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REVIEW ARTICLE

Obstetrics

Preservation of female fertility: The current therapeutic strategy

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Abstract

Background: Preservation of female fertility is a relatively new field in medicine that has grown very rapidly in recent decades. At the beginning, embryo freezing remained the most effective technique. Thereafter, cryopreservation of oocytes and ovarian tissue was considered a secure tool in human fertility preservation. Storage of cortical ovarian tissue is moreover relevant for children, prepubertal girls, and adult patients who cannot benefit from cryopreservation of oocytes.

Objective: To analyze and review recent and relevant scientific literature on medical and social reasons for preservation of fertility.

Methods: The review was conducted based on articles identified from PubMed databases using keywords.

Main results: Oocyte vitrification allows women to preserve their fertility without the need for fertilization. Nowadays, thousands of healthy children have been born from this procedure. Occurrence of pregnancy depends on two main factors: the number of mature oocytes in storage and the age of the patient at the time of vitrification. Numerous adaptations have been developed to suit the ovarian stimulation regiments to patients with cancer. In young prepubertal girls, freezing of ovarian tissue remains the best and only option.

Conclusion: Oocyte vitrification therefore appears to be the gold standard technique of preserving fertility in young women.

KEYWORDS
fertility preservation, oocyte vitrification, ovarian stimulation, ovarian tissue, pregnancy

1 | INTRODUCTION

Over the last few decades, anticancer treatments such as chemotherapy and radiotherapy have led to a significant decrease in the mortality rate among pediatric and young adult women. An annual decline in mortality of 1.5% is observed in the United States.[1] However, an improvement in the survival rate must be accompanied by a reduction in the side effects of treatment and an enhancement in the quality of life of survivors of cancer. Unfortunately, alteration of ovarian function and development of premature ovarian insufficiency (POI) are frequent consequences of anticancer treatments.

Consequently, fertility preservation programs have been developed for adolescent and young adult (AYA) survivors of cancer in recent years. The American Society of Clinical Oncology was the first

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society to publish guidelines concerning ovarian toxicity of cancer treatments and the possibilities of preserving fertility.[2] Since then, many other international scientific societies have also published recommendations on this subject.

Different techniques for the preservation of fertility have been developed in recent years. The most appropriate technique for a given patient depends on multiple parameters, including the type of pathology, the treatment required, the urgency of treatment, the age of the patient, and the presence or absence of a partner.

In pathologies treated by radiotherapy only, oophoropexy may be proposed to remove the ovary from the radiation field.[3] For some diseases requiring chemotherapy with moderate gonadotoxicity, such as breast cancer, administration of gonadotropin-releasing hormone (GnRH) analogs was proposed in order to suppress ovarian activity.[4]

In some cases, severe ovarian toxicity cannot be avoided, and cryopreservation of gamete or gonadal tissue must be proposed to preserve the patient's fertility. In women, vitrification of a mature oocyte after controlled ovarian stimulation (COS) or cryopreservation of ovarian tissue are the two best options available. When the risk of amenorrhea in the patient is high, clinicians can combine two or even three methods of fertility preservation.[5,6]

Moreover, the techniques for fertility preservation can be proposed to other patients at risk of POI regardless of the underlying cause (neoplasia, benign pathology as endometriosis,[7] or simply aging ovarian dysfunction).

2 | MATERIALS AND METHODS

The present review provides a literature overview on current knowledge about techniques used to preserve female fertility in case of medical and non-medical indications or in banking of donor eggs.

2.1 | Search strategy

The PubMed database (National Library of Medicine, https://pubmed.ncbi.nlm.nih.gov/) was searched up to February 2021. A combination of Medical Subject Headings (MeSH) descriptors has been used: “oocyte vitrification” and “fertility preservation” or “ovarian stimulation” or “ovarian tissue” or “pregnancy.”

2.2 | Screening of publications

A search using the specific MeSH resulted in hundreds of publications. One of the first co-authors (LH) performed a global screening based on title, authors, and year of publication in order to select data likely to enhance understanding of and updating the topic of interest. Abstracts from the selected papers were read by the two first co-authors and articles recognized as relevant by both were analyzed in more detail.

