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Ovarian tissue and oocyte cryopreservation prior to iatrogenic premature ovarian insufficiency

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A B S T R A C T

Gonadotoxic treatments like chemotherapy or radiotherapy and ovarian surgery may result in an accelerated depletion of the ovarian reserve and subsequent premature ovarian insufficiency. Important determinants of this severe risk that require fertility preservation strategies are patient age, ovarian reserve, type of treatment, and administered dose. Oocytes and ovarian tissue can both be cryopreserved, with encouraging results in terms of pregnancy and live birth rates according to recent publications. Moreover, since ovarian tissue transplantation also results in long-term endocrine resumption, it represents a potential future therapeutic option for complete ovarian function restoration in patients with premature ovarian insufficiency.

Introduction

The development of the ovaries during embryonic growth is a highly regulated process and is one of the major determinants of fertility potential in women. Primordial follicles reside in the ovarian cortex in a quiescent state. Their number (range, 600,000 to 1 million per ovary) is determined at birth and a continuous and progressive decline ensues during childhood and throughout reproductive life, as

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primordial follicles are recruited and leave their quiescent state [1]. The majority undergo atresia after initial recruitment and do not reach the antral stage, while a small number continue their growth to reach ovulation, an event occurring around 450 times in the reproductive lifespan [1,2]. Only a very small number of follicles develop into competent oocytes. Depletion of almost the entire primordial follicle stockpile, leaving only around 1000 primordial follicles, results in menopause [1].

Early depletion of the ovarian reserve not only negatively affects fertility potential but may also lead to untimely cessation of ovarian endocrine activity, often with a far-reaching impact on health and quality of life [3]. This condition is defined as premature ovarian insufficiency (POI) and is suspected in the presence of menstrual disturbance (amenorrhea or oligomenorrhea) with elevated follicle-stimulating hormone (FSH) levels and low estrogen values in under-40 women [4]. The diagnostic criteria according to the European Society of Human Reproduction and Embryology (ESHRE) guidelines are (i) oligo/amenorrhea for at least four months, (ii) FSH levels >25 IU/L on two occasions more than four weeks apart [5].

Age at menopause appears to be dependent on both the number of primordial follicles formed during fetal life and present at birth and the speed of follicle recruitment and depletion, which can be modulated by various events during a woman's lifetime [3]. Gonadotoxic treatments, namely chemotherapy, radiotherapy, and surgery in girls and women diagnosed with cancer or benign disease requiring these treatments, can compromise ovarian function, resulting in iatrogenic POI.

Menopausal status is related to various morbidities associated with the lack of estrogen, including cardiovascular disease, osteoporosis, and neurodegenerative conditions, and its delayed occurrence is associated with an increased lifespan [6]. Earlier age at menopause has been connected to a higher risk of cardiovascular events, amounting to ~2% for each year POI [6], and all-cause increased mortality [6]. Moreover, hypoestrogenism encompasses a broad spectrum of symptoms, with impairment to sexual and psycho-social health [8]. As iatrogenic POI is often characterized by sudden onset, the perception of menopause-related symptoms may be more extreme than in physiological menopause, especially when it occurs as a consequence of cancer treatments with all the associated stress [9].

This review aims to provide an up-to-date overview of the pathogenesis of iatrogenic POI and existing therapeutic strategies for both fertility preservation and hormone replacement therapy in young patients affected by this condition.

Risk of iatrogenic POI

One in 800 children is diagnosed with cancer today, but long-term survival rates have increased in recent years, reaching around 70–80% [10]. However, young cancer survivors have to contend with numerous sequelae, including a higher risk of iatrogenic POI. Therefore, fertility preservation strategies have acquired greater relevance in recent years. Fertility preservation is limited not only to patients with cancer but also has increasingly extended to all pathologies associated with an elevated risk of iatrogenic POI [11,12].

Fertility prognosis after cancer treatment needs to be assessed at the time of cancer diagnosis; if the risk of infertility is high, special counseling on fertility preservation measures is required [13]. According to ESHRE recommendations, oncologists and fertility specialists should adopt a multi-disciplinary approach and offer comprehensive discussion on the infertility risk with individual cancer patients at the earliest opportunity, in order to inform their choice on fertility preservation options [13].

Treatments engendering the highest risk of POI are total body irradiation and chemotherapy before bone marrow transplantation, pelvic irradiation, and some chemotherapic treatments with alkylating agents [12,14]. Sensitivity to gonadotoxic treatments is age-dependent. The relative risk of POI is approximately 10% in patients <18 years of age [15], but around 30–40% in subjects aged <40 years [16].

Along with developing novel fertility preservation strategies ever more tailored to individual patient populations, research has been focusing on identifying biological markers to predict the risk of ovarian reserve injury after gonadotoxic treatments [14]. Among them, the anti-Müllerian hormone (AMH) has gained ground in recent decades [17,18]. AMH, a member of the transforming growth factor β (TGF-β) family, is responsible for the regression of Müllerian ducts during male fetal differentiation

[19]. In females, AMH is produced by granulosa cells of growing follicles at preantral and antral stages and acts on the follicle pool by inhibiting primordial follicle recruitment. AMH serum levels reflect the number of antral follicles present in the ovaries, hence the size of the ovarian reserve, fertility potential, and the process of senescence [20]. AMH variability is high in women's life, depending not only on the number of antral follicles under development but also on personal characteristics like BMI, ethnicity, and other variables like the nutritional state and smocking habits [16]. While it is useful in assessing the quantitative variations of the ovarian reserve, like in the case of ovarian damage, it fails to predict the natural fertility potential in young healthy women, which appeared not to be compromised in their natural conception chances with low AMH values [17,21], and also after ovarian tissue transplantation for fertility restoration [22].

