormone-sensitive cancers or with Polycystic Ovarian Syndrome (PCOS), since COS is not required. This also allows the possibility of immediate cancer treatment. Oocytes will be matured Invitro (IVM) as cryopreservation of mature oocytes has shown better survival outcomes than immature cryopreserved oocytes (18). The retrieval of immature oocytes can also be achieved during an Ovarian Tissue Cryopreservation (OTC) procedure.

Ovarian Tissue Cryopreservation (OTC)

Although this technique is still considered experimental, it is currently the only option for pediatric patients and for hormone-dependent diseases as it is COS-independent and does not delay the oncological treatment. It does not require a male partner nor a sperm donor.

OTC is an invasive procedure, as it requires general anesthesia to surgically remove the ovarian tissue. This tissue, with a high content on follicles, will be cryopreserved and then be used for: 1) reimplantation into the pelvic cavity (e.g. remaining ovarian tissue or peritoneum) - orthotopic implantation - or outside of it (e.g. resectum, pectoralis muscle, abdominal wall, chest wall) - heterotopic implantation 2) isolation of follicles from the thawed tissue for in vitro growth, maturation and fertilization. During ovarian tissue cryopreservation, it is possible to aspirate immature oocytes from antral follicles of the ovarian tissue. Isolated oocytes can be cryopreserved or matured in vitro (IVM) for later vitrification (19).

Either ovarian cortical tissue cryopreservation (slow freezing) or whole oocyte cryopreservation can be performed. All egg-containing follicles are in the outer one millimeter of the ovary, so removal of this layer of tissue is sufficient for cryopreservation. The success rate of live-birth after reimplantation is around 30% (7). Cryopreservation of the whole ovary is still a technical challenge due to the bigger size of the tissue, which hinders a homogeneous and adequate dispersion of cryoprotectant, and the vascular damage in form of ice crystals. More studies are necessary so that this technique is used in the clinical practice.

Until 2015, 60 live births have been reported with OTC, yet only in adult patients. In fact, just one live birth after autograft of cryopreserved tissue before menarche has been published (20). The total number of reimplantations performed until that time was unknown, so no success rates could be concluded. In 2015 Donnez, M. Dolmans et al. (16), published a large case of series (n=111) which showed a pregnancy rate proportion of 29% (n=32). Two women delivered three babies each, proving the efficacy of the technique and the possibility of conceiving naturally after only one procedure.

The most feared concern of OTC is the possibility of re-introduction of carcinogenic cells into the cured patient or the malignant transformation of the ovarian tissue, which has been already reported (21). For this reason, a thorough examination of the ovarian tissue prior to cryopreservation and reimplantation is required.

Ovarian Transposition (Oophoropexy)

This procedure aims to prevent ovarian damage during radiation therapy by relocating the ovaries away from the radiation field. Therefore, it will be of use in women who will undergo pelvic or low abdominal radiation therapy without additional gonadotoxic chemotherapy (22). According to the radiation field outlined by the radiation oncologist, the surgeon will decide the optimal location in the abdominal wall for ovarian transposition. Altogether, the ovaries will not be harmed by the therapy and ovarian failure will be prevented. The procedure is normally performed laparoscopically before the start of radiation. Success rates are not conclusive, as they vary from 16 to 90% (23).

Fertoprotective Adjuvant Agents

Another approach to preserving fertility is to protect follicles during oncological treatment by administrating fertoprotective agents. One example is the use of gonadotropin-releasing hormone (GnRHa) agonists, which are administered 10 days before the beginning of the chemotherapy. GnRH analogues interfere with the hypothalamic-pituitary-gonadal axis and inhibit the ovarian function by suppressing gonadotrophin levels to prepubertal levels (6). Two meta-analysis of randomized trials concluded a reduced risk of premature ovarian failure (POF) in young breast cancer patients (24)(25), whereas its use was unclear in ovarian cancer and lym
phoma (25). A later study showed no effect in young patients with lymphoma (26). The quality of evidence is insufficient to draw meaningful conclusions; high-quality studies are needed to study the long-term effects of GnRHa use on Premature Ovarian Insufficiency (POI).