2.3 | Data synthesis

A total of 36 references consisting of reviews, clinical studies, guidelines, and recommendations published between 2005 and 2021 were selected to document the present work. The collected data were organized as a literature review synthesis structured on paragraphs and sub-paragraphs.

3 | INDICATIONS FOR PRESERVATION OF FEMALE FERTILITY

3.1 | Malignant diseases

Malignant diseases treated by surgery, chemotherapy, or radiotherapy associated with POI are good indications for preservation of fertility.

The impact of chemotherapy depends on several parameters, including the nature of the agent used, the dose and duration of administration, and the patient's age at the time of treatment. Alkylating agents, such as cyclophosphamide, have a very pronounced gonadic toxicity by inducing massive follicular loss. It is obvious that the higher the dose used, the higher the toxicity. Follicular loss can also be increased when several chemotherapy agents need to be combined. The impact on gonadal function can be reversible or irreversible. While temporary amenorrhea results from the destruction of mature follicles, definitive amenorrhea can arise from the loss of primordial follicles.[3]

Radiotherapy can also induce infertility. The impact on ovarian tissue depends on the cumulative dose administered but also on the fractionation of doses and the irradiation site. Treatment in the pelvic field is very likely to induce POI, with an irradiation dose of less than 2 Gy resulting in the destruction of half of immature human follicles.[8] Total body irradiation causes infertility in 90% of patients. Beside follicular loss, radiotherapy can induce major tissue remodeling such as ovarian stroma fibrosis or extensive vascular damage following tissue hypoxia. Ovarian atrophy may therefore arise, resulting in tissue dysfunction.[9] Cerebral irradiation, particularly in the hypothalamic-pituitary zone, may also induce infertility by hypogonadotropic hypogonadism. Radiotherapy also has deleterious effects on the myometrium, especially in prepubertal children who are particularly sensitive.

The age of the patient plays an important role in the ovarian toxicity of radiotherapy. Older women are at a higher risk of POI due to the physiological decrease in the number of follicles and degradation of quality over time. At birth, irradiation of 20 Gy is needed to cause sterility in 97% of patients, while the same effect is observed with 18, 16, and 14 Gy in patients aged 1, 20, or 30 years.[3]

Nevertheless, the probability of POI depends on the intrinsic ovarian reserve, which varies considerably from one patient to another.

The most frequent indications for oncologic preservation of fertility are hematologic pathologies (Hodgkin's lymphoma,

non-Hodgkin's lymphoma, and leukemia) and breast cancers. Other indications include sarcoma, colorectal cancer, borderline ovarian tumors, and central nervous system malignancies among others.[10] In many countries, different strategies for the preservation of fertility are allowed. For example, in Belgium, women and men aged under 38 and 45 years, respectively, are reimbursed in case of malignant disease.

3.2 | Benign diseases

The preservation of fertility must also be proposed to patients at risk of POI due to benign conditions and their treatments, such as autoimmune or hematological disorders requiring chemotherapy and bone marrow transplantation.

Some ovarian pathologies can also impair fertility, such as the presence of bilateral ovarian tumors, severe or recurrent ovarian endometriosis, and recurrent ovarian torsion. Genetic predisposition to premature depletion of the ovarian reserve is also a good indication for the preservation of fertility[10] (e.g. blepharophimosis, ptosis, and epicanthus inversus syndrome [BPES], autoimmune polyendocrinopathies, and some enzyme deficiencies), although preservation of fertility may be controversial in some cases such as Turner syndrome.[11]

3.3 | AGE-Banking, oocyte donation, and transgenders

"AGE-Banking" relates particularly to preservation of gametes undertaken for personal reasons or in order to anticipate natural exhaustion. This concept has emerged in recent decades as women's age at the time of first pregnancy has been progressively rising worldwide. Lack of a stable partner, financial reasons, self-realization, and career status are some of the factors that convince women to postpone childbearing.[10] Consequently, the cryopreservation of oocytes increases their chances of conceiving their own genetic offspring.