AMH is a good predictor of ovarian function after gonadotoxic treatment like chemotherapy or radiotherapy, with sensitivity higher than inhibin B or FSH [23]. Iatrogenic damage to the ovaries can result in temporary or permanent loss of menstrual activity. However, menstrual cycle recovery is a late marker of follicle activity resumption, distinct from AMH, which may be considered a real-time indicator of both follicle depletion and renewal [18]. Longitudinal studies on young cancer patients treated by chemotherapy showed a dramatic drop in AMH just after initiation of chemotherapy, irrespective of the ovarian reserve prior to treatment, suggesting accelerated damage to AMH-secreting antral follicles [23,24]. High-risk therapy with alkylating agents results in falling AMH levels, without further resumption in most cases [24,25], suggesting significant impairment to the primordial follicle pool (Fig. 1). AMH recovery after gonadotoxic damage depends not only on the type of gonadotoxic agent but also the age and size of the ovarian reserve [23,26]. AMH values at the time of gonadotoxic treatment are also predictive of fertility recovery after gonadotoxic damage since there is a greater likelihood of menstrual cycle and fertility resumption with higher pretreatment AMH values [17,25].

AMH has also been investigated as a predictor of the impact of ovarian surgery on ovarian reserve, as in the case of ovarian endometriosis. Declining AMH values after surgery suggest the elimination of a significant part of the ovarian follicle pool [27,28]. Ovarian endometriosis also appears to have a direct detrimental effect on the ovarian reserve, since it causes accelerated follicle depletion [27]. Chronic inflammation, oxidative stress, and mechanical changes due to the presence of endometriomas may trigger abnormal activation of primordial follicles, thus increasing follicle atresia and ovarian tissue fibrosis [29,30]. Hence, fertility preservation strategies need to be considered in young patients suffering from endometriosis, especially in cases of repeated surgery, bilateral endometriomas, fast-growing endometriomas, and extremely young age at the time of diagnosis (Fig. 2) [31].

Chemotherapy

Chemotherapy drugs can cause all kinds of damage to the ovary [12,14]. First, since they target proliferating cells, they may harm the growing follicle pool with a sudden reduction in ovarian function. Damage to the ovarian reserve can be both quantitative, with a significant decline in the ovarian follicle stockpile, and qualitative, with impairment to follicle and oocyte competence [32]. Moreover, indirect vascular damage in the ovarian tissue may be detrimental to follicle growth and lead to tissue fibrosis [33,34].

Of all chemotherapeutic drugs, alkylating agents like cyclophosphamide (CPM) and procarbazine are most known to exacerbate the risk of POI. CPM is a prodrug and its primary active metabolite is phosphoramide mustard, inducing DNA crosslinking and ultimately preventing DNA replication [34]. It is used for several types of cancer, especially childhood malignancies, autoimmune diseases like systemic lupus erythematosus and rheumatoid arthritis, and prior to stem cell transplantation for hematological conditions [32]. Ovarian exposure to CPM leads to depletion of the ovarian reserve through a significant drop in numbers of both growing and primordial follicles [34,35]. For growing follicles, there is considerable evidence linking CMP to granulosa cell apoptosis, demonstrated in studies on murine models [36] and in vitro experiments on human growing follicles [37].

However, the impact of CMP on the primordial follicle pool remains debatable. Some authors have suggested that alkylating agents trigger primordial follicle activation and 'burnout' through the phosphoinositol-3-kinase (PI3K)/protein kinase B (Akt) signaling pathway [38,39]. This pathway induces loss of quiescence in primordial follicles through activating numerous signaling effectors,