**Emerging Techniques**

**Activation of ovarian follicles**

Cryopreserved ovarian tissue from prepubertal patients and patients with POF contain immature primordial follicles which need to be activated in order to start developing. This can be induced either in vivo (by interrupting the Hippo signaling pathway (27) or in vitro, before autotransplantation, by acting in PI3K-PTEN-AKT-FOXO3 pathway, which regulates primordial follicle activation in oocytes (27). This pathway also plays a crucial role in the FSH stimulation of granulosa cell differentiation in antral follicles and in oocyte maturation of preovulatory follicles (27). This could be a promising fertility option for prepubertal patients and patients with primary ovarian insufficiency, whose cryopreserved tissue contains immature primordial follicles suitable for this technique. In vitro protocols involving PTAN-AKT pathway are being developed in order to increase the pool of viable activated follicles available for Invitro growth (IVG) procedures (28).

**Invitro follicle culture**

This technique could be an option for those patients who need urgent oncological treatment – and therefore are not good candidates for oocyte or embryo cryopreservation such as acute leukemia or acute myeloblastic leukemia (AML). Ovarian tissue cryopreservation is the available option momentarily for these patients. However, since the possibility of re-seeding original cancer cells from the ovarian tissue exists, other alternatives needed to be raised.

The ovarian follicle culture in vitro, aims to mitigate the risk of re-implanting malignant cells from the cryopreserved ovarian tissue. It is therefore useful in patients with cancers whose metastasis appear often in the ovary or patients with BRAC1 and BRAC2 mutations, due to the increased risk of an ovarian cancer, which would not make possible the transplantation of cryopreserved ovarian cortex (29). However, complete maturation of primordial follicles has not been achieved in humans yet (30).

In this procedure individual follicles are isolated from the patient’s bank tissue, which will afterwards be matured in vitro to become a functioning oocyte. These will be fertilized, and the embryos will be transferred to the uterus. The follicles can be cultured in Two-Dimensional (2D) or Three-Dimensional (3D) systems. These 3D culture methods are the most successful in maintaining the sphericity and the communications between cells (29) and have also shown greater follicular viability, follicle and oocyte diameters and hormone production (6).

**Artificial ovaries**

The creation of an artificial ovary for transplantation is a very promising fertility-restoring technique. Isolated preantral follicles obtained from ovarian cryopreserved tissue, together with other ovarian cells in a 3D-matrix, or scaffold, result in a ovary-like environment, which could allow the growth of follicles and therefore could restore both fertility and endocrine function of the ovary once they are transplanted (6). Luyckx et al. (31) achieved survival and growth of murine ovarian follicles (primary, secondary and antral follicles) one week after transplantation of ovarian cells in a fibrin matrix. Moreover, M.M. Laronda et al. (32) accomplished to initiate puberty in ovarioctomized mice after an artificial ovary transplant.

**Specific target tissue drugs**

Both nanoparticle and fertoprotective agents share the aim of protecting ovarian cells during gonadotoxic oncological treatments. Nanoparticles. This procedure entails encapsulating the therapeutic agent in order to reduce its plasma clearance and therefore its toxicity. For such purpose, a nanoparticulate formulation of the therapeutic agent is developed and encapsulated within liposomal vesicles or "Nanobins" (NB) (33). Ahn, Richard W. et al. (34) demonstrated a superior antitumor efficacy of the nanoparticulate formulation of arsenic trioxide (As2O3) in nanobins [NB(Ni,As)] in a murine model of lymphoma as well as a reduced fertotoxicity.

New fertoprotective agents. Current research focus on two different pathways: (A) anti-apoptotic agents, such as imatinib, sphingosine-1-phosphatase (AS101), granulocyte colony-stimulating factor (G-CSF), thyroid hormone (T3) and tamoxifen (28), and they have shown to diminish follicle loss in animal models (35); and on (B) agents which prevent follicle activation, such as AS101, an immunomodulator interacting with the PI3K/PTEN/AKT follicle activation pathway (36) and the anti-Mullerian hormone (35). In brief, many new fertoprotective agents to protect oocytes against gonadotoxic treatments are being investigated and may be available soon (6).

