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Quality Assurance Committee

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Fertility Preservation in post pubertal women and men

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INTRODUCTION

Chemotherapy and radiotherapy often result in reduced fertility in cancer patients. With increased survival rates, fertility is an important quality-of-life concern in many cancer survivors of reproductive age. If cancer therapy can cause infertility or will delay the time until parenthood can be considered, the risk of infertility and fertility preservation options must be discussed with the patients of reproductive age before the initiation of treatment. Patients who express an interest in fertility preservation and those with a need for further information, should be referred to a specialist in reproductive medicine. Impact of cancer treatments on fertility should be addressed early and patient should ideally be referred before treatment starts. The question of fertility preservation (FP) can be discussed in a large number of malignant diseases. However, women diagnosed with breast cancer, lymphomas, leukemia or gynecologic malignancies represent the main candidates for FP. Fertility preservation options should also be addressed in a planned and less urgent fashion in women with non-oncologic medical conditions with a future impact on their future fertility (systemic autoimmune diseases, major hemoglobinopathies, risk of premature ovarian insufficiency etc.).

IMPACT OF CANCER TREATMENTS ON FERTILITY

Treatment of cancers in young adults often requires chemotherapy and/or radiotherapy, with a detrimental impact on both endocrine and reproductive gonadal functions.

Chemotherapy

In women, chemotherapy leads to persistent unrepaired DNA breaks activating oocytes apoptosis in growing follicles. Moreover, the loss of inhibitor factors leads to an increased cohort of growing follicles, which subsequently undergo apoptosis. This "burn-out" effect leads to accelerated oocyte depletion (1). Clinical manifestations of follicular loss range from reduced ovarian reserve with either regular or irregular cycles to premature ovarian insufficiency and varying degrees of infertility. The impact of cytotoxic treatments depends on the chemotherapy agent used, the dose given, the age of the patient and her baseline ovarian reserve. Alkylating agents, such as cyclophosphamide, have a highly damaging effect and are responsible for the highest ovarian failure rates. Platinum-based compounds carry a medium risk of amenorrhea, whereas anthracyclins induce oxidative stress and are associated with a medium to low risk of amenorrhea. Very often chemotherapeutic agents are used in combination resulting in an increase in efficacy and at the same time, a higher toxicity.

In men, reduction in sperm count or azoospermia can occur after chemotherapy. Many alkylating agents and cisplatin, which create adduct and cross-links in DNA, can produce long term or permanent azoospermia.

Radiotherapy

Gonads are very sensitive to radiotherapy: a testicular radiation >2.5Gy in adult men is associated with a high risk of azoospermia; in adult women, pelvic or abdominal radiation is associated with a high risk of amenorrhea. The estimated sterilization dosage is age-dependant: at 20 years: 16.5 Gy, 30 years 14.3 Gy, 40 years 6.0 Gy. Smaller doses are associated with an intermediate risk in both sexes. Total-body irradiation (TBI) for bone marrow or stem cell transplantations induces a high risk of azoospermia and amenorrhea.

Level of evidence

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Biological targeted therapies

Biological targeted treatments, mostly humanized antibodies, are designed to interfere with specific molecules expressed on the surface of tumor cells (trastuzumab with HER-2 in breast cancer; rituximab with CD20 antigen on lymphoma cells). Fertility risk data with those agents are limited. The risk is assumed to be low, since they target specific cells. Caution with another monoclonal antibody, bevacizumab, an anti-angiogenic agent, is required, since it might interfere with follicular growth. Tamoxifen, a selective estrogen receptor modulator, is given as adjuvant treatment for 5-10 years in breast cancer and this delay is likely to decrease fertility by postponing maternity.

METHODS TO PRESERVE FERTILITY IN FEMALES

Ovarian stimulation with oocyte/embryo cryopreservation

This technique is recommended if: 1) the ovarian reserve is sufficient to allow the retrieval of a sufficient number of oocytes, 2) the patient's medical condition allows a safe stimulation and oocyte retrieval, 3) there is sufficient time to perform the stimulation (2 weeks). Stimulation protocols should be adapted to the specific oncologic situation in order to minimize the risk of ovarian hyperstimulation syndrome (use of antagonist protocol, GnRH agonist triggering), the exposure to high estrogen levels in hormone-dependant cancers (use of aromatase inhibitor) and the treatment time (random start of stimulation, regardless of the menstrual cycle phase).

Oocyte cryopreservation is the preferred method in women without a male partner or in those who want to preserve gametes to be used with the partner of their choice at the time of recovery. Mature oocytes that are retrieved after ovarian stimulation are directly cryopreserved using a technique called vitrification. This technique, as opposed to slow-freezing, avoids formation of ice crystals and its deleterious effect on the oocyte. Studies comparing the use of fresh versus vitrified oocytes have shown similar pregnancy rates. In cancer patients, data regarding pregnancy rates after using cryopreserved oocytes remain limited. This technique is now considered established and no longer experimental.