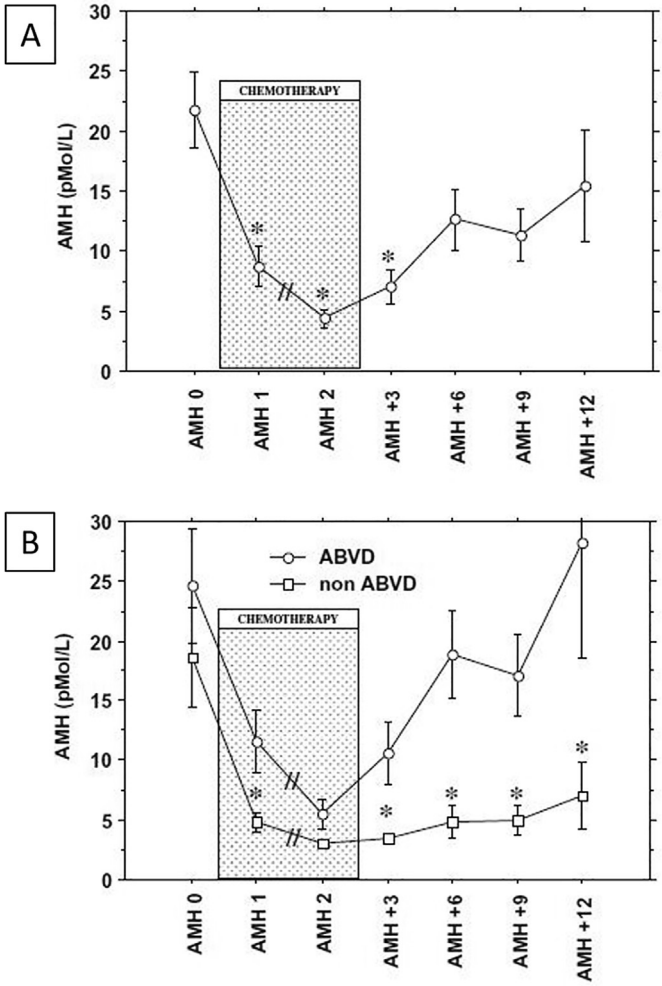

Fig. 1. (A) Longitudinal evolution of mean (±SD) serum AMH concentrations in a group of 30 women (mean age 24 years) undergoing chemotherapy for lymphoma. (B) Longitudinal evolution of mean (±SD) serum AMH concentrations in the ABVD group (n = 17) and non-ABVD group (n = 13). AMH variations were analyzed as a function of time by ANOVA. AMH0 = before initiation of chemotherapy, AMH1 = 15 days after the first cycle of chemotherapy, AMH2 = 15 days before the last cycle of chemotherapy and AMH+3, +6, +9, +12 = every 3 months after the end of chemotherapy. * = $p < 0.05$.//indicates that the time lag between AMH1 and AMH2 was not the same for every patient. Adapted from Decanter et al., 2010 [21]. AMH: anti-Müllerian hormone; ABVD: doxorubicine, bleomycine, vinblastine, dacarbazine).

including the Forkhead box O3A (FOXO3A) translocation from the nucleus and thus forming the mechanistic target of rapamycin (mTOR) complex responsible for cell survival and proliferation [38–40]. The PI3K/Akt pathway may either be activated directly by pro-inflammatory and pro-oxidant effectors, with potential DNA damage to the oocyte or indirectly by lessened secretion of suppressive factors like AMH due to death of growing follicles [12]. Other authors have suggested that CMP-induced damage occurs through the apoptosis cascade as a consequence of the rapid triggering of DNA breaks [41]. Recent studies have shown that the DNA damage-induced pro-apoptotic protein, p53 upregulated modulator of apoptosis (PUMA) plays a key role in the oocyte initiation of apoptosis [42].

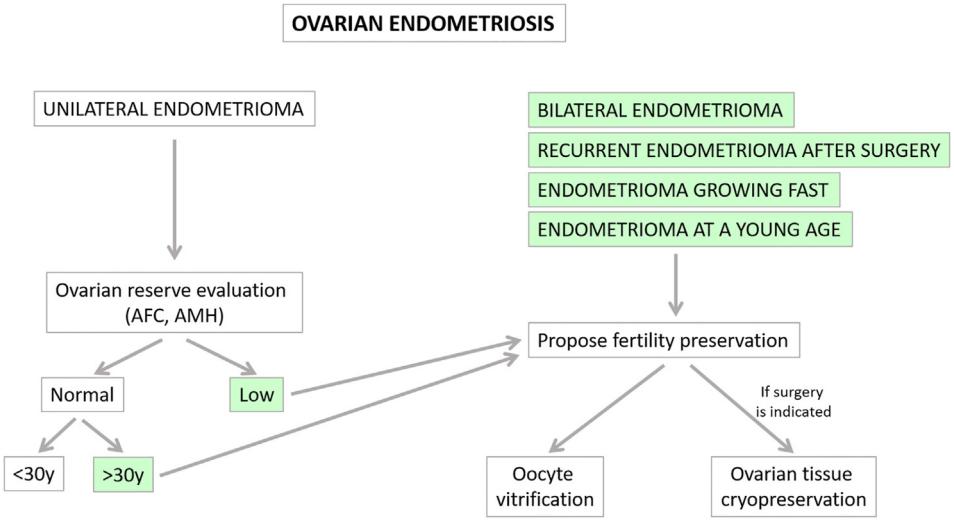

Fig. 2. Algorithm for fertility preservation in women with ovarian endometriosis. Items in green (diminished ovarian reserve, age >30 years, bilateral endometriomas, recurrent endometriomas after surgery, fast-growing endometriomas, endometriomas at a young age) are indications for fertility preservation by either oocyte or ovarian tissue cryopreservation (Adapted from *Dolmans and Donnez, 2021* [28].

While the impact of alkylating agents has been known since the 1970s and there is strong evidence on all the ovarian damage caused [23,43], establishing the extent of gonadotoxicity of other chemotherapic drugs is becoming more challenging as they are used in various combinations in cancer treatment protocols.

Cisplatin (CIS) is often part of multidrug regimens commonly used in young patients and considered to exert moderate toxicity on the ovary, with low risk of inducing POI [44]. It acts as a DNA cross-linking agent that interferes with DNA repair mechanisms, blocks cell division, elicits DNA damage, and triggers apoptotic cell death, thus showing high toxicity in tissues with rapid turnover [34,45]. Studies on murine models demonstrated that CIS-mediated damage may be due to both abnormal primordial follicle activation and apoptosis induction after DNA damage [46,47].