**Fertility Preservation Techniques in Men**

In men undergoing gonadotoxic treatment, both sperm cryopreservation or testicular tissue cryopreservation are currently available (7,6). The American Society of Clinical Oncology (ASCO) guidelines recommend that oncologists inform about the risk of infertility in patients with cancer during their reproductive stages of life, as well as to refer them to specialists in fertility treatment.

**Cryopreservation of spermatogonia**

Cryopreservation of ejaculated semen is the recommended fertility preservation technique for adult males and pubertal boys producing sperm in the ejaculate, who will be undergoing gonadotoxic treatment (37). For patients receiving radiation therapy only, gonadal shielding may be an option if sperm collection is not possible.

The spermarche starts at puberty, but it is not exactly known when this onset begins, since clinical parameters, such as Tanner stage or increase on reproductive hormones, do not always correlate with spermatogenesis onset, according to some data from urine examination and electro-ejaculation in pubertal boys (38,39). Successful sperm collection after masturbation has been reported for boys aged 12 years and older (40,41).

The procedure includes the collection of – ideally - at least three semen samples, with an abstinence period of at least 48 hours in between samples, and the following cryopreservation of the sperm samples, although often more than one semen sample must be taken in the same day to avoid the oncological treatment delay (8). In case of ejaculation failure or when no spermatozoa are found in the ejaculate, sperm can be retrieved by epididymal sperm aspiration – either percutaneous (PESA) or with Microsurgery (MESA) –, Testicular Sperm Extraction (TESTE) or electro-ejaculation (42)(43). Assisted reproductive treatment such as Invitro Fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI) are afterwards needed. ICSI has the advantage of also allowing reproduction when the semen is of very poor quality or with only a few spermatozoa (8).

The pregnancy rates vary from 12% for intrauterine insemination to 32% for ICSI. Up to this moment, no follow-up data for large cohorts of children born after assisted reproductive treatment using frozen-thawed sperm of men with cancer are available in the literature.

It is worth saying that the European Germ Cancer Consensus Group and the ASCO strongly recommend informing patients about the possibility of cryopreservation techniques before undergoing orchiectomy or gonadotoxic treatment (30). Unfortunately, such recommendations are oftentimes not followed by health-care professionals and many patients remain without counseling in the matter.

**Cryopreservation of Spermatogonia Stem Cells (SSC) in Prepubertal Children**

Prepubertal children do not perform spermatogenesis yet and therefore they do not have mature sperm in their testis. Hence, cryopreservation of spermatogonia is not possible. The only possibility for them is to preserve testicular tissue, which contains spermatogonial stem cells.

In an analogous way to the cryopreservation of ovarian tissue
in women, the testicular tissue can be obtained (through a testicular biopsy) and cryopreserved in form of spermatogonia or in form of testicular tissue (using slow-freeze or ultrarapid techniques). This will be thereafter available to use when the patient is free of oncological illness and desires to have children. Once the tissue is thawed, it would allow in vitro spermatogenesis (44) or autotransplantation of the cryopreserved tissue, either by infusion of a cell suspension into the seminiferous tubules or intratesticular grafting of the tissue (8).

The reintroduction of testicular stem cells into the seminiferous tubules could restart the sperm production (8). Orthotopic transplantation entails the risk of re-seeding malignant cancer cells (eg, in patients with leukaemia), like it happened with the ovarian auto-transplantation. To mitigate the problem, a decontaminated cell suspension could be a possible solution (45). In-vitro culture of testicular cells to obtain mature spermatocytes also circumvents the risk of reseeding malignant cells in the auto-transplant of testicular tissue, being another branch of research at the moment (46). It is important to say that fertility restoration strategies by auto-transplantation of cryopreserved testicular tissue have not been tested yet for safe clinical use in humans and therefore it is still considered experimental (7). More research is still needed regarding the use of frozen-thawed tissue to obtain mature spermatocytes in vitro (10).

