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Mini-review

Oncofertility: What can we do from bench to bedside?

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ABSTRACT

Continuous improvement in diagnosis and treatment has significantly increased the survival of cancer patients. Treatments for neoplastic disease, including radiotherapy, chemotherapy, and surgery or combined therapy with the above methods, may lead to premature ovarian insufficiency (POI) or substantial male germ cell loss. For the patients it is a seriously double whammy. Therefore, reproductive medicine experts strongly suggest that all young patients diagnosed with a malignant tumor should immediately undergo a consultation with suggestions for fertility and endocrine function protection and preservation. Here, we discuss the background knowledge, methods, indications, pros and cons, and experimental and clinical applications of fertility preservation, and new strategies for future fertility conservation to help physicians, especially oncologist, pediatrician, hematologist, and surgeons, become aware of the concepts, methods, and importance of fertility and endocrine function protection. We also hope to help doctors develop novel personalized strategies for fertility conservation according to patients' own conditions, tumor types, treatment methods, recurrence rate and so on. This review focuses on changing and enhancing the fertility preservation idea, further investigations in clinical and translational medicine will help ensure the development of novel personalized treatments, to help cancer patients have healthy children or maintain endocrine function once they are in remission. This is just the ultimate dream of oncofertility.

1. Introduction

Over the past two decades, advances in cancer treatment have markedly improved patient survival rates. In England and Wales, the 5-year survival rate for many common cancers is now > 70% [1], and the 5-year survival rate for breast cancer patients in China is up to 90% [2]. Over the past 5 years, the rates of cancer death among women have decreased > 1.6% per year [3–5]. Though these increases in patient survival are remarkable, the surgery, chemotherapy, and radiation used to treat patients can cause premature ovarian failure [6] or reduced ovarian reserve [1,7] in some circumstances [8], and substantial germ cell loss in males. Oocytes are extremely sensitive to radiation, with a dose < 2 Gy killing roughly half of the primordial follicles [9,10], and 5–10 Gy being directly toxic to oocytes, especially with exposure to high doses of alkylating agents and abdominal irradiation. Thus, these treatments can deplete the follicular pool, resulting in 70%–100% of patients suffering premature ovarian dysfunction, and a 20-time increased risk of early menopause [11,12]. Similarly, cancer treatment can compromise male fertility, especially exposure to alkylating agents and whole body irradiation, which causes substantial germ cell loss [13].

Loss of reproductive potential after cancer treatment, including chemotherapy, radiotherapy, hormonal, medical, and surgical interventions, represents an important issue for a patient's well-being and negatively affects quality of life in young survivors [11,12]. The impact of different cancer treatments on men and women's subsequent fecundability has not yet been measured accurately, but it is undoubtedly significant. This population of primordial follicles can vary greatly from one woman to the next [14], and the probability that premature ovarian insufficiency will develop after chemotherapy or radiotherapy is related to the ovarian reserve. Other factors affect gonadal function in men with cancer, but cancer treatment protocols have long-term health consequences, including toxic gonadal effects.

Approximately 50% of women and men of reproductive age who are diagnosed with a malignancy will undergo fertility-compromising treatment [15]. The long-term survival rates of young women and men

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with cancer have been enhanced, and advances in cryobiology and reproductive medicine have culminated in an increased interest in FP methods in women and men with cancer, and the number of women and men who could benefit from FP is gradually increasing. Many cancers are considered curable, and quality of life after cancer now needs to be improved [16]. As such, FP has emerged as a new discipline within reproductive medicine that aims to increase chances for future parenthood in the case of fertility-threatening circumstances [17].

The current problem is that patients do not understand fertility protection and preservation methods. Many physicians, especially those in oncology, pediatrics, and hematology, as well as breast surgeons, are also not fully aware of the concepts and methods for protecting fertility and endocrine function, and may even have the mistaken idea of saving life first, then considering fertility. Even some doctors who know about fertility protection and preservation are not sure how to operate. Therefore, the protection and preservation of fertility in patients with malignant tumors is receiving more and more attention worldwide. International fertility protection experts strongly suggest that all young cancer patients immediately receive a doctor's advice on fertility protection and preservation when diagnosed with a malignant tumor.

In this review, we describe fertility preservation strategies that apply to different patients based on differences in sex, age, and cancer stage (Fig. 1).

2. FP counseling

According to informants with many patients, oncologists do not currently regard fertility preservation as a priority and do not discuss fertility preservation options with their patients or refer them to a fertility specialist. Patients who request fertility preservation are mostly self-referred [18]. Andrologist said that, sometimes, oncologists are not comfortable talking about fertility preservation, so they shy away from bringing it up [18].

All women and men with cancer who wish to retain fertility options are entitled to a consultation, during which they are informed that there is a risk that first-line treatment will compromise their fertility. However, because of the emotional shock of the cancer diagnosis, as well as multiple investigations and procedures and the fact that health care workers do not have knowledge about how cancer treatments can impact fertility or the options to preserve fertility in cancer patients, only a relatively small proportion of cancer patients ultimately discuss FP options with a specialist prior to undergoing cancer treatment [8,14]. Optimizing FP after cancer treatment faces a complex process and huge challenges, such as assessing fertility risk and selecting an individualized strategy. Therefore, specialists in FP and oncology, other health-care workers, and the patient must cooperate [19]. Not only gynecologists, but also pediatricians and oncologists need to know when to refer patients for possible FP [10].

Although the type of cancer and diagnosis are the greatest predictors of fertility preservation counseling (FPC), disparities are evident in the counseling of cancer patients for FP treatment. Research on FPC of young female cancer patients has also revealed that equality in counseling female patients for FP treatment is imperative to reduce the risk of emotional harm and future infertility [20]. A retrospective investigation and analysis of experiences with FPC revealed that 83 patients experienced FPC with a specialist in reproductive medicine and subsequent decision-making on FP. These patients generally had positive experiences with FPC [21], but negative experiences were associated with decisional conflict and decision regret (not enough time for counseling). The survey found that patient decisions are more objective after a long and in-depth consultation. Crawshaw [22] stated that fertility-related social concerns adversely affect the well-being of men facing cancer treatment and proposed discussing these matters at every stage of fertility preservation in a study of male cancer survivors. Furthermore, Macfarlane et al. [23] suggested that young men who are diagnosed with cancer should be offered counseling on fertility by professionals who feel comfortable talking about the subject.

Most scholars believe that many cancer patients can safely and effectively participate in FP, such as egg or embryo cryopreservation, before undergoing gonadotoxic radiation and chemotherapy [24–27]. Some questionnaires have found that, despite the safety of FP treatment, fewer than half of women pursue treatment [28–30], and this decision may lead to regret [31–33]. Feelings of regret may be lessened for those who engage in decision-making after receiving FPC from their oncologist and a fertility specialist [13]. Fertility protection experts strongly suggest that all young cancer patients immediately receive a doctor's advice on fertility protection and preservation when diagnosed with a malignant tumor.

Our goal is to raise awareness that FPC care and spermatogenesis is important, and that interventions should be developed to help patients make wise decisions about FP [34]. Patients need to gain a better understanding of FP and be supported in decision-making [34]. Being made aware of the risk of infertility is an essential first step in safeguarding future fertility; therefore, more educational initiatives are needed to spread knowledge about oncofertility [4].