Doxorubicin (DOX), a chemotherapeutic agent acting on the nuclear enzyme topoisomerase II with an impact on DNA damage repair capacity, has also been associated with an increased risk of iatrogenic POI [48]. However, it is difficult to establish its precise gonadotoxicity, since it is used in association with other drugs and long-term follow-up is needed. Studies in murine models evidenced an effect of DOX on cortical blood vessels, with more extensive fibrosis [49]. DOX accumulation has also been proven in oocytes, showing a dose-dependent detrimental effect [50,51]. Studies on ovarian tissue confirmed the DOX direct damage to follicles through escalation of the apoptotic cascade after DNA damage [52,53].

Among possible strategies to protect the ovarian follicle pool from gonadotoxicity during chemotherapy and hence reduce the risk of POI, tamoxifen has been tested in the human ovary but had no significant impact on ovarian function after chemotherapy [54]. Moreover, numerous investigations have been conducted into the role of GnRH agonists in protecting the ovarian reserve during oncological treatment, with contentious results concerning their effectiveness at preserving fertility, other than restoring menstrual cycles [55–57].

Radiotherapy

Radiation is directly gonadotoxic and leads to oocyte death within a few hours of irradiation, followed by removal by phagocytosis within a few days [58]. This toxicity is dose-dependent and around

2 Gy is found sufficient to cause 50% depletion of the non-growing follicle pool [59]. However, other factors, including the field of radiation, the fractionation schedule, patient age at the time of treatment, and the size of the ovarian reserve, play a role in radiation-mediated insults, causing either immediate ovarian failure or POI subsequently. By considering the average decline in the ovarian reserve with increasing age, it is possible to calculate the effective sterilizing dose of radiation treatment for each age [10]. The estimated sterilizing dose naturally falls with advancing age, as the ovarian stockpile progressively diminishes [57]. While around 18 Gy is needed to induce POI at the age of 12 years, only 14 Gy will have the same effect at around 28 years of age [10].

In the case of total body irradiation, the radiation dose to the ovaries sometimes can be limited to adult women by shielding the gonads or targeting only the tumor site, hence reducing the risk of iatrogenic POI. Nevertheless, it is difficult to identify the correct anatomical position of the ovaries in the pelvis, especially in young girls [60].

In the presence of malignancies originating in the pelvis, the ovaries may need to be irradiated with doses of around 6–15 Gy, as in the case of advanced cervical cancer (from stage IIB) in order to lower the risk of ovarian metastasis [61,62]. In earlier-staged cervical cancers (IB-IIA) or malignancies without a greater risk of ovarian metastases, like rectal or anal cancer, the ovaries can be shielded or transposed. However, this yields little or no advantage in terms of gonadoprotection, as radiation doses reaching the ovaries remain quite high [62,63]. Moreover, pelvic radiotherapy is responsible for more widespread fertility impairment, since it not only damages the ovaries, causing iatrogenic POI, but also the uterus and entire pelvic vasculature. Radiotherapy-mediated uterine damage depends on patient age at the time of treatment and the total dose administered and is associated not only with fertility issues but also with a wide range of adverse obstetric events in case of pregnancy [64]. Risks of miscarriage, premature birth, and low birth weight are increased in case of total body irradiation by > 12 Gy in adults [65]. Higher radiation doses are associated with more unfavorable infertility and pregnancy outcomes. Therefore, pregnancy is not recommended in case of radiation of >25 Gy in children and >45Gy in adults [65]. Recent data on fertility outcomes after ovarian tissue transplantation in patients with previous pelvic radiotherapy confirm dose-dependence of uterine damage. No live births were achieved in women with anal or cervical cancer having received the highest pelvic radiation dose, while births were reported in patients receiving total body irradiation for systemic diseases like lymphoma or leukemia, with lower radiation doses to the pelvis [14].

Radiotherapy is also associated with a decrease in quality of life due to sexual dysfunction [66]. Pelvic radiation may directly damage the lower genital tract, leading to the formation of ulcers and epithelial necrosis. It also may induce vaginal wall thinning, progressing to fibrosis and stenosis, with an increased risk of developing chronic pelvic pain and severe dyspareunia [66].

Pelvic surgery

Among all pathological conditions requiring surgery to the ovaries that may entail an increased risk of ovarian damage, ovarian endometriosis management has been the subject of most controversy [67]. While surgical treatment is indicated in the case of large endometriomas and pelvic pain, management of endometriosis-related infertility remains contentious, with arguments in favor of both surgery and assisted reproductive technology as first-line treatment.

Various factors contribute to making endometriosis one of the ovarian conditions most associated with a high risk of surgical damage. First, ovarian endometriomas are characterized by the absence of a capsule, and are therefore more difficult to excise without damaging the surrounding ovarian cortex, unlike other ovarian cysts, like dermoid tumors, whose excision is not related to a threat of ovarian cortex damage [68]. Ovarian endometriomas have been proven to be detrimental to the ovarian reserve irrespective of surgery, since local chronic inflammation increases follicle atresia [29], explaining why AMH is diminished in patients with ovarian endometriosis even before surgery [69]. Moreover, patients with ovarian endometriosis run a risk of disease recurrence of around 10% per year when no postoperative adjuvant treatment is associated [70]. The likelihood of natural conception after second surgery is half of that seen after primary intervention [71]. These data point to an increased risk of ovarian reserve damage with repeated surgery.