Cryopreservation of embryos, either at the zygote or blastocyst stage, as performed routinely for IVF, is currently an established technique for fertility preservation. According to the Swiss law embryos created after IVF considered the joint property of both partners.

Ovarian tissue cryopreservation and transplantation

Ovarian tissue cryopreservation involves surgically harvesting (by laparoscopy, rarely laparotomy) and freezing ovarian strips / half an ovary (in rare cases with a very high risk of premature ovarian insufficiency a whole ovary), allowing the preservation of oocytes within primordial follicles. This tissue is later reimplanted to restore fertility in the case of premature ovarian insufficiency. This option is preferred, if there is insufficient time to perform ovarian stimulation or if ovarian stimulation cannot be performed at all.

Ovarian tissue cryopreservation is the only option for prepubertal girls. Until now, only a single pregnancy has been reported after reimplantation of ovarian tissue preserved before puberty.

One concern of tissue reimplantation is the reintroduction of malignant cells at the time of transplantation. Risk categories have been developed: breast cancer (Stage I-II), squamous cell cervical carcinomas, Hodgkin's lymphoma, osteogenic carcinomas and Wilms' tumour are considered to be at low risk. Breast cancers (Stage IV) and lobular invasive breast cancer, colorectal carcinomas, adenocarcinoma of the cervix, non-Hodgkin's lymphoma, Ewing sarcoma are at moderate risk, and leukemia, neuroblastoma, Burkitt's lymphoma and ovarian cancer are at high-risk. Cryopreservation of ovarian tissue is considered to be experimental in the high-risk group and patients should be informed that there is a possibility that the tissue cannot be transplanted. The only other option would instead be in vitro maturation of follicles from the ovarian cortex, a technique than is not yet feasible.

Gonadotrophin-releasing hormone agonists (GnRHa)

The role of GnRHa in the protection of ovarian function during chemotherapy is still controversial. However, recent data in breast cancer and lymphoma patients have brought new evidence regarding the effect of GnRHa on ovarian function. In a randomized trial including 257 premenopausal with receptor-

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negative operable breast cancer, administration of GnRHa during chemotherapy significantly reduced the risk of ovarian failure compared to the chemotherapy-group-alone with more pregnancies and improved disease-free survival in the GnRHa group. In another randomized trial including 281 premenopausal women with receptor positive or negative breast cancer, administration of GnRHa during chemotherapy was associated with a significantly higher chance of long-term ovarian function recovery compared to the chemotherapy alone group with no difference in terms of pregnancy rate. The effect of GnRHa administration on ovarian function and fertility in women with lymphoma was evaluated in a prospective randomized trial after 2, 3, 4, and 5 to 7 years of follow up. This long-term study failed to show that GnRHa could prevent premature ovarian failure and improve pregnancy rate, even if a benefit of GnRHa administration could be demonstrated in terms of ovarian reserve after 1-year follow-up. Another potential role of GnRHa during chemotherapy in women with hematological malignancies is to prevent severe/irregular menstrual bleeding. The indication for GnRHa during chemotherapy to protect ovarian function depends on the type of cancer and available data. This treatment should not solely be relied upon as a fertility preservation option.

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METHODS FOR FERTILITY PRESERVATION IN MEN

Sperm cryopreservation

The collection and cryopreservation of semen is the most accessible, cheapest and safest method for the preservation of fertility in postpubertal and adult male patients facing a gonadotoxic treatment. Sperm banking through rapid freezing in the presence of various cryoprotectants has been used for decades without any obvious negative impact on the offspring. Therefore, semen cryopreservation should be offered to all postpubertal and adult male patients before any gonadotoxic treatment is initiated.

In malignant disease, semen collection should ideally be organized as soon as possible upon diagnosis. Moreover, in azoospermia, a testicular biopsy can be performed in order to collect testicular spermatozoa.

Prior to cryopreservation patients should be informed that the usage of the cryopreserved sperm will require some form of assisted reproductive technology (in vitro fertilization, intra-uterine insemination) to achieve pregnancy. Even with a very limited number of spermatozoa, fertilization can be made possible by using technologies such as intracytoplasmic sperm injection (ICSI).

Within few days, chemotherapy deteriorates sperm quality and after a few months, testicular involution will progressively lead to azoospermia. Moreover, chemotherapy rapidly induces apoptosis in the seminiferous tubules causing DNA breaks and chromosomal aneuploidy in residual gametes. Therefore, semen collection after initiation of chemotherapy is not appropriate for fertility preservation.

Recovery from oligo- or azoospermia is variable and depends on the extent of both stem cell killing and impairment of the somatic environment that normally supports stem cell differentiation. It is important to inform the patient that the recovery of sperm production may last up to several years after the end of the gonadotoxic treatment.