Cryopreservation of oocytes also ensures accessibility for infertile women to oocyte donation programs and preservation of fertility in transgender people before their medical and surgical transition.[12,13]

4 | CRYOPRESERVATION OF OOCYTES

Vitrification of oocytes is now a routine technique available worldwide for women who wish to preserve their fertility. The European Society of Human Reproduction and Embryology recently published a guideline on the preservation of female fertility [14] and a part of this working group, specialized in the cryopreservation of oocytes, reported a total of 34 705 cycles of oocyte preservation between 2010 and 2014 in 17 European countries.[15] Egg banking is therefore the best option for patients who undergo preservation of fertility for social reasons, especially those under the age of 35 years, where a probability of 85.2% for a live birth can be expected with 15 vitrified oocytes.[16]

Unfortunately, the vitrification of mature oocytes has some limitations. For example, the need for prior hormonal stimulation can delay oncological treatments. Moreover, that technique cannot be carried out in prepubertal children. Nevertheless, a major advantage is the limitation of the transmission of cancer cells when compared to ovarian cortex transplantation.[17] A prospective cohort study comparing oocyte vitrification versus ovarian cortex transplantation for the preservation of fertility in adult women undergoing gonadotoxic treatments has shown that live birth rates might be better in the oocyte vitrification group. Moreover, the vitrification of oocytes is a less burdensome intervention to undertake and is less intrusive.[18] However, the banking of ovarian tissue is an acceptable technique of fertility preservation and is no longer considered experimental.

Today, the banking of ovarian tissue remains the only method to preserve fertility in prepubertal girls since ovarian stimulation and in vitro fertilization (IVF) are not options, as recently reported by Dolmans et al.[19]

4.1 | Ovarian stimulation protocols

Prior COS is needed to obtain several mature oocytes for cryopreservation.

Assessment of a woman's ovarian reserve is a prerequisite to maximize the efficacy of the retrieval of oocytes and to limit the risk of ovarian hyperstimulation syndrome (OHSS). It cannot predict the outcome of the vitrified oocytes but is useful in counseling patients, helping to develop realistic expectations, and choosing a safe and effective protocol for ovarian stimulation for cancer patients undergoing preservation of fertility.[20] Ovarian reserve is routinely performed by one or more of the following three markers: antral follicle count (AFC) by ultrasonography; level of anti-Müllerian hormone (AMH); and level of early follicle-stimulating hormone (FSH). In the case of preservation of fertility, AMH and AFC are the more frequently used markers because their levels vary only slightly during the menstrual cycle [20-22] and are less affected by the oral contraceptives frequently administered in young patients compared to levels of FSH, although an underestimation of about 30% can be achieved with this type of contraception.[23]

In most cases, administration of GnRH antagonists is used to prevent unwanted surges of luteinizing hormone (LH) during COS. When compared to GnRH agonist, the antagonist allows the time of COS to shorten and the risk of OHSS to be reduced, as ovulation triggered by human chorionic gonadotropin (hCG) can be replaced by the administration of GnRH agonists.[21]

For non-oncological patients, COS is initiated on day 2 or 3 in a spontaneous cycle by daily injection of 150 to 300 IU of recombinant FSH or highly purified human menopausal gonadotropins (hMG). On day 6, the dosage of gonadotropins is re-evaluated according to the levels of serum estradiol (E_2) and follicular count assessed

by transvaginal ultrasound scan. When a leading follicle reaches 14 mm, the GnRH antagonist is administered.[24] Final maturation of oocytes is triggered by 250 mg of recombinant hCG or with 0.1 to 0.2 mg of GnRH agonist triptorelin in case of a high risk of OHSS.[16,24] Ultrasound-guided transvaginal retrieval of ova is scheduled 36 hours after the trigger, as performed in the conventional IVF program.