For all these reasons, correct management of ovarian endometriosis is vital and should be carefully determined for each patient, considering not only current symptoms of chronic pain and infertility but also future fertility potential in the presence of chronic and recurrent disease. Ovarian endometriosis is increasingly becoming an indication for fertility preservation, since it is associated with both an elevated risk of ovarian damage due to surgery and also accelerated follicle depletion, potentially leading to future infertility.

Clinical management of women at increased risk of iatrogenic POI

Management of women at increased risk of POI should have two main goals:

- To assess the degree of infertility-associated risk and propose a suitable and effective fertility preservation strategy.
- To alleviate postmenopausal symptoms, like vasomotor disorders and bone density loss, and reduce long-term consequences related to hypoestrogenism with hormone replacement therapy (HRT).

The choice of fertility preservation strategy is determined by the age and pubertal status of patients. Options include oocyte and ovarian tissue cryopreservation (OTC), which will be discussed further in this chapter (Fig. 3). HRT is recommended to relieve menopausal symptoms until the age of natural menopause at around 50 years. When iatrogenic POI occurs before pubertal development, complete clinical management includes initial puberty induction with sex hormone administration, followed by long-term HRT.

Oocyte cryopreservation

Of all fertility preservation strategies, mature oocyte cryopreservation is the approach of choice in postpubertal subjects (Fig. 3). It is a valid option for cancer patients because it addresses ethical concerns around creating embryos after a cancer diagnosis or in the absence of a partner. Moreover, thanks to the development and spread of the vitrification technique, which involves rapid cooling in the presence of high concentrations of cryoprotectant, the procedure of oocyte vitrification guarantee high survival rates and optimal cell competence after thawing [72].

While some authors have observed an impaired ovarian response to controlled stimulation in cancer patients, this only appears to be true of specific malignant diseases like ovarian cancer [73] or BRCA mutations [74]. In all other conditions, there is too much bias due to the use of different stimulation protocols in terms of drug, types, and doses, and duration of stimulation. Recent studies reveal that patients diagnosed with cancer do not appear to have an impaired response to controlled ovarian stimulation [75].

However, the number of patients who have undergone oocyte cryopreservation because of an elevated risk of iatrogenic POI and already attempted pregnancy remains limited. Rates of return have been calculated to be around 7% in cancer patients according to recent publications [75]. Nevertheless, some data on clinical outcomes, such as live birth rates and cumulative live birth rates, can be extrapolated from patients undergoing elective oocyte cryopreservation for age-related fertility decline, and these show a strong correlation between the aforementioned clinical outcomes and the age at the time of oocyte cryopreservation (Fig. 4). Even in the presence of the same number of oocytes, there is a significantly higher likelihood of live birth in women under 35 years of age [76,77]. In patients undergoing oocyte cryopreservation for oncological reasons, on the other hand, while ongoing pregnancy rates and live birth rates were found to be similar to those encountered with age-related fertility decline, cumulative live birth rates were significantly lower, particularly in the group aged under 35 years (Fig. 5) [75]. This is due to the limited number of oocytes retrieved from cancer patients unable to delay their oncological treatment and repeat the oocyte retrieval procedure to recover more.