3. Strategies for fertility preservation in females

3.1. Strategies for ovary preservation

There are three key reasons why FP is an important facet of reproductive medicine. First, advances in early diagnosis and new treatments have greatly increased long-term survival rates for childbearing patients with cancer, and FP is the only option for patients with cancer hoping to conserve their fertility. Second, FP at a young age could reduce the risk of fertility loss later in later when dealing with the consequences of socioeconomic forces; FP is attractive for healthy couples who wish to postpone childbearing. Finally, FP can do a great service to reproductive medicine by developing new techniques, such as pluripotent stem cells, with the hope of restoring lost fertility in various diseases.

Although FP has potential value for individuals suffering from cancer, a personalized preservation scheme that takes into account age, marital status, status of the illness, classification of the patient's tumor, genetic considerations, and other relevant factors is needed. Several FP options are currently available to women with cancer, and these women are able to conceive after recovery (e.g., cryopreservation of the embryo, oocytes, and ovarian tissue; drug inhibition of ovarian follicle development; and ovarian transposition surgery). Of the current approaches, embryo and mature oocyte cryopreservation are routine reproductive clinical practice, and ovarian transposition is indicated in women undergoing pelvic irradiation. Ovarian tissue cryopreservation is now supported by sufficient evidence and no longer an experimental or investigational method [35–37]. Over the next 5 years, FP will be a major challenge in the context of treating cancer or benign diseases, or for social reasons [38].

3.1.1. Oocyte in-vitro maturation

Although the cryopreservation of in-vitro matured oocytes is still an experimental approach, it is chosen by an increasing number of prepubertal girls who cannot undergo ovarian stimulation and women who need chemotherapy soon after diagnosis. This technique is suitable for both prepubertal girls and reproductive-age women. In addition, it does not require hormone stimulation and does not have the risk of re-exposure to cancer cells after transplantation. Antral follicles are observed on ultrasound in most prepubertal girls. We can record several small antral follicles on a random day and obtain them through transvaginal aspiration. These follicles form the oocyte pool for FP. However, we cannot tell which of the retrieved immature oocytes are able to develop continually. Investigations suggest lower pregnancy rates after in-vitro maturation than conventional assisted reproductive technology [39]. Thus far, the in-vitro maturation of oocytes in a fresh cycle has

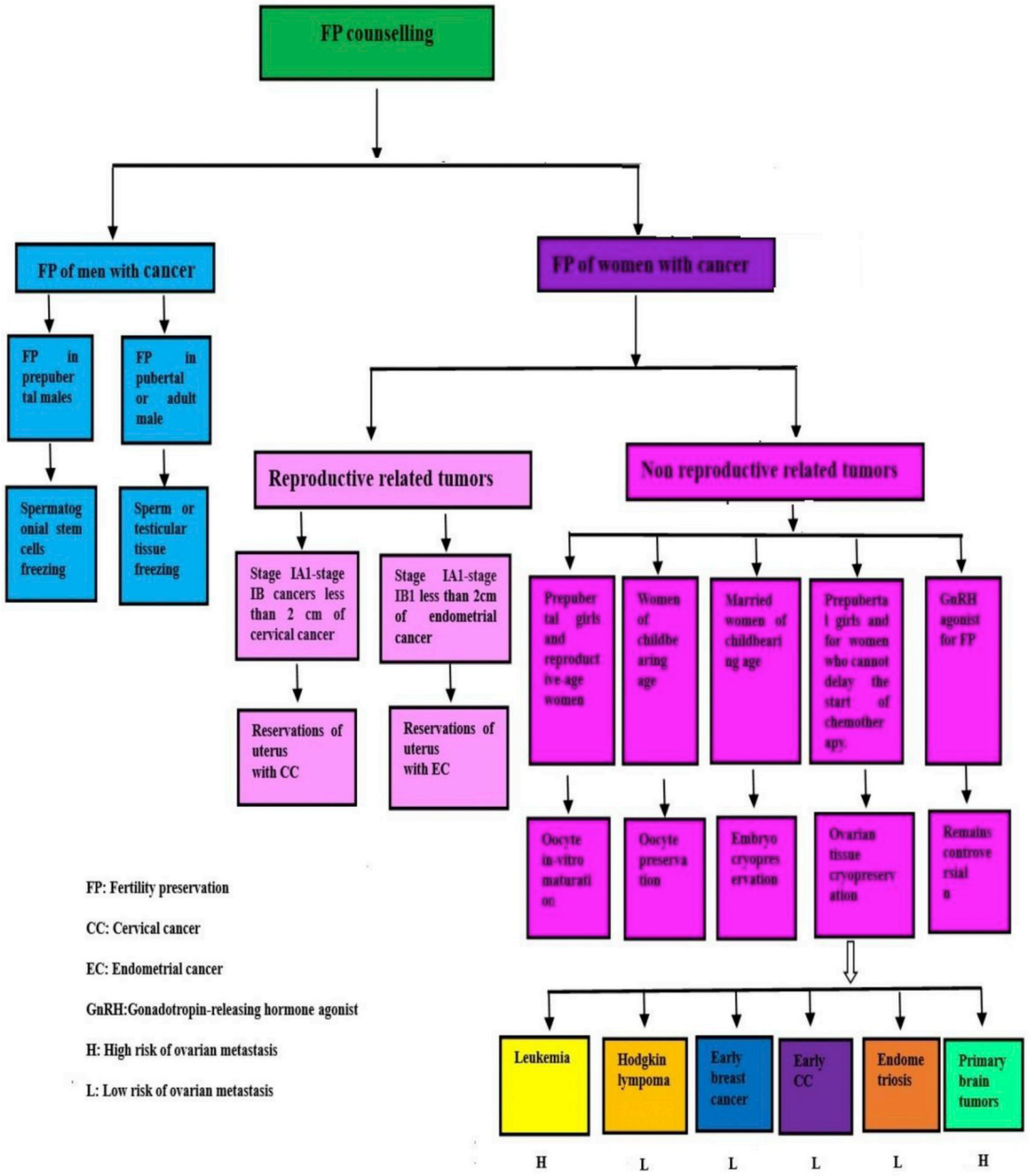

Fig. 1. Recommended fertility preservation approaches in patients with cancer.

contributed to the birth of over 2000 children. However, when this technique was used in cryopreserved and thawed cases, few live births were achieved [19].

Culturing human follicles in vitro is difficult, as extended culture duration and a stricter culture environment are required compared to the follicles of other species. Several in vitro follicle culture systems have successfully supported the growth and maturation of ovarian follicles in mice and several large mammalian species [19]. However, translation of this work to humans has been challenging, and in vitro growth and development of meiotically competent human oocytes from preantral follicles has not yet been achieved [40]. Shuo Xiao has shown that in vitro human follicle growth and oocyte maturation requires a 'dynamic environment'. This study attempted to find a two-step follicle culture strategy to generalize the dynamic environment favoring human follicle growth in vitro while supporting the maturation of follicles and oocytes. Follicles were grown from the preantral to antral stage using a two-step culture strategy, and for the first time meiotically competent MII oocytes were produced [41].

Continued progress has been made in follicle culture protocols for high-quality and competent oocytes. This will be a future option for young women and girls in need of FP [41].