In hormone-dependent patients with cancer, conventional COS with gonadotropins must be adapted to limit the rise of the level of serum E_2. A high level of E_2 could promote tumoral growth in estrogen-sensitive cancers, such as endometrial and estrogen-receptor-positive breast cancers.[20] In these cases, letrozole, an aromatase inhibitor, can be used (5 mg/day) from day 2 or 3 of cycle until the day of triggering. Gonadotropins are started 2 days after letrozole, a GnRH antagonist is administered when the leading follicle reaches 14 mm, and final maturation of the oocyte is triggered with 0.2 mg of the GnRH agonist triptorelin as soon as two follicles are 20 mm or greater.[24] Until recently, the outcome of the safety of administration of letrozole on IVF children was unclear. A recent study published in 2016 provides reassuring data on this subject. One study shows that letrozole significantly decreases the risk of miscarriage and does not increase the risk of major congenital anomalies, adverse pregnancy, or neonatal outcomes when compared with natural cycles in patients undergoing antiretroviral therapy.[25]

In oncological patients, time is a limiting factor preventing the use of conventional COS in a subsequent menstrual cycle. Increasing evidence indicates that multiple waves of recruitment of antral follicles arise during the human menstrual cycle.[26] Therefore, it does not seem mandatory to start a COS on day 2 or 3. Based on this concept, a "random start" protocol has been proposed, in which ovarian stimulation can be started at any time during the cycle. One possibility is to administer a GnRH antagonist (0.25 mg/day) for 3 days after measuring the levels of serum E_2. If the level of E_2 is under 60 pg/mL, COS can be started regardless of menstruation. If the level is higher, an extra dose of the GnRH antagonist is given before the start of COS.[24]

Other stimulation protocols exist depending on the phase of the cycle, including in the late follicular and even luteal phases[20] (Figure 1).

In the late follicular phase – after day 7 when the dominant follicle is present – the induction of ovulation can be performed if the leading follicle is already 14 mm or larger, with possibly a first monofollicular retrieval, followed by luteal phase stimulation.[27] If the leading follicle is smaller than 14 mm, doses of gonadotropins alone are started, and the GnRH antagonist is added later when follicles reach 14 mm or larger to prevent a premature, secondary surge of LH.

All these types of stimulation end like the conventional antagonist COS protocol where the administration of gonadotropins and GnRH antagonists is continued until the final maturation of the oocytes triggered by hCG or GnRH agonist.[20] Data show similar outcomes whatever the phase of the menstrual cycle chosen for the startup of COS.[28,29] Moreover, clinical, obstetric, and perinatal outcomes seem unaltered depending on the phase of stimulation. Indeed, a recent multicenter study comparing these outcomes after a single blastocyst transfer obtained from 182 patients after follicular phase stimulation to 207 patients after luteal phase stimulation showed the same results for both groups.[30]

Mature oocytes retrieved are conserved by vitrification. Fertilization of the thawed oocytes must be performed by