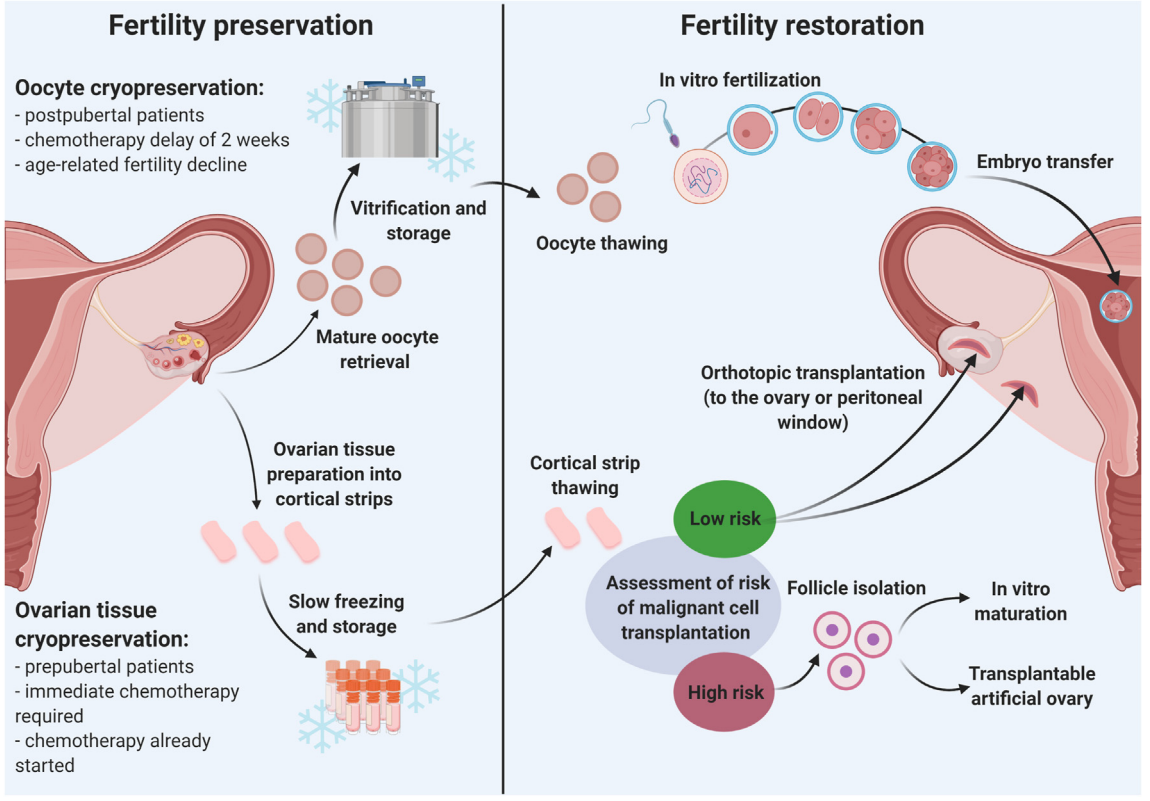

Fig. 3. Cryopreservation by vitrification of mature oocytes after controlled ovarian stimulation in patients of postpubertal age, subjects in whom chemotherapy can be postponed for approximately 2 weeks, or those in a fertility preservation program for age-related fertility decline. After thawing, in vitro fertilization to obtain embryos for transfer to the uterine cavity.

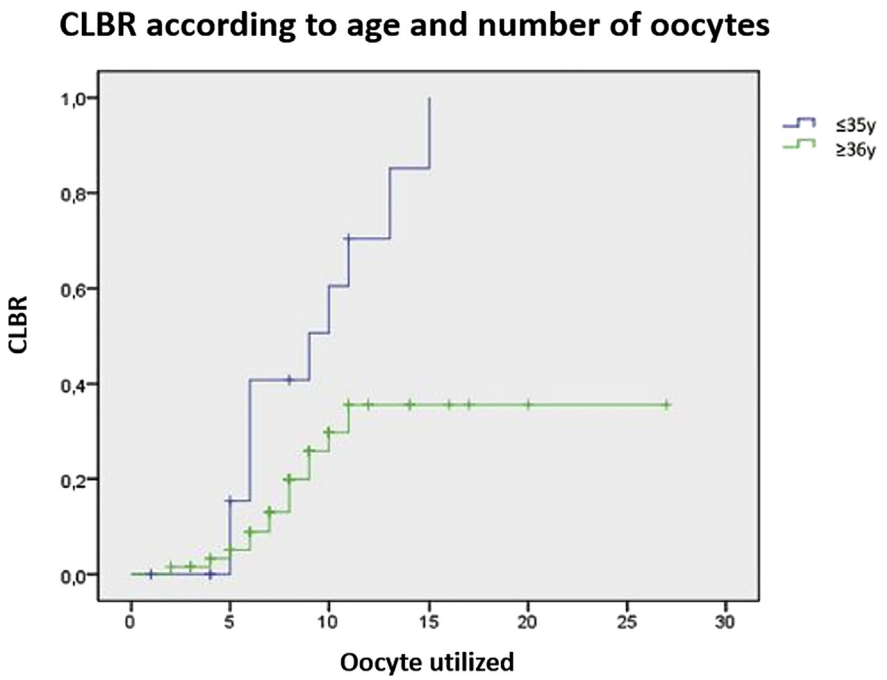

Fig. 4. Kaplan-Meier plotting of CLBR according to the total number of used oocytes and patient age at cryopreservation (<35 years in green, >36 years in blue). Adapted from Cobo et al., 2016 [73]. CLBR: cumulative live birth rate.

Oocyte vitrification for fertility preservation in patients with endometriosis has higher return rates (around 46%), suggesting the suitability of this strategy to enhance the chances of pregnancy in these women [78]. In this case, fewer oocytes are retrieved per patient on average, confirming a detrimental effect of this disease on the ovarian reserve. The probability of a live birth appears to be related to both age at cryopreservation and previous ovarian surgery [78]. The latter has a negative impact on cumulative live birth rates, especially in patients under 35 years of age, since it limits the number of oocytes that can be recovered and used to attempt pregnancy [72].

Oocyte cryopreservation looks to be a valid option for women at high risk of iatrogenic POI, especially for patients with malignancies or endometriosis. The main determinant of success appears to be the age at cryopreservation, so particular attention should be paid to patients <35 years of age with medical conditions threatening their fertility. The other determinant is the number of retrieved oocytes, with an ideal range of 10–15. This latter element may be a limiting factor for cancer patients, who need to start life-saving gonadotoxic treatments without delay.