3.1.2. Oocyte preservation

Oocyte cryopreservation is the most widely used technique in the world for the protection of fertility, including benign disease and delayed childbirth [42,43]. However, both embryo freezing and egg freezing require superovulation. For patients with malignant tumors, chemotherapy needs to be delayed for at least 10–12 days [44,45], and the patient must be a woman who has gone through puberty [8,13,17]. Some patients with hormone-sensitive malignancies are unable to undergo superovulation, but information on oocyte quality in women with cancer is lacking because the priority for such women is achieving complete disease remission, and because the option of collecting oocytes for vitrification is relatively new. Among women with cancer, the cumulative live-birth rate after vitrification of oocytes is 34%, 31% probably because of inferior oocyte quality in women affected by the

disease [8,46]. However, for women of advanced childbearing age who do not yet wish to conceive, this technique may be used to extend their fertility potential due to the age-related decline in oocyte quality [42].

Vitrification is more efficient in avoiding crystallization than slow-freezing. Therefore, cells suffer reduced damage caused by the formation of ice crystals and chilling injury during the freezing process [47,48]. Two reviews concluded that lower survival rates are achieved after slow-freezing mature oocytes than vitrification, which suggests impaired embryo development after fertilization [49]. Data from a recent review suggest that the strategy of oocyte vitrification and warming is superior to slow-freezing and thawing in terms of clinical outcomes. Direct contact with liquid nitrogen is controversial, but open systems of vitrification seem to be more efficient than currently available closed systems of slow-freezing, at least for oocytes [49]. Moreover, compared to natural conception, the incidence of congenital anomalies in born children was not different after oocyte cryopreservation [50]. Studies of oocyte vitrification in egg donation programs have shown that outcomes are promising, but this cannot be extrapolated to outcomes after treatment for cancer. If chemotherapy can be delayed, oocyte vitrification should be proposed, but further studies are needed to confirm this recommendation in egg donation programs [10,11].

The efficacy of FPA could be improved by combining the cryopreservation of oocyte and ovarian tissue [51], but it is difficult and inefficient to cryopreserve ovarian tissue on oocyte-retrieval day. This strategy of combining the cryopreservation of oocyte and ovarian tissue has led to zero live births in patients with cancer and needs to be studied further [10,11].

3.1.3. Embryo cryopreservation

Embryo cryopreservation has been carried out for more than 30 years and has reliable success rates. Randomized controlled trials evaluating the effect of cryopreservation on the health of children who are born from the technique are lacking, but outcome data on health status after frozen embryo transfer are reassuring [52]. Embryo cryopreservation has been proven to be a safe and effective technology for patients undergoing IVF-ET treatment. It is a well-established procedure for FP in women with an available partner. Because a male partner or use of donor sperm is required, this leads to ethical and legal concerns. For example, what to do with orphan embryos if the patient dies or the couple divorces [53].

Currently, embryo cryopreservation methods mainly include slow-freezing and vitrification techniques. Vitrification is a fast-freezing technique using vitrified frozen reagent and storage directly in liquid nitrogen (−196 ˚C) [54,55]. The slow-freezing method is controlled by a computer program. The ovarian tissue is cooled to −140 ˚C according to the set rate and stage, and then stored in liquid nitrogen. Controlled-rate freezers and large quantities of liquid nitrogen are required for this freezing procedure. With the development of cryopreservation techniques, slow freezing has gradually been replaced by vitrification, which provides good results when used by experienced specialists. Vitrification is increasingly popular and regarded as a simpler and less expensive alternative in more and more reproductive centers [56,57].

Despite the increasing success rates for oocyte vitrification, more scholars think that embryo cryopreservation should be provided as an important approach in FP, as it seems to achieve better clinical results than other methods [5,58,59]. In addition, frozen embryos are the joint property of the couple in most countries, and problems may occur when they are used in the future [10,11].

3.1.4. Ovarian tissue cryopreservation

Due to radiation scattering in pelvic radiotherapy and the ovary being extremely sensitive to radiation, more and more clinical practice and studies have shown that traditional ovarian transposition has a limited protective effect on the ovaries, and the pelvic cavity provides the optimal environment for follicular development compared to heterotopic sites; temperature, pressure, paracrine factors, and blood supply are more similar to those observed in a physiological situation.

Ovarian tissue cryopreservation and transplantation is not part of the conventional in vitro fertilization (IVF) technique [60]. After successful ovarian transplantation, the patients not only have restored reproduction ability, but also restored ovarian endocrine function. The extraction of multiple ovarian tissues from one side of the ovary may not affect hormone production [61]. However, cryopreservation of ovarian tissue is the only FP option available for prepubertal girls and women who cannot delay the start of chemotherapy. Currently, there is no uniform standard for ovarian tissue cryopreservation, but the commonly used standards include the Edinburgh selection criteria [62] and FertiPROTEKT network [63]. A more unified view of the important screening index is that the patient has a certain ovarian reserve, the prognosis of the primary disease is good, and the risk of POI is high [62]. Recently, the first Expert Consensus on Ovarian Tissue Cryopreservation and Transplantation was established in China according to agreement between gynecologists, embryologists, oncologists, pediatricians, breastologists, and hematologists, among others, regarding the selection criteria and major indications. The selection criteria established by this consensus are age < 35 years with good ovarian reserve function, good prognosis of the primary disease, and high POI risk due to the primary disease and treatment. The age limit can be relaxed according to the status of the ovarian reserve and individual willingness. In addition, ovarian malignancy or ovary metastasis must be excluded in patients with tumors, and patients with high risk of metastasis should be selected carefully (Table 1). All patients must tolerate laparoscopic or open ovarian tissue biopsy, and the procedure must be performed at least 3 days before chemotherapy with informed consent from the patient or her guardian. The main indication established in the consensus [10] is ovarian tissue cryopreservation for the protection of fertility and ovarian endocrine function in patients with tumor and non-tumor diseases, primarily in pre-pubertal patients, patients who are unable to delay chemoradiotherapy, and patients with hormone-sensitive tumors [65,66].

Even though pregnancies achieved using frozen ovarian tissue from adult women have been reported worldwide, the technique remains experimental because the overall total number of live births is relatively low and the effectiveness and safety of the technique in everyday clinical practice uncertain [66]. The first pregnancy to occur with this procedure was reported in 2004 [67] and the second in 2005 [68]. The pregnancy and live birth rates have continued to climb steadily, increasing exponentially. Taking into account the latest published series [79–74], the number of live births as of June 2017 exceeded 130. Thus,

Table 1
The risk of ovarian metastasis in different types of malignant tumor [9].

High risk (> 11%)	Medium risk (0.2–11%)	Low risk (< 0.2%)
leukemia	Breast cancer stage IV, invasive lobular carcinoma	Breast cancer stage I ~ II, invasive ductal carcinoma
Neuroblastoma	Colon cancer	Cervical squamous cell carcinoma
Burkitt's lymphoma	Cervical adenocarcinoma	Hodgkin's lymphoma
	Non-hodgkin's lymphoma	Bone cancer
	Juve sarcoma	Non-genital rhabdomyosarcoma
		nephroblastoma

it may move toward broader clinical implementation with the use of strict selection criteria [75].