Although DNA damage in sperm has been shown to persist for as long as 2 years after treatment, this effect generally seems to be transient without lasting damage to the spermatogonial stem cells. There is no consensus about the optimal duration of contraception after the end of chemotherapy, but the general recommendation is at least 6 months.

Other methods

Other methods such as testicular tissue cryopreservation and grafting are experimental and should only be performed in the context of studies. Hormonal gonadoprotection is not effective in men and therefore not recommended.

Indications for fertility preservation

Fertility preservation can be considered for the following indications:

1. In malignant and non-malignant disease if therapy (surgery, chemotherapy, radiotherapy, medical therapy) or the condition itself (e.g., autoimmune disorder) can cause infertility, reduces ovarian reserve or delays the time until pregnancy.
2. As an individual decision in women who might postpone parenthood until their late reproductive years and risk age-related infertility.

Prerequisites and Limitations

1. The upper age limit for fertility preservation depends on the technique used and on the ovarian reserve. Due to poor outcomes, it is not advisable to perform fertility preservation in women older than 40 years of age. An upper age limit in men cannot be defined medically.
2. In fertility preservation for malignant and non-malignant medical indications:
 - 2.1. Patients should have a reasonable chance of cure and of being able to carry a pregnancy.
 - 2.2. The oncological treatment and the subsequent health status need to be compatible with a later pregnancy. In case of radiation of the uterus with >25 Gy in *childhood* and with >45 Gy in *adulthood* fertility preservation is not advisable.
 - 2.3. Patients should have a substantial risk of infertility due to the expected therapy. However, it is often difficult to define exactly the risk, which qualifies patients for fertility preservation counseling, as it is highly subjective which risk is considered relevant.
 - 2.4. The health risks of fertility preservation procedures need to be very low and postponing the oncological treatment should not reduce its efficacy.

COUNSELING IN THE CONTEXT OF FERTILITY PRESERVATION

The following points should be discussed by the reproductive physician:

- The impact of treatment on fertility is sometimes hard to evaluate as it depends on individual situations (age, ovarian reserve, sperm quality), type of chemotherapy, and combination of chemotherapeutic agents. Data is sometimes insufficient for precise evaluation.
- Treatment chances have to be discussed in detail according to the actual scientific data, especially regarding the individual situation (age, ovarian reserve, sperm quality etc.)
- Other family building options should also be addressed (adoption, gamete donation), some of which are not legal/available in Switzerland at the moment. However, as laws change and patients might live elsewhere all options should be discussed, independently of the current reimbursement or legal regulations.
- Treatment costs: Patients should be informed that fertility preservation treatments are reimbursed by insurance companies.
 - in post-pubertal children and female and male adults until the completed 40th year (until the last day before the 40th birthday). Fertility preservation is not reimbursed in children before puberty.
 - in malignant diseases requiring gonadotoxic treatment with a treatment induced risk of persistent amenorrhea/azoospermia of >20% (since 01.07.2019)
 - in non-malignant diseases requiring gonadotoxic treatment with a treatment induced risk of persistent amenorrhea/azoospermia of >20%. In women and men receiving stem cell transplantation (01.07.2020)

The following treatments are reimbursed:

- Women: Ovarian stimulation with oocyte retrieval and cryopreservation of oocytes. Resection, cryopreservation and re-implantation of ovarian tissue.
- Men: Cryopreservation of sperm, testicular sperm extraction (TESE)
- Storage: Storage of gametes and gonadal tissue is reimbursed for up to 5 years. Reimbursement of storage can be extended for another 5 years in case of persistent ovarian insufficiency /azoospermia

In order to indicate and perform fertility preservation centers must:

- be multidisciplinary
- participate in a multi-centric quality control program with a registry for fertility preservation procedures in men and women with cancer or being associated with such a center.

GnRH agonists are prescribed off-label for fertility preservation and are not reimbursed in that indication.

- Complications of the treatment (ovarian hyperstimulation syndrome, bleeding, infection etc.) and the fact that ART's successful completion cannot be guaranteed (insufficient ovarian responses and sperm quality).
- The time interval before pregnancy and the fact that this is incumbent upon full recovery from cancer also needs to be discussed. Additional specific psychological counseling and/or timely psychological support in this difficult decision making process under the constraint of time, and in most vulnerable times is helpful and should likewise be considered.

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Classification of evidence levels	Grades of recommendations
Ia Evidence obtained from meta-analysis of randomised controlled trials.	A Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
Ib Evidence obtained from at least one randomised controlled trial.	
IIa Evidence obtained from at least one well-designed controlled study without randomisation.	B Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.	
III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.	C Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)
IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.	
	Good practice point
	<input checked="" type="checkbox"/> Recommended best practice based on the clinical experience of the guideline development group.

Guideline RCOG Nr. 44, 2006

Conflict of interest declaration:

Streuli I: Member of the Board "réseau romand de cancer et fertilité", Consultative member of the Human Swissmedic Expert Committee, HMEC

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