Ovarian tissue cryopreservation

Prepubertal girls at high risk of iatrogenic POI and women who cannot postpone the start of their gonadotoxic treatment or have already begun may preserve their fertility through OTC. The majority of centers slow-freeze multiple ovarian biopsies obtained by laparoscopy since this protocol has yielded almost all live births after reimplantation so far [31]. Ovarian fragments are transplanted back to the pelvis (orthotopic graft to the medulla of the ovary or a specially created peritoneal window) by laparoscopy or minilaparotomy [14]. Recent data show that pregnancy and live birth rates after

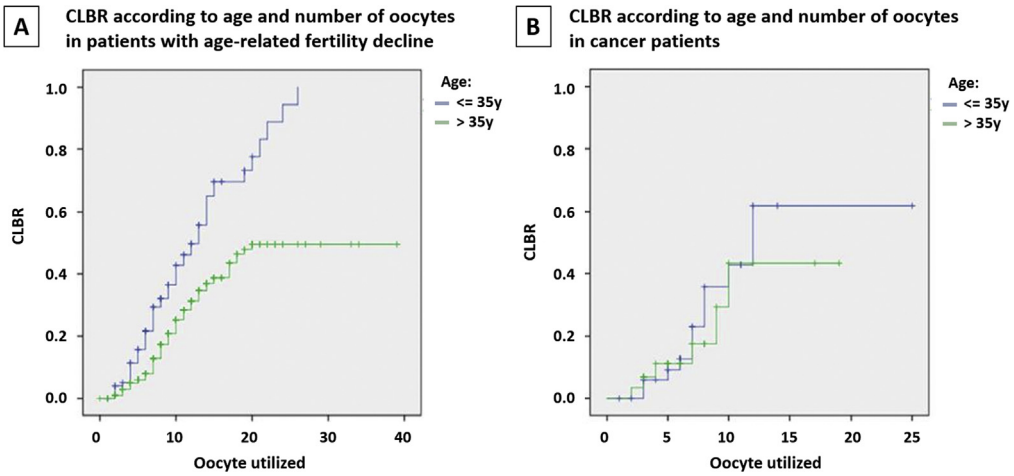

Fig. 5. Kaplan-Meier plotting of CLBR in patients who have undergone oocyte cryopreservation for age-related fertility decline (A) and oncological reasons (B), according to the total number of used oocytes and patient age at vitrification (<35 years in green, >36 years in blue). Adapted from Cobo et al., 2018 [72]. CLBR: cumulative live birth rates.

transplantation are around 30%, and are strongly associated with age at the time of OTC, but tend to be lower when conception is achieved by in vitro fertilization (IVF). Miscarriage rates also appear to be higher in subjects undergoing IVF. This may well be due to the ovarian stockpile in transplanted ovarian tissue being quantitatively diminished and is therefore related to high empty follicle rates of around 30% [14,79], with responses to controlled ovarian stimulation of mature oocytes similar to poor responder patients [14,80]. However limited, the grafted follicle pool is composed mainly of primordial follicles that are less sensitive to cryoinjury and thus able to survive cryopreservation, thawing, and transplantation that ensures long periods of endocrine activity after transplantation [14]. Ovarian function longevity depends on patient age and ovarian reserve at the time of OTC. With the option of transplanting some fragments of frozen-thawed ovarian cortex in the course of different procedures and therefore over repeated transplantations, it yields an average ovarian lifespan of 4–5 years, with around 55% of patients experiencing ovarian activity for more than five years (Fig. 6) [14]. OTC followed by transplantation represents a clear advantage over oocyte cryopreservation, since it allows spontaneous and multiple pregnancies and can replace HRT for long periods.

Chronic hypoestrogenism and hormone replacement therapy

Chronic lack of estrogens contributes to numerous changes in the body, resulting in increased morbidity and mortality [6,7]. Since estrogen production protects the coronary arteries by limiting atherosclerosis, hypoestrogenism, particularly in women under 40 years of age, is associated with a greater risk of adverse cardiovascular events [81]. Increased bone resorption is also a consequence of chronic hypoestrogenism, leading first to osteopenia, encountered in up to 25% of patients with POI, and then osteoporosis, with elevated morbidity rates due to a greater risk of bone fracture [82]. Estrogens also appear to exert a neuroprotective effect on the brain. Women with POI seem to be at increased risk of neurological disorders, including Parkinson's disease [83] and dementia [84]. Moreover, some physiological and cognitive symptoms related to a depressive mood may be exacerbated by menopausal symptoms like repeated hot flushes, sexual dysfunction, and diminished quality of sleep [85,86].

HRT is beneficial for the prevention of menopause-related sequelae, decreasing mortality and enhancing the quality of life, especially in the case of POI [87]. There are various HRT formulations containing estrogens combined with progesterone. Estrogens can be administered continuously without progesterone if the uterus is absent or has been removed [88]. The choice of drug preparation