**DISCUSSION**

The oncological health-care is nowadays far from being solely the cure of cancer. Providing hope of future fertility after oncological treatment, significantly increases the quality of life of the patients and helps coping emotionally with cancer (30). Fertility preservation in both female and male oncological patients is nowadays possible and should be integrated as part of the oncological health care. Different techniques exist and the most appropriate should be chosen depending on the characteristics of the patients: male, female, prepubertal or postpubertal. Some of them have already proven successful outcomes whereas others, newer and more innovative, are still in need of more improvement and development.

On the one hand, sperm banking is now considered the first line FP option for male patients; on the other hand, oocytes vitrification is currently considered the first line option for postpuberal female patients in which it is possible to delay chemotherapy and hormonal stimulation is authorized. Embryo banking gets in ethical conflict when it comes to preserving fertility, as healthcare’s aim is to solely preserve the woman’s fertility and not other individuals, which is the reason why it is not considered the first-line treatment anymore. Furthermore, growing evidence of safety and efficiency success in oocyte vitrification, upholds this technique to be the preferred one. When facing a therapeutic emergency or contraindication for hormonal stimulation exists, ovarian tissue cryopreservation or puncture of immature oocytes are available. Immature oocytes will then be cryopreserved, directly or after being matured in vitro, to be vitrified as mature oocytes or as embryos after a fertilization technique (Figure 1).

Among all the patients to whom these techniques address, pediatric and adolescent patients are the ones with the most restricted FP options (Figure 2), higher survival rates, and thus those with the longest life expectancy. Therefore, special effort should be made to improve quality of life in this unique population and fulfill their reproductive wish.

As Oncofertility is a recent concept and it is rapidly gaining importance, new procedures involving emerging technological advances are being developed. In vitro activation of ovarian follicles has proven itself to be a very promising technique for future approaches, as it could be addressed to patients with restricted FP options: prepubertal children, hormone-sensitive tumors and those at urge to start treatment. OTC and subsequent transplantation, although still considered experimental, is currently the only hope for Prepubertal children (Figure 2). This technique has shown encouraging results in adult patients but literature regarding pregnancy in prepubertal children is very scarce. Until this moment, just one live birth after autograft of cryopreserved tissue before menarche has been published (20).

Development of specific target chemotherapeutical treatment such as nanobins and creation of artificial ovaries from stem cells, would respectively avoid and completely restore the ovarian function. Therefore, further development in these emerging techniques may lead to ground breaking advances of this field in the not so far future. Certainly, new fertility preservation techniques will continue to develop in the following years. However, despite the growing advances in the subject, optimal counselling coming from healthcare professionals is lacking.

**CONCLUSIONS**

Fertility preservation in both female and male oncological patients is nowadays possible and should be integrated as part of the oncological health care. Different techniques exist and the most appropriate should be chosen depending on the characteristics of the patients: male, female and Prepubertal or postpubertal. Many of the techniques are still in under experimental trials, whereas some others are standardized and established. Oocyte vitrification for female patients and sperm banking for male patients are now considered the first line FP option.

**ABBREVIATIONS:** AKT: Protein Kinase B; As203: Arsenic Trioxide; ASCO: American Society Of Clinical Oncology; AYA-Adolescent And Young Adults: COS: Controlled Ovarian Stimulation; ESGO: European Society Of Gynecological Oncology; E.P.N.C. Federation Española De Padres De Niños Con Cáncer; IVF: In Vitro Fertilization; FOXO3: Transcriptional Factor Forkhead Box O3; FP: Fertility Preservation; G-CSF: Granulocyte Colony-Stimulating Factor; Gnrh: Gonadotropin-Releasing Hormone; ICSI: Intracytoplasmic Sperm Injection INCIP: International Network On Cancer, Infertility And Pregnancy; IVF: In Vitro Fertilization; IVM: In vitro Maturation; NB: Nanobins; OTC: Ovarian Tissue Cryopreservation; PCOS: Polycystic Ovarian Syndrome; PGD: Pre-Implantation Genetic Diagnosis; PI3K: Phosphatidylinositol3 - Kinase; POF: Premature Ovarian Failure; POI: Primary Ovarian Insufficiency PTEN: Phosphatase And Tensin Homologue Enzyme.
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