Among the numerous factors influencing ovarian graft longevity, ovarian reserve and absence of chemotherapy before cryopreservation are the most important [81]. After transplantation of ovarian tissue, the number of primordial follicles decreases over 50%. Ovarian tissue ischemia is the main factor after transplantation while awaiting angiogenesis [76]; it takes 4–5 days to reoxygenate the graft. During this time, follicles decline and granulosa cells dysregulate communication with the oocyte [77]. Some drugs could reduce ischemia and oxidative stress by stimulating revascularization of the graft or inhibiting hormones that normally operate in an intact ovary [8].

However, despite these concerns, ovarian cortex freezing is highly recommended in girls who are scheduled for chemotherapy and at high risk of complete depletion of the ovarian reserve after the end of treatment [69].

3.1.4.1. Vitrification or slow-freezing of ovarian tissue. Treatment and freezing of ovarian tissue must be carried out in laboratories that meet stringent standards. When ovarian tissue is processed, a sterile scalpel and tweezers are used to carefully remove the medulla and preserve an intact cortex. After processing, the thickness of the ovarian tissue is approximately 1 mm, and the size of each piece of tissue is roughly 4 mm × 8 mm. The processed ovarian tissue slices are placed in the cryoprotectant for precooling balance, and then in a frozen storage tube containing cryoprotectant for cryopreservation.

The freezing method is divided into slow-freezing and vitrification. Vitrification is a fast-freezing technique using vitrified frozen reagent and storage directly in liquid nitrogen (−196 °C) [50,51]. The slow-freezing method is controlled by a computer program. The ovarian tissue is cooled to −140 °C according to the set rate and stage, and then stored in liquid nitrogen. Currently, of the more than 130 healthy children born from ovarian tissue cryopreservation technology, only 2 were born using the vitrification freezing technique [78].

In the past decade, vitrification has been used increasingly for the cryopreservation of embryos and oocytes instead of slow programmed freezing. Compared to slow-freezing, vitrification improves the preservation of ovarian follicular and stromal structures [36] and increases follicle survival rates [79,80]. Therefore, the function of ovarian tissue should be better preserved after transplantation.

However, vitrification requires high concentrations of cryoprotectant chemicals and an ultra-rapid cooling rate, which requires direct contact with liquid nitrogen. This leads to concerns about the safety of this method. The efficiency of vitrification and slow freezing of ovarian tissue need to be investigated in prospective randomized trials using healthy live birth rates as an endpoint [19].

As far as the freezing procedure is concerned, there is no evidence that vitrification of ovarian tissue is superior to slow-freezing, as vitrification has resulted in only two live births thus far [19,78].

3.1.4.2. Ovarian transposition. The application of ovarian tissue transplantation technology has resulted in more than 130 live births worldwide [10], which indicates that ovarian tissue cryopreservation and transplantation is an effective method for preserving female fertility and endocrine function. Interestingly, distant heterotopic sites, such as the abdominal wall, forearm, or breast, have been reported to be a better place for transplantation than the ovarian medulla, ovarian fossa, or broad ligament. Consistent endocrine function and embryo development has been reported after heterotopic transplantation. However, only three pregnancies have been achieved using oocytes retrieved after heterotopic transplantation [76,81].

There are no unified international guidelines to limit the time of cryopreserved ovarian tissue transplantation, as it is based on the patients' primary diseases and their clinical rehabilitation. After full communication with the patient and oncologist, individualized treatment is applied. The timing of transplantation should take into account at least the following. Generally, the primary disease is relieved and the recurrence rate low, the function of the remaining ovarian tissue in the patient has been exhausted, and the patient has the symptoms of menopause, such as hot flashes and sweating. Blood levels of follicle-stimulating hormone (FSH) is > 25 IU/L and anti-Mullerian hormone (AMH) < 1.1 ng/mL. Transplantation should occur at least 3–6 months after radiotherapy and chemotherapy. The patient has the intention of fertility or the desire to restore ovarian endocrine function and the patient's physical condition allows laparoscopic surgery. After comprehensive assessment, the patient is in good condition and allows laparoscopic ovarian retransplantation.

Restoration of ovarian activity occurs 3.5–6.5 months after grafting [35], which is consistent with follicle growth from the primordial to the antral stage. Although some variations have been observed that are attributable mainly to differences in the follicular reserve at the time of cryopreservation, ovarian activity is restored in more than 95% of cases after reimplantation of ovarian tissue in the pelvic cavity [82,83]. If follicular density is well preserved, the mean duration of ovarian function is 4–5 years after transplantation but can persist until 7 years [35].

Success, which means the survival of the follicle pool within the graft, mainly depends on the ability of the graft to revascularize. Capillaries could develop from the bed of the graft into the tissue within a few days [76]. Mechanical interventions or vasoactive substances that contribute to the development of the vascular bed may improve graft survival and its functionality [19,34]. The survival of preserved follicles increases with improved cryopreservation and grafting techniques, and fewer women with cancer require multiple grafts [19,34].

A systematic review conducted in 2003 reported that laparoscopic ovarian transposition would help preserve ovarian function in 88.6% of cases when used in women < 40 years old [84]. In a study of 107 women with cervical cancer, 104 underwent bilateral ovarian transposition [85], indicating that ovarian transposition is safe and effective. However, the main risk of this method is ovarian failure, which has been reported in cases with external radiation therapy [85]. Chemotherapy would increase this risk [86]. Furthermore, the risk of ovarian involvement should be considered if pelvic malignancy is present. To avoid this risk, we should restrict the use of ovarian transposition to women < 40 years old with low-grade cervical cancer [86].

3.1.4.3. Treatment before and after ovary transplantation. After radiotherapy and chemotherapy, as ovarian function is impaired, patients may appear to have a variety of perimenopausal symptoms, such as hot flashes and insomnia. In the long-term, this can lead to osteoporosis, which will affect the patients' quality of life and long-term health. Before and after ovarian tissue transplantation, some effective traditional Chinese medicine or Chinese patent medicine, such as Kun tai capsule, can be added to relieve the symptoms of menopause and protect ovarian follicle function. For non-hormone-dependent tumors, such as cervical squamous cell carcinoma, sex hormone therapy can be combined with the treatment, with natural estrogen supplemented (oral or percutaneous, 50 μg/week) for 1 week before ovarian transplantation [87]. For patients with a uterus, progesterone is also used for menstruation. Estrogen is contraindicated in patients with hormone-dependent tumors, such as breast cancer, and plant medicine or traditional Chinese medicine without estrogen can be used to relieve symptoms [87].

In recent years, research progress has been made on the protection and improvement of ovarian function by traditional Chinese medicine and Chinese patent medicine. The efficacy and safety of Chinese patent medicine have received widespread attention from the industry. Clinical studies have found that Chinese medicine can relieve the main clinical symptoms of menopausal syndrome in patients, including hot flashes, night sweats, cold feeling, the waist and leg pains, and mood disorders [87]. It will improve and delay the long-term pathological

changes in menopause. Chinese patent medicine widely used to treat menopausal syndrome includes Kun tai capsule, Kun bao pill, and Jiao rong tablet. Kun tai capsule has been shown to improve the microenvironment of follicular development, improving ovarian function and the quality of life [88,89]. Therefore, appropriate medication should be used to treat the patients before and after transplantation of frozen ovarian tissue, according to the clinical syndrome and the combination of syndrome differentiation and disease differentiation. This will protect ovarian function and improve the postmenopausal symptoms of declining ovarian function [87].

