Review Article

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Overview of fertility preservation

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Preserving fertility from damage by medical conditions or their treatments is increasingly popular. With the extended progression-free survival among young cancer survivors, oncofertility is an important subfield about preserving gonadal function and fertility among oncological patients. In this review, we discuss the gonadotoxicity of various anti-cancer treatments including radiotherapy and chemotherapy. We describe the current fertility preservation strategies including fertility-sparing surgery, radiation techniques, gonadal transposition, and assisted reproductive technology. We also discuss future trends including gonadal tissue cryopreservation and the current situation in Hong Kong. This review aims to promote the awareness, knowledge, and utilisation of fertility preservation so that more patients can benefit from it.

Keywords: Cryopreservation; Fertility Preservation; Infertility; Neoplasms; Quality of life

Introduction

Preserving fertility from damage by medical conditions or their treatments is increasingly popular. Cancer is the most common medical indication for fertility preservation (FP) [Table 1][1-4]. Oncofertility is an important subfield about preserving gonadal function and fertility among oncological patients. In patients with cancer during reproductive or pre-pubertal age, increasing efficacy of anti-cancer treatment and hence prolonged progression-free survival may result in subfertility and even infertility. Cancer management has shifted to a more holistic approach to consider the patients' quality of life, including fertility. In addition to FP for medical reasons, there is a trend of FP for social reasons including career planning, age-related fertility loss, and the absence of partners. The European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine include transgender patients as an indication for FP before sex transition[1,5]. To promote the awareness, knowledge, and utilisation of FP, this review discusses the gonadotoxic effect of anti-cancer treatment, FP strategies, future trends of FP, and the current situation of FP in Hong Kong.

Gonadotoxic effect of anti-cancer treatment

Gonads are vulnerable to anti-cancer treatments (surgery, radiotherapy, chemotherapy, and/or their combination), which may result in loss of endocrine and reproductive functions. The gonadotoxicity depends on disease, treatment, and patient factors (Table 2). Patients of reproductive or pre-pubertal age should be counselled about the gonadotoxic effect of the treatment. FP should be discussed as a part of the management in the early stage[1,6,7]. The window period for seeking FP advice between cancer diagnosis and treatment commencement varies. Timely referral to fertility specialists is crucial to maximise the future fertility potential.

Radiotherapy

In pelvic and abdominal cancers (eg, uterine, cervical, and rectal cancer) and some haematological malignancy requiring pelvic irradiation, unintentional irradiation to ovarian follicles inflicts DNA damage and leads to follicular atrophy and decreased follicular reserve[8]. The irradiation effect is dose-dependent and may lead to premature ovarian insufficiency[9]. Cranial radiotherapy inadvertently irradiates central neuroendocrine organs (such as the hypothalamus and the pituitary gland) and leads to endocrinopathy including central hypogonadism and hyperprolactinaemia. In addition, irradiation damages the uterine vasculature, the myometrium, and the endometrial epithelium[10]. Impaired ovarian function lowers the level of circulatory oestrogen and uterine function and hence increases the risks of miscarriage, preterm delivery,

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Table 1. Medical indications for fertility preservation

Medical indication for fertility preservation
Malignancy
Breast cancer
Gynaecological cancer (selective cases)
Testicular cancer
Childhood cancer (neuroblastoma, Ewing sarcoma, osteosarcoma, Wilms tumour)
Haematological malignancy (Hodgkin lymphoma, non-Hodgkin lymphoma, leukaemia)
Haematological diseases
Thalassemia major
Sickle cell anaemia
Other haematological diseases requiring bone-marrow transplantation
Autoimmune diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Juvenile idiopathic arthritis
Other autoimmune diseases requiring chemotherapy
Genetic diseases
Mosaic Turner syndrome
Family history of premature ovarian failure
BRCA mutation carrier opting for prophylactic oophorectomy
Klinefelter syndrome
Gynaecological / urological diseases
Severe endometriosis
Recurrent ovarian cysts
Cryptorchidism

Table 2. Factors affecting fertility after anti-cancer treatment

Factors affecting fertility
Disease factors
Primary site of disease
Involvement of reproductive organs in systemic disease
Treatment factors
Type of treatment (surgery, chemotherapy, radiotherapy, immunotherapy, target therapy, or any combination)
Cumulative dose administered (depends on duration, dosage, number of cycles, fractionation)
Patient factors
Physical factors
Sex
Age
Comorbidity
Pre-treatment gonadal reserve
Psychosocial factors
Relationship status
Presence of a previous child
Religious background
Cultural background
Financial status
Educational level

low birth weight, and uterine rupture in future pregnancy. Vaginal stenosis and loss of vaginal lubrication after irradiation of the vagina contribute to sexual dysfunction and infertility[11].