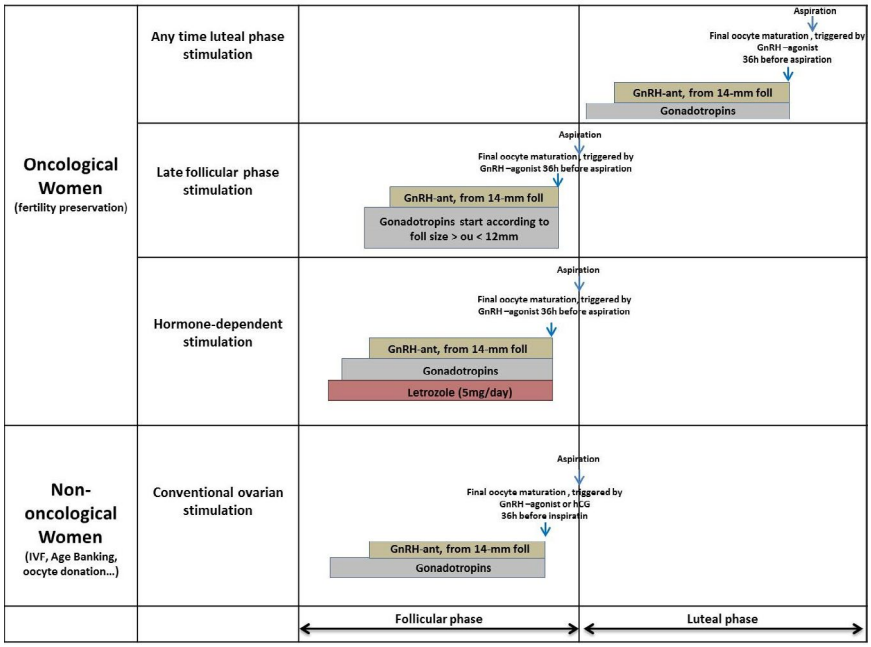

FIGURE 1 Examples of conventional, hormone-dependent, and Random Start stimulation cycles for the cryopreservation of oocytes. Inspired and modified from von Wolff et al.[27] Abbreviations: foll, follicle; GnRH-ant, gonadotropin-releasing hormone antagonist; IVF, in vitro fertilization

intracytoplasmic spermatozoa injection due to hardening of the zona pellucida.

4.2 | Pregnancy rate after the preservation of oocytes

The vitrification of oocytes is a routine effective tool in assisted reproduction. Several thousands of pregnancies have already been reported with obstetrical and neonatal outcomes similar to those obtained with fresh oocytes.[16]

The survival rate of oocytes, pregnancy, and cumulative live birth rates (CLBRs) are highly dependent on the patient's age at the time of vitrification and the number of oocytes in storage.[16] The probability of childbearing is significantly lowered over the age of 35 years. Caution should therefore be exercised when counseling patients, despite the excellent data obtained from donor oocyte programs where the survival rate can exceed 95%.[16] A recent publication demonstrated that live birth rates were significantly higher in the group with preservation of fertility indicated by benign conditions compared to oncological reasons (21% vs 47%) but women in the oncological group were significantly older when attempting pregnancy.[31] A retrospective multicentric study of more than 8000 cycles published in 2018 [32] showed a lower rate of success in patients with cancer when compared to age-banking indications. However, there was no statistically significant association between malignant disease and reproductive outcome after correction for age and COS regimen.[32]

4.3 | Limitations of the cryopreservation of oocytes

The main limitations of oocyte cryopreservation are the risks of OHSS during stimulation, the time required for COS, and the poor CLBR in older women.

The prevalence of OHSS is approximately 3% to 8% per COS. In its most severe form, OHSS is associated with hemoconcentration, ascites, liver dysfunction, pulmonary edema, electrolyte imbalance, and thromboembolic events. The COS protocol must be personalized to avoid OHSS, especially in patients with cancer where the risk of thromboembolic events is already increased by the neoplasm itself. Occurrence of OHSS could also delay the oncological treatment. Therefore, optimal customization of the stimulation regimen according to the patient's ovarian reserve is necessary to maximize the number of oocytes collected while minimizing the risk of OHSS.[20]

Despite the use of a modified COS and the advent of the "random start" protocol, a delay of approximately 2 weeks is still necessary for the completion of COS before the retrieval of oocytes. Unfortunately, delaying oncological treatments is not always possible. In this case, cryopreservation of ovarian tissue could be suggested. Another option is in vitro maturation (IVM) of oocytes, as discussed below.

Finally, age is a limiting factor in the cryopreservation of oocytes. This technique cannot be used in prepubertal children. Moreover, the CLBR falls dramatically with patient aged above 35 years.