3.1.4.4. Risk of reimplanting malignant cells. What scholars are currently most worried about is the risk of reimplanting malignant cells after retransplantation of ovarian tissue. Avoiding reintroduction of malignant cells through the tissue graft in the autotransplantation of cryopreserved ovarian tissue is important. In a recent review including 391 candidates for ovarian tissue cryopreservation [90], metastases in ovarian tissue were observed under light microscopy in 1.3% of all patients with cancer. The risk of reimplanting malignant cells is highest in patients with leukemia. In another study including 422 patients [91], infiltration of malignant cells was detected in 7% of tissue specimens using biochemical and histological methods. Therefore, the key to safe ovarian tissue transplantation lies in detecting and avoiding malignant cells in transplanted ovarian tissue. Ovarian tissue purging and in vitro culture of isolated primordial follicles for transplantation have been used to eliminate cancer cells [92], and researchers are working on artificial ovaries including primordial follicles and stromal elements free from disease [93].

3.1.4.5. Application of ovarian tissue cryopreservation and transplantation in several diseases

3.1.4.5.1. Leukemia. For patients with leukemia, there is no ideal fertility-protection scheme. If hematopoietic stem cell transplantation is needed, ovarian tissue cryopreservation should be considered. Unfortunately, more than half of ovarian tissues in leukemia patients have been found by PCR to contain malignant cells; therefore, the scholars concluded that ovarian retransplantation in these patient is unsafe [90]. However, no malignant cells were observed in ovarian tissues from patients with leukemia in complete remission [94]. As the risk of introducing cancer cells is very high, ovarian tissue transplantation should be carefully considered. Recently, it was reported that, after the application of maximum security measures in patients with leukemia, freeze-thaw ovarian tissue was transplanted back into the patients. The patients experienced restored endocrine function and successfully achieved pregnancy, and there has been no recurrence of malignant tumors. Therefore, the criteria for ovarian tissue cryopreservation and transplantation in leukemia patients should be relaxed [71]. In addition, for high-risk patients, alternative approaches, such as in-vitro maturation of primordial follicles or an artificial ovary, are needed before IVF and other technologies can be used after maturation of primordial follicles in vitro [71].

3.1.4.5.2. Hodgkin lymphoma and non-Hodgkin lymphoma. Currently, the 5-year relative survival rate of Hodgkin's lymphoma in women under 49 years of age is 90%–95%. Several studies in patients with Hodgkin lymphoma have investigated the safety of grafting cryopreserved human ovarian tissue and reported that ovarian tissue transplantation may be safe in these patients [95]. Thus far, patients with Hodgkin lymphoma who have undergone autotransplantation have been followed up for more than 10 years [68]. In a study including 16 Hodgkin lymphoma patients who underwent autotransplantation, zero disease recurrence was observed [96]. The 5-year relative survival rate of non-Hodgkin lymphoma in women under 49 years of age is 80%–85% [2]. After chemotherapy and before hematopoietic stem cell transplantation, the fertility rate was 3%–8% [97]. Transplantation of ovarian tissue without disease recurrence has also been reported in six non-Hodgkin lymphoma survivors [71]. However, cancer cells are detected histologically in 6% of non-Hodgkin lymphoma patients [66]. Immunohistochemical assessment found non-Hodgkin lymphoma cells in the cortex (1/32) and medulla (1/32) of the ovary. This requires further study of the potential risk, though the risk is low [66]. For patients of childbearing age, if malignant tumor treatment can be delayed, embryo cryopreservation or oocyte cryopreservation can be performed. However, most patients with lymphoma require immediate treatment. Therefore, ovarian tissue cryopreservation should be considered as a fertility protection scheme. For pre-pubertal women, ovarian tissue should be frozen and stored if the risk of ovarian failure is very high after treatment of a malignant tumor. Lymphoma is the second largest indication (28%) for European fertility protection network cryopreservation [98]. In addition, for blood system diseases requiring hematopoietic stem cell transplantation, such as aplastic anemia, Mediterranean anemia, and myelodysplastic syndrome, fertility protection should be pursued before ultrahigh doses of chemotherapy.

3.1.4.5.3. Gynecological and breast cancer. China has approximately 272,000 new breast cancer patients every year, and the 5-year tumor-specific survival rate is roughly 90% [99]. Of the Chinese breast cancer cases, the proportion of premenopausal patients is 62.9% [100]. Although more than 50% of the young patients have reproductive needs, the pregnancy rate is less than 5% [101]. The reason for this is closely related to the gonadal toxicity of chemotherapy drugs. Cyclophosphamide has strong reproductive toxicity; it is an alkylating agent used in the adjuvant chemotherapy scheme recommended by all breast cancer diagnosis and treatment guidelines [102]. In addition, 5–10 years of endocrine therapy in breast cancer significantly reduces the recurrence rate and mortality, but significantly affects the fertility of patients [101]. Breast cancer is a good indication for ovarian tissue cryopreservation. There is no need for ovarian stimulation and no delay in chemotherapy. Among the more than 5000 cases of ovarian tissue cryopreservation from the European fertility protection network, the proportion of breast cancer patients is 41% [89]. In two studies of patients with breast cancer, frozen–thawed ovarian tissue was studied by various experimental methods [103], but no evidence was found to support the infiltration of malignant cells in cryopreserved ovarian tissue, histologically or immunohistochemically. Moreover, in patients with early-stage breast cancer, autotransplantation of frozen–thawed ovarian fragments is safe [71]. Therefore, frozen–thawed ovarian tissue transplantation seems to be safe in women with breast cancer, though further investigations are needed to provide more evidence [103].

For breast cancer patients, the ideal interval between diagnosis and pregnancy is unclear. Two major problems with the interval should be considered. The patient is at a lower risk of recurrence and the patient does not require anti-cancer treatment (e.g., 3–6 months after the last drug treatment) [104]. This time should be individualized by analyzing the patient's age, ovarian reserve function, primary treatment and completion time, and the risk of recurrence. For patients on adjuvant endocrine therapy, fully communicating the cancer risk and fertility requirements can allow the patient to carefully choose to get pregnant after at least 2–3 years of endocrine therapy. However, it is strongly recommended that patients be treated with endocrine therapy after giving birth [105].