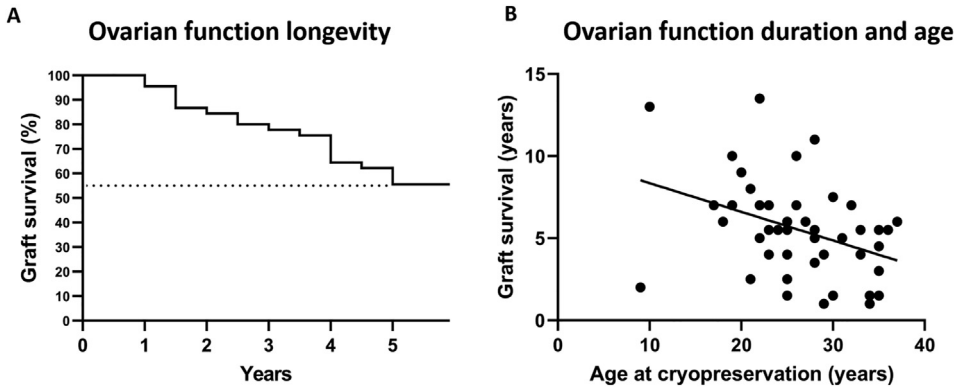

Fig. 6. (A) Ovarian function longevity in a subgroup of 45 subjects transplanted more than 5 years ago, with complete hormone follow-up calculated over time using the Kaplan-Meier plot. (B) A negative correlation was seen between ovarian function duration and increasing age in the same subgroup of patients ($y = -0.174x + 10.1$; $p = 0.009$; $R^2 = 0.146$). Adapted from Dolmans et al., 2021 [13].

(in the form of a transdermal patch, transdermal gel, oral tablets, or a vaginal ring) depends on the clinical situation and personal preference. Transdermal estrogen administration appears to have a safer risk profile for adverse cardiovascular events [89].

A long ovarian tissue lifespan after transplantation may also do their job of HRT, providing both estrogen and progesterone secretion [90]. Restoration of natural endocrine function could prevent chronic hypoestrogenism sequelae, such as osteoporosis and cardiovascular events [87]. Although extending natural endocrine function after physiological menopause may not yet be considered an indication for OTC, women with ovarian tissue already frozen should be given this option [90]. Continued dissemination of this application in the near future may settle some existing doubts about the appropriateness and safety of this clinical approach, like adequate endometrial and breast tissue protection with progesterone production from grafted tissue [91,92]. Both medical and ethical issues need to be addressed before ovarian tissue transplantation is considered an established alternative to HRT [87,93].

Conclusions

Growing survival rates after experiencing cancer at a young age have been the major catalyst in recent decades for the development of new therapeutic strategies to address the long-term consequences of oncological treatments. The risk of iatrogenic POI, with subsequent infertility and a significant decline in quality of life, is one of the main concerns of young female patients undergoing gonadotoxic therapy for malignant or benign conditions requiring these drugs. Counseling on fertility preservation options like oocyte freezing or OTC with oncologists and fertility experts is now considered one of the key elements in POI clinical management. Recent publications on clinical outcomes in terms of pregnancy rates and endocrine restoration are increasingly demonstrating that these approaches are not only effective for restoring fertility in young POI patients but may also prove beneficial for alleviating menopausal symptoms over time.

Summary

Premature ovarian insufficiency (POI) may occur as a consequence of iatrogenic damage (chemotherapy, radiotherapy, or ovarian surgery). The risk varies from patient to patient according to age, the existing ovarian reserve, and the type of treatment required. Evaluation of anti-Müllerian hormone levels has proved helpful to assess the ovarian failure and/or resumption after gonadotoxic therapy. Women at high risk of iatrogenic POI need to be directed to a fertility preservation program, which may

either involve oocyte vitrification (adult patients and those who can safely delay cancer treatment) or ovarian tissue cryopreservation (prepubertal patients or if immediate chemotherapy is imperative). Both techniques are effective in restoring fertility by encouraging live birth rates. However, ovarian tissue transplantation also has the advantage of ensuring endocrine resumption, hence contributing to the alleviation of postmenopausal symptoms to enhance the quality of life and improve survival in POI patients.

Surgical removal and cryopreservation of ovarian tissue by slow-freezing in patients of prepubertal age, subjects requiring immediate chemotherapy, or those who have already started chemotherapy. After thawing, if there is no risk of malignant cell transmission, the tissue can be grafted back to the pelvis (ovary or peritoneal window). If there is a risk of malignant cell transmission, ovarian follicles can be isolated and either grown in vitro to obtain mature eggs or used to create a transplantable artificial ovary. Figure created in BioRender.com, adapted from Dolmans et al., 2021 [13].

Practice points

- A multidisciplinary approach should be offered to patients at risk of iatrogenic POI at the earliest opportunity, in order to discuss their fertility preservation options.
- Mature oocyte vitrification is a valid alternative for postpubertal patients and those who can delay their gonadotoxic treatment at no added risk.
- Cumulative live birth rates using cryopreserved oocytes for oncological reasons depend on age at cryopreservation and the number of oocytes, which may be limited by the need to start gonadotoxic treatment.
- Ovarian tissue cryopreservation and further transplantation is a legitimate option in prepubertal patients when immediate chemotherapy is required or has already started.
- Grafted tissue ensures long-term endocrine resumption and fertility restoration, with the best live birth rates achieved by spontaneous conception, compared to outcomes after in vitro fertilization.
- The qual of hormone replacement therapy is to alleviate menopausal symptoms and reduce the long-term consequences of chronic hypoestrogenism and should be continued until the age of natural menopause.

Research agenda

- The mechanisms of damage to the primordial follicle pool in the ovaries need to be investigated in the near future to develop novel chemotherapeutic drugs and appropriate combinations.
- New potential strategies to protect the ovarian reserve from gonadotoxic therapy should be explored and attempted.
- Ovarian tissue endocrine resumption may be studied further as a potential long-term hormone replacement strategy.

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Declaration of competing interest

The authors have no conflicts of interest.

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