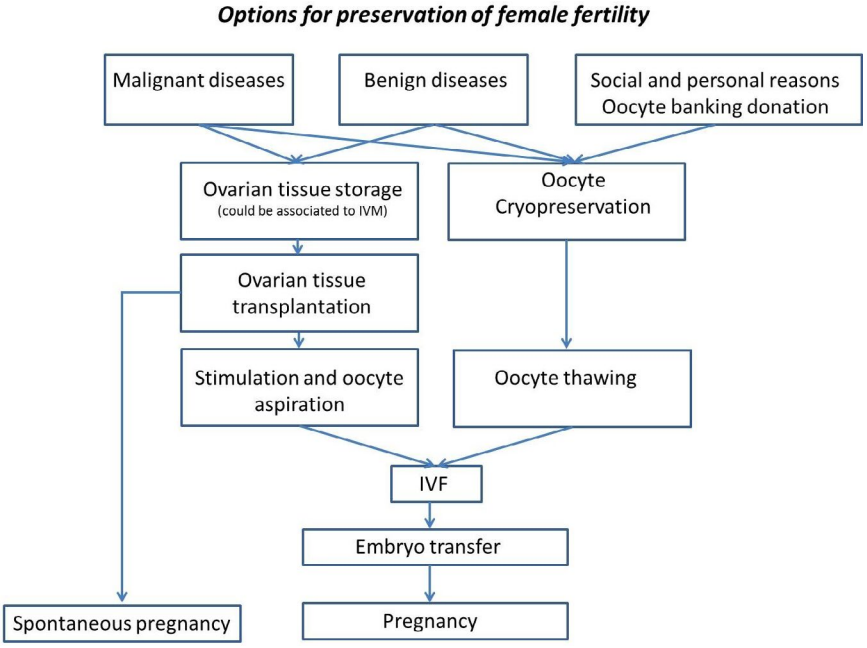

FIGURE 2 Different options and possibilities for the preservation of fertility for malignant and benign diseases, social and personal reasons, and oocyte donation. Abbreviations: IVF, in vitro fertilization; IVM, in vitro maturation

4.4 | Possibility of cryopreservation of embryos

The freezing of embryos is an option for the preservation of fertility in postpubertal women involved in a stable relationship. It is not applicable to single or homosexual patients, even if the use of a sperm donor remains possible. However, this option can become problematic in case the couple separate.

4.5 | Particular case: in vitro maturation of oocytes

Another way to preserve fertility when a complete COS cannot be achieved due to time constraints is IVM of germinal vesicles into metaphase II oocytes (MII). According to Seang Lin Tan, an IVM cycle could be defined as any collection cycle of eggs where the majority of the oocytes obtained should be at the germinal vesicle stage.[21] There is no or minimal need for ovarian stimulation, but it seems that an hCG trigger 36 hours before the retrieval of oocytes remains necessary.[21] In practice, IVM is mainly proposed to patients with polycystic ovaries at high risk of OHSS.

IVM is not yet a routine technique for the preservation of fertility. In 2016, Yin et al.[33] published a study on the maturation rate of immature oocytes aspired from ovarian medulla tissue discarded during ovarian cortex dissection. Despite a low rate of maturation, the authors suggest that this add-on method could potentially increase the fertility outcome in women with cancer.[33] Another study of 119 patients with cancer showed a high rate of maturation among oocytes retrieved by transvaginal ultrasound-guided aspiration just before ovarian tissue sampling. However, the reproductive outcomes were poor,[34] with low numbers of embryos, a low rate of implantation, and a high rate of miscarriage.

5 | CONCLUSION

Over the last few decades, survival rates in girls and young women with cancer have increased significantly. Unfortunately, anticancer treatments may alter ovarian function and lead to POI. For such patients, the fertility preservation program was developed to allow them to conceive after recovery with their own gametes. This concept of the preservation of fertility also concerns patients who are at risk of developing ovarian failure and even healthy patients who want to prevent age-related exhaustion of gametes.

Two main procedures allow the preservation of fertility in women, regardless of the presence of a partner: vitrification of oocytes and cryopreservation of ovarian tissue. Even though the number of births achieved after self-transplantation of cryopreserved ovarian tissue strips has increased exponentially in recent years,[35] the vitrification of oocytes must be the first choice in postpubertal women (Figure 2).

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

LH conceived the idea and wrote the manuscript. SL contributed to the writing, the layout, and the revision of the manuscript. CJ and MN revised the manuscript.

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