3.1.4.5.4. Cervical carcinoma. Cervical cancer is the fourth most frequent tumor. The incidence of gynecological tumors in young women is increasing yearly with age. The proportion of cervical cancer patients under 45 years old is 38.5% [105]. More than 40% of women with early cervical cancer are affected during their reproductive years and wish to retain their fertility [106]. Ovarian involvement is more frequent in adenocarcinoma than in squamous cell carcinoma. The metastasis rates are 0.7–2.5% in patients with squamous cell carcinoma, but 6.8% in individuals with cervical adenocarcinoma [107]. The lymph node metastasis rate of early cervical cancer is very low, and conservative surgery aiming for fertility preservation in those desiring future pregnancy is an accepted treatment. On the basis of treatment experience, Rema suggested that conservative surgery with

fertility preservation is possible in early cervical cancer, including micro invasive cancer and stage IB cancers < 2 cm. Stage IA1 cervical cancer is treated effectively by cervical conization. In stage IA2 cancers and stage IB1 cancers < 2 cm, the fertility preservation surgery is radical trachelectomy. Radical trachelectomy removes the cervix, retaining the uterus and adnexa to allow future pregnancy [108]. Pelvic radiotherapy is one of the most important treatment for higher-stage tumors and is not recommended for fertility preservation [109]. In order to reduce the damage to the ovary due to radiation, clinicians often use the ovarian transposition method. However, due to the effect of radiotherapy and reduced blood supply to the displaced ovary, the effect of ovarian transposition is limited. Therefore, for cervical cancer patients who require pelvic radiotherapy, more effective fertility protection methods should be considered together with ovarian transposition, such as ovarian tissue cryopreservation. In the five reported cases of ovarian tissue grafting and transplantation, there have been no instances of cancer recurrence for cervical cancer patients to date [110]. A total of 2777 patients with early-stage cervical cancer were accepted for fertility-sparing surgery, and 944 pregnancies resulted [111]. Because of the widespread use of cervical cytology screening, cervical cancer and precancerous lesions can be detected and treated early, significantly decreasing the incidence and mortality of cervical cancer and protecting the fertility of women of childbearing age.

3.1.4.5.5. Endometriosis. Endometriosis affects up to 10% of women of reproductive age [112]. Ovarian endometriosis cysts may cause ovarian reserve function to decline [113]. In addition, there is increasing evidence that inappropriate ovarian endometriosis cyst excision may damage the ovarian reserve [114]. A recent study compared the results of ovarian biopsies from a healthy ovary and the contralateral ovary in 11 women with an endometrioma < 4 cm in size. A significantly decreased number of follicles was found in the endometrioma group [115]. A recent prospective study compared anti-Mullerian hormone (AMH) and antral follicle count (AFC), confirming that patients with endometriomas had reduced AMH levels, and the AFC in patients with endometriomas > 2 cm was similar to patients of the same age with no ovarian cysts [116].

Surgical management may cause additional damage, with decreasing reserve function and surgical adhesions. A single-center retrospective study of 17 excisions of non-endometriotic cysts averaging 37 mm found that, after excision, the ovarian reserve decreased in volume by 40%, and loss of the follicular reserve increased compared to a healthy ovary [117]. The small prospective cohort study showed a significantly greater decrease in the AMH level after cystectomy for the seven non-endometriotic cysts compared to the removal of 13 endometriomas [118]. Therefore, for endometriosis, attention should be paid to the evaluation of ovarian function before surgery, and the operation must consider fertility protection in the patients, especially unmarried infertile patients. In assisted reproductive technology, although the quantitative response to ovarian stimulation appeared to be lower, the rates of top-quality embryos, pregnancies, and live births per cycle were similar as in normal infertility patients [119]. Therefore, we suggest that long-term infertility patients with ovarian endometriosis cysts and patients who have undergone cystectomy be treated with assisted reproductive technology as soon as possible to have a good pregnancy outcome.

For the endometriosis patients, internal lesions and cyst skin should be avoided lest the tissue preservation be affected, especially in patients with multiple lesions, who may have small undetected lesions that should be carefully screened.

3.1.4.5.6. Primary brain tumors. Advances in the diagnosis and treatment of primary brain tumors have led to significant periods of disease control. Case reports has been published of both men and women who have produced healthy children after treatment with temozolomide and radiotherapy [120,121]. DeAngelis demonstrated that, in 70 patients with primary brain cancer referred for FP counseling, after treatment three men conceived naturally, two men conceived using banked sperm, and two women conceived naturally [122]. However, patients with primary brain tumors have poor prognoses or advanced disease, and initiating PF discussions with patients can be challenging or seem inappropriate to many oncologists [122,123]. In addition, there have been small series and case reports suggesting possible glioma progression during pregnancy [124,125], which may inhibit clinicians from discussing FP with their female patients. Furthermore, many oncologists feel that discussions of FP are inappropriate for patients with advanced disease, poor prognosis, and functional limitations [126,127]. Therefore, the number of primary brain cancer patients receiving FP consultation is very small. Jacqueline thinks that, despite the historically poor prognosis of patients with primary brain tumors, there is significant interest in FP among these patients, particularly if they have no prior children. Clinicians should develop strategies to incorporate FP counseling into practice [122]. Finally, Jacqueline hoped to clarify reproductive outcomes in this patient population in a prospective study to provide further information regarding the feasibility of conception after treatment, effect of conception on brain tumor biology, and the utilization of banked fertility specimens. Having data available on this subject will help clinicians appropriately counsel brain tumor patients, allowing patients to make informed decisions about FP [122].

3.1.5. GnRH agonist for FP

The evidence that gonadotropin-releasing hormone agonist (GnRH) protects female fertility by inhibiting ovarian follicle development is thought to be insufficient [128,129], but GnRH agonists may reduce vaginal bleeding for patients with low platelet levels after undergoing chemotherapy. A meta-analysis of published clinical studies concluded that GnRH analogue co-treatment does not reduce gonadotoxicity [130]. However, in a separate systematic review and meta-analysis, a potential benefit of GnRH agonist co-treatment was suggested in premenopausal women, and pregnancy rates were not found to improve with resumption of menses and ovulation [131]. A later study demonstrated that GnRH agonists are of no benefit when used in patients with breast cancer receiving chemotherapy [132].

Based on these results, the effects of GnRH agonists for FP remain controversial. We cannot rely on GnRH agonists to preserve fertility [28]. Some patients will not achieve complete ovarian suppression for several weeks after using this class of drugs, and some adverse effects are induced, such as hot flashes [129,133].

3.2. Strategies for uterus preservation

Cervical cancer and endometrial cancer are the most common gynecological tumors worldwide, and the incidence rate have been increasing gradually. Cervical cancer is the third most common malignancy affecting women's health and fertility. In China, nearly 130,000 cervical cancer cases are newly diagnosed each year, and approximately 30,000 women die of cervical cancer annually [134]. Endometrial cancer is more common in postmenopausal women than premenopausal women, and approximately 5.5% of cases occur in women younger than 40 years old [135]. In recent years, the incidence of endometrial cancer has increased gradually in young women [136]. Currently, cervical cancer and endometrial cancer are basically treated with radical hysterectomy and radiotherapy. The radiation therapy reduces uterine volume, causes myometrial fibrosis, damage to the endometrium, and decreases uterine vascular perfusion [137]. For young women who have not had children, this is undoubtedly a great blow. Therefore, the early detection and treatment of cervical cancer and endometrial cancer is important. How do we protect the fertility of young women with gynecological tumors? Obstetrics and gynecology experts are continuously studying new treatments. Such improvements in radiotherapy techniques may also result in specific targeting to the site of solid malignancies, which should reduce the chance of damage to

neighboring gonadal tissue [135].

3.2.1. FP in cervical cancer

There is an increasing incidence of early cervical cancer in young patients as a result of screening and early detection. Treatment of cervical cancer by surgery or radiotherapy results in permanent infertility, which affects the quality of life of cancer survivors. With improved survival rates among early cervical cancer patients, conservative surgery to preserve fertility in those desiring future pregnancy is an accepted treatment. The treatment depends mainly on the stage of cancer. According to most international guidelines, the standard treatment for IA2 microscopic tumors is conization [138]. Because the risk of lymph node involvement is very low in patients with stage IA1 tumors, if there is no clinical contraindication, the cone biopsy may represent definitive treatment. For young patients with fertility requirements, conization is a reasonable option for preserving fertility [139]. The standard treatment for IA2 tumors consists of radical hysterectomy with pelvic lymphadenectomy. However, for patients desiring to preserve fertility, cone biopsy or radical trachelectomy with pelvic lymph node dissection with or without para-aortic lymph node sampling may also be considered [140]. In stage IB1 cancers < 2 cm, the fertility preservation surgery is radical trachelectomy. Radical trachelectomy removes the cervix with the medial parametrium and upper 2 cm of the vaginal cuff, retaining the uterus and adnexa to allow future pregnancy. In order to improve the quality of life and fertility requirements of patients of childbearing age with cervical cancer, a large number of clinical studies have suggested adopting conservative treatment to protect the fertility of patients with IA stage cervical cancer [141,142].

Fertility-preserving surgery may be an option for early-stage cervical cancer in patients desiring future pregnancy, but fertility-preserving surgery deviates from the standard of care. Therefore, patients with cancer should be extensively counseled by oncologists and reproductive experts regarding the oncological risks and subsequent pregnancy-related problems [139]. After all, life and health are the most important to patients.

3.2.2. FP in endometrial cancer

Endometrial cancer is the most common gynecological tumor. The main symptom of early endometrial cancer is vaginal bleeding. Thus, it is often detected early and has a better prognosis, with a 5-year survival rate of 85%–91% in stage I patients with endometrial cancer [143]. Atypical endometrial hyperplasia (AEH) is a precancerous lesion, and approximately 29% of AEH cases progress to endometrial cancer within several years [144]. The standard treatment for atypical endometrial hyperplasia or endometrial cancer includes a total hysterectomy with bilateral oophorectomy resulting in total loss of fertility [145]. Endometrial cancer should be staged by careful clinical examination. However, lymph node metastases are relatively rare in early endometrial cancer. The risk of pelvic lymph node metastasis is approximately 8% in stage IA2 endometrial cancer. The incidence of lymph node metastasis increases to 15–20% in stage IB1 tumors. Stage IB1 endometrial cancer with tumors > 2 cm and stage IB2 endometrial cancer are considered to be unsuitable for fertility-sparing surgery because the rate of lymph node metastasis is 30–40% [143]. Therefore, assessment of the nodal status is critical in deciding whether a conservative surgical approach is appropriate for treating endometrial cancer.

However, with the delay of women's marriage age, many elderly patients with endometrial cancer or atypical endometrial hyperplasia do not accept the standard treatment. Instead, conservative treatment using medroxyprogesterone acetate (MPA) is increasingly used as an effective fertility-preserving therapy for early-stage atypical endometrial hyperplasia or endometrial cancer without myometrial invasion or extra-uterine spread. The combination of MPA and progesterone receptors inhibits cancer cell growth, estrogen action [146], and angiogenesis [147]. MPA may also reduce the number of glandular cells and decidualization of the stroma [146,148]. A disadvantage of conservative treatment with MPA is the need for frequent intrauterine surgeries, including dilation, curettage, and endometrial biopsy, which can cause endometritis, endometrial thinning, and intra-uterine adhesion. To assess the clinical outcomes and fertility of young women with stage I low-grade endometrial stromal sarcoma (ESS) treated with fertility-sparing surgery, 17 patients with stage I low-grade ESS were treated with MPA; 5 of 8 (62.5%) patients who attempted pregnancy conceived. Xie recommended that fertility-sparing surgery may be considered for young patients with stage IA low-grade ESS who wish to preserve their fertility [149]. A large number of clinical studies have shown that young women with stage IA endometrial cancer are suitable for fertility-sparing surgery [149–152]. Therefore, patients treated with MPA are advised to try establishing pregnancy early after the treatment.

4. Strategies for fertility preservation in males

Impaired spermatogenesis, testosterone insufficiency, and sexual dysfunction are a common concern and often a source of distress for male survivors of childhood, adolescent, and young adult cancer [153]. Spermatogenesis is highly sensitive to the effects of chemotherapy and irradiation. These conditions can be the direct result of damage to male reproductive organs by cancer-directed therapy [153,154]. Radiation doses > 20 Gy in prepubertal boys and > 30 Gy in pubertal adult males have been associated with hypoandrogenism [155]. In a cohort of 166 survivors of pediatric optic pathway/hypothalamic/suprasellar gliomas, a hypothalamic location and radiotherapy were independently associated with hypogonadotropic hypogonadism [156]. Thus, surgery or radiation can significantly lower the rates of sexual dysfunction. Therefore, the main strategy to minimize germ cell loss is to choose treatment and combinations that have a less severe effect on spermatogenesis. Cryopreservation and the subsequent storage of semen samples is the main option for fertility preservation in men who are undergoing chemotherapy or radiotherapy regimens that may affect gonadal function. The objective is to collect enough sperm for subsequent infertility treatment without delaying chemotherapy or radiotherapy.

4.1. FP in prepubertal males

Currently, there are no proven fertility preservation techniques with cryopreservation of sperm for prepubertal patients not yet producing mature sperm, but we can freeze spermatogonial stem cells to preserve fertility for survivors of childhood cancer [157] via an open testicular biopsy procedure under general anesthesia and cryopreservation of testicular tissue. Spermatogonial transplantation has been successful in animal models, but this approach is still at the experimental stage for humans [158]. Theoretically, as a preventive strategy, prepubertal boys with cancer can opt to undergo a testicular biopsy to cryopreserve testicular stem cells. After being cured from cancer, this cryopreserved testicular tissue can be thawed and the germ cells reimplanted into the patient's own testes to restore spermatogenesis [159]. Data from studies in mice [160,161] and humans [162] suggest that cryopreservation of testicular tissue containing spermatogonial stem cells can be done in an uncontrolled slow-freezing procedure [160,161] or an ultrarapid vitrification protocol [159–161]. Freezing tissue allows subsequent transplantation by either the infusion of a testicular cell suspension into the seminiferous tubules or intratesticular tissue grafting [161]. Orthotopic intratesticular grafting has the disadvantage of testicular malignant contamination exists. Infusion of decontaminated cell suspensions is a possible solution, but the efficacy of this decontamination procedure is low in animal models. The quantity of stem cells obtained from a testicular biopsy specimen needs to be increased to translate this autotransplant technology to humans. Scientists suggest that in vitro expansion of the stem cells either before freezing or after thawing may improve the success of the procedure in humans [163]. Therefore,

testicular germ cell transplantation may be restricted to children who have a high risk (> 80%) of becoming sterile.

An alternative innovative strategy is to enrich the cryopreserved testicular sample for gonadal stem cells that can be matured into viable spermatids in vitro through a novel culturing procedure [164]. Fertilization could then be achieved by intracytoplasmic sperm injection. For these strategies to come to fruition for prepubertal patients with cancer, laboratory science needs to advance and transform to serve the clinic.

4.2. FP in pubertal males

Pubertal spermatozoa are produced at puberty [165]. Spermatozoa can even be found in the urine of boys who have no clinical signs of puberty [166]. In a cohort of 80 pubertal boys [167], only 14 did not have frozen sperm because of azoospermia or the absence of motile spermatozoa. The production of semen through masturbation is not always possible in pubertal boys because of psychosexual reasons. Thus, electro-ejaculation can be offered. Hovav [168] reported that electro-ejaculation in six 15 to 18-year-old of boys successfully obtained sperm in all cases. A study of 30 adolescents treated with electro-ejaculation demonstrated a sperm recovery rate of 60% [169].

If no spermatozoa can be found in the semen or urine, testicular sperm extraction can improve the sperm retrieval rate. After the sperm are thawed, using ICSI in assisted reproductive technology can increase the chance of a successful pregnancy by selecting sperm with good activity [170]. With the continuous improvement of sperm storage technology, sperm stored for 28 years can now be obtained successfully [171]. Moreover, viable sperm can be collected successfully from adolescents and young adults who have received a new diagnosis of cancer [172].

Some scholars claim that, when male patients are at high risk for infertility, they can apply for sperm at the sperm bank. Sperm banking is recommended before any chemotherapy, because even low doses can impair sperm. There are also more invasive alternatives, such as penile vibratory stimulation, microsurgical epididymal sperm aspiration, electroejaculation, and testicular sperm cell extraction [173,174].

5. Future prospects

Despite the progress in FP technology for young patients with cancer, there are still some problems that require solutions. Some researchers are currently working on improving the following technologies:

5.1. Follicle culture and in vitro development

Strategies for culturing follicles in vitro have been under development for many years, and this highlights fundamental questions of follicle development, as well as applications in FP. There are two approaches to culturing primary and primordial follicles [175]: using whole slices of ovarian tissue (organ culture) and using isolated primordial and primary follicles. Studies applying the first method have reported culturing human primordial follicles to the secondary stage only [176,177]. The optimal matrix for growing human primordial follicles in ovarian tissue culture is unknown. Better results were obtained with alginate scaffolds in later studies [178]. A two-step culturing system has been utilized to grow murine [179], bovine [180], and human [181] primordial follicles. Thus far, in vitro follicular growth from primordial stage to functioning oocytes has been achieved with this method only in mice [179] and sired many offspring, but these pups were abnormally obese, and postmortem evaluation revealed multiple internal malformations [182]. Recently, the same group retrieved GV-stage oocytes from cultured human antral follicles; 10% of the initial primordial follicle underwent IVM and developed to metaphase II oocytes [183]. In the second approach to follicular culture, a 3D supporting matrix is required because of the fragility of isolated primordial and primary follicles [174], embedding isolated primordial follicles from mice [184], cows [185], and humans [186] in collagen gels before culture [187]. This approach leads to an increase in follicular size to the secondary stage without antrum development within 24 h. Currently, alginate hydrogel beads are the most popular means of embedding and culturing isolated preantral follicles [187]. They have been used mainly for murine follicles [179], as well as human unilaminar [188] or secondary follicles [189], but at the experimental stage.

Such efforts rely on a multi-stage culture system based around the different follicular growth stages in vivo [172,190]. Without these multiple stages, oocytes and stromal cells will not properly interact to favor accurate development [172,190]. The final goal of this multi-step approach is to obtain developmentally competent oocytes that can produce embryos and yield live births. Ensuring the effective maturation and development of these follicles is very complicated and represents a key challenge for future FP research efforts.

5.2. The artificial ovary

Artificial ovaries containing isolated follicles may serve as a revolutionary means of restoring fertility [191]. One alternative to obtaining mature oocytes would be using the so-called transplantable artificial ovary. Isolating primordial follicles and transferring them onto a scaffold to create an artificial ovary would serve to eliminate the risk of transmitting malignant cells [8].

The first step of developing an artificial ovary is a biodegradable scaffold onto which isolated preantral follicles and ovarian cells can be grafted [141]. To allow forfolliculogenesis and blood vessel formation, the fragile isolated follicles need to be embedded in a 3D supporting matrix that degrades with time [191]. Initially, plasma clots were used as the supporting matrix for implantation into immunodeficient mice [192], but this carrier potentially promotes follicle loss. Therefore, researchers changed it to hydrogels of alginate [193], but not only was their rate of degradation very slow, but vascularization was observed mainly in the grafts' periphery [191]. An alternative material is fibrin with natural fibrinogen polymer, provides hydrogels in the presence of thrombin dynamic mechanical properties [191]. Growing antral follicles have been observed after autografting primordial follicles inside a fibrin scaffold in a mouse model [190], and after xenografting human primordial follicles in mice with severe combined immunodeficiency [194]. Fibrin or fibrin supplemented with hyaluronic acid seems promising for use with human preantral follicles [194]. In the future, researchers will be able to preserve the 3D follicular structure and gap junction communication between oocytes and granulosa cells by combining slow degrading alginate with fibrin [195].

5.3. Ovarian stem cells

Oogonial stem cells can be cultured and develop into oocytes in vitro [196]. Attempts have been made with the combined use of oogonial stem cells and support cells to obtain oocytes that will grow, develop into mature oocytes, and get fertilized [197]. There are currently ethical concerns related to obtaining early follicle-like structures after xenotransplantation of human OSCs (germline stem cells). A numbered-step culture system is being developed and could be an interesting option for developing mature oocytes from OSCs completely in vitro [198].

Researchers have successfully cultured mouse oogonial stem cells in vitro. After these cells were transplanted back into recipient ovaries, positive fertilized oocytes, embryos, and live offspring were obtained [196]. However, some controversial issues persist. In vitro-derived oocytes may influence the complex genomic imprinting and alter epigenetic mechanisms, interfering with the development of fully competent oocytes. In addition, their potential use remains unclear [199].

Oogonial stem cells producing new oocytes to replace the ovarian reserve destroyed by chemoradiotherapy and surgery may be possible [200], not only offering a way to restore fertility in young women with cancer, but also preventing premature ovarian failure and the loss of ovarian hormones. Therefore, this approach would have far-reaching health benefits in cancer survivors of advancing age.

6. Conclusion

With the development of cancer therapeutics, the long-term survival rate has greatly improved. Therefore, the protection and preservation of fertility in patients with malignant tumors is receiving more and more attention worldwide. Optimizing techniques and minimizing the risks of FP strategies are the challenges faced in the next decade. Specifically, the viability of frozen testicular tissue and spermatogonial stem cells needs to be proven, and the culture conditions need to be determined for expansion of human spermatogonial stem cells. There are case series of cancer survivors fathering children using testicular sperm cell extraction combined with ICSI, but the success rate of this intervention after treatment of childhood cancer has not been confirmed. The above remains to be studied and confirmed, and is well applied to clinical practice.

In the future, cryopreservation of ovarian tissue may be combined with the removal of small antral follicles, making it possible to freeze both ovarian tissue and isolated immature oocytes. Improved freezing techniques, ensuring safe ovarian-tissue transportation, will be increasingly implemented among women with benign diseases, such as recurrent endometriosis, and those with age-related fertility decline, with vitrification of oocytes emerging as the technique of choice for non-oncologic indications in the near future.

Conflicts of interest

The authors have no conflicts of interest to report.

Declarations of interest

None.

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