In testicular cancers, cancer sites that are close to the testes (prostate, rectum, anus, and bladder), intracranial malignancy, and leukaemia requiring prophylactic cranial irradiation, radiotherapy may damage the testes and the hormonal axis[12]. Irradiation interferes with the process of spermatogenesis, particularly on the immature differentiating spermatogonia, and depletes the mature sperms[13]. Leydig cells that produce testosterone are also damaged[14]. Pelvic radiotherapy can result in erectile dysfunction[15]. Damage inflicted by irradiation can be transient or irreversible, and the risks vary in different dosages (Table 3)[3,16]. Irradiation

Table 3. Risks of prolonged azoospermia in men or amenorrhea in women after radiotherapy[3,16]

High-risk
Total body irradiation for bone marrow transplant or stem cell transplant
Pelvic or whole abdominal radiation dose
≥6 Gy in adult women
≥10 Gy in post-pubertal girls
≥15 Gy in pre-pubertal girls
Testicular radiation dose
>2.5 Gy in adult men
≥6 Gy in pre-pubertal boys
Intermediate risk
Craniospinal radiotherapy dose ≥25 Gy
Pelvic or whole abdominal radiation dose
5-10 Gy in post-pubertal girls
10-15 Gy in pre-pubertal girls
Testicular radiation dose
1-6 Gy from scattered pelvic or abdominal radiation

of 2 Gy to the female gonadal area can destroy up to 50% of the ovarian reserve[17]. The maximum dosage that ovaries can withstand before ovarian failure decreases with age[17,18]. Spermatogonia are sensitive to radiation damage, whereas Leydig cells are more radio-resistant after puberty[19]. Thus, hormonal function in post-pubertal men is less affected by radiotherapy.

Chemotherapy

Alkylating agents are the most gonadotoxic, as their cell-cycle non-specific property renders toxicity to primordial follicles. Damage to the follicle is immediate after exposure to cyclophosphamide, owing to the high sensitivity of the follicle to the agent[20]. Women with reduced primordial follicle reserve have a shortened reproductive lifespan[21]. For men, alkylating agents adversely affect spermatogenesis and can lead to azoospermia within 90 days of exposure, which can persist for years after treatment[22]. Other chemotherapeutic drugs are more target-specific and thus less gonadotoxic (Table 4)[23-26]. Nevertheless, toxicity accumulates when combining different chemotherapeutic agents; oncologists should prescribe regimens that are least gonadotoxic while ensuring adequate anti-cancer effects.

Table 4. Level of gonadotoxicity of chemotherapeutic drugs[23-26]

Drug	Risk level in women	Risk level in men
Alkylating agent		
Busulfan	High	High
Chlorambucil	High	High
Cyclophosphamide	High	High
Mechlorethamine	High	High
Melphalan	High	High
Platinum analogue		
Cisplatin	Intermediate	High (intermediate if <6g/m^2)
Carboplatin	Intermediate	Intermediate
Anthracycline antibiotic		
Doxorubicin	Intermediate	Intermediate
Daunorubicin	Low	Intermediate
Antimetabolite		
Cytarabine	Low	Intermediate
Methotrexate	Low	Low
Vinca alkaloid		
Vinblastine	Low	Low
Vincristine	Low	Low
Antitumor antibiotic		
Bleomycin	Low	Low
Purine analogue		
Fluorouracil	Low	Low
Immunotherapy	Unknown	Unknown
Monoclonal antibodies	Unknown	Unknown
Small-molecule targeted therapy	Unknown	Unknown

Fertility preservation strategies

Fertility preservation strategies for cancer patients depend on sex and pubertal status. For surgical treatment involving reproductive organs, fertility-sparing surgeries are alternatives for patients of reproductive age, but they are limited to early-stage diseases or tumours with low malignancy (Figure). Patient selection should balance the potential increased risk of recurrence versus the fertility potential. For cervical cancer, early-stage diseases can be treated with fertility-sparing surgery. Stage IA1 disease with no lymphovascular space invasion can be treated with cone biopsy[27]. Stage IA1 disease with lymphovascular space invasion, stage IA2 disease, and stage IB1 can be treated with additional radical trachelectomy (resection of the cervix, upper third of the vagina, and parametrial tissues) with bilateral pelvic lymphadenectomy. Stage IB1 disease can be treated with additional para-aortic lymph node dissection[28]. For ovarian cancer, early-stage unilateral disease and borderline epithelial ovarian tumours can be treated with unilateral salpingo-oophorectomy[11]. For atypical endometrial hyperplasia and very early-stage endometrial cancer, hysterectomy is the standard treatment, but conservative treatment with high-dose progesterone, followed by close monitoring, can be offered to those with fertility wish[29]. For testicular cancer, testicular-sparing surgery can be considered in cases of nonpalpable small masses (≤2 cm), a solitary mass, and bilateral tumours, without compromising oncological and functional outcomes[30]. Intraoperative frozen section should be performed to ensure a safe margin of malignant tissue.

Pelvic shielding and transposition of gonads

For radiotherapy, to minimise the gonadotoxic effect, shielding the pelvic organs is an easy and non-invasive way. For men, gonadal shielding effectively lowers the irradiation dose the gonads received unintentionally by >60%[31]. When shielding is not feasible, the gonads can be transposed surgically out of the irradiation field. Ovarian transposition enables preservation of ovarian function in 90% of the cases[32]. Lateral transposition by laparoscopic surgery is more common; the utero-ovarian ligament and tubes are divided, and the ovary is placed 3 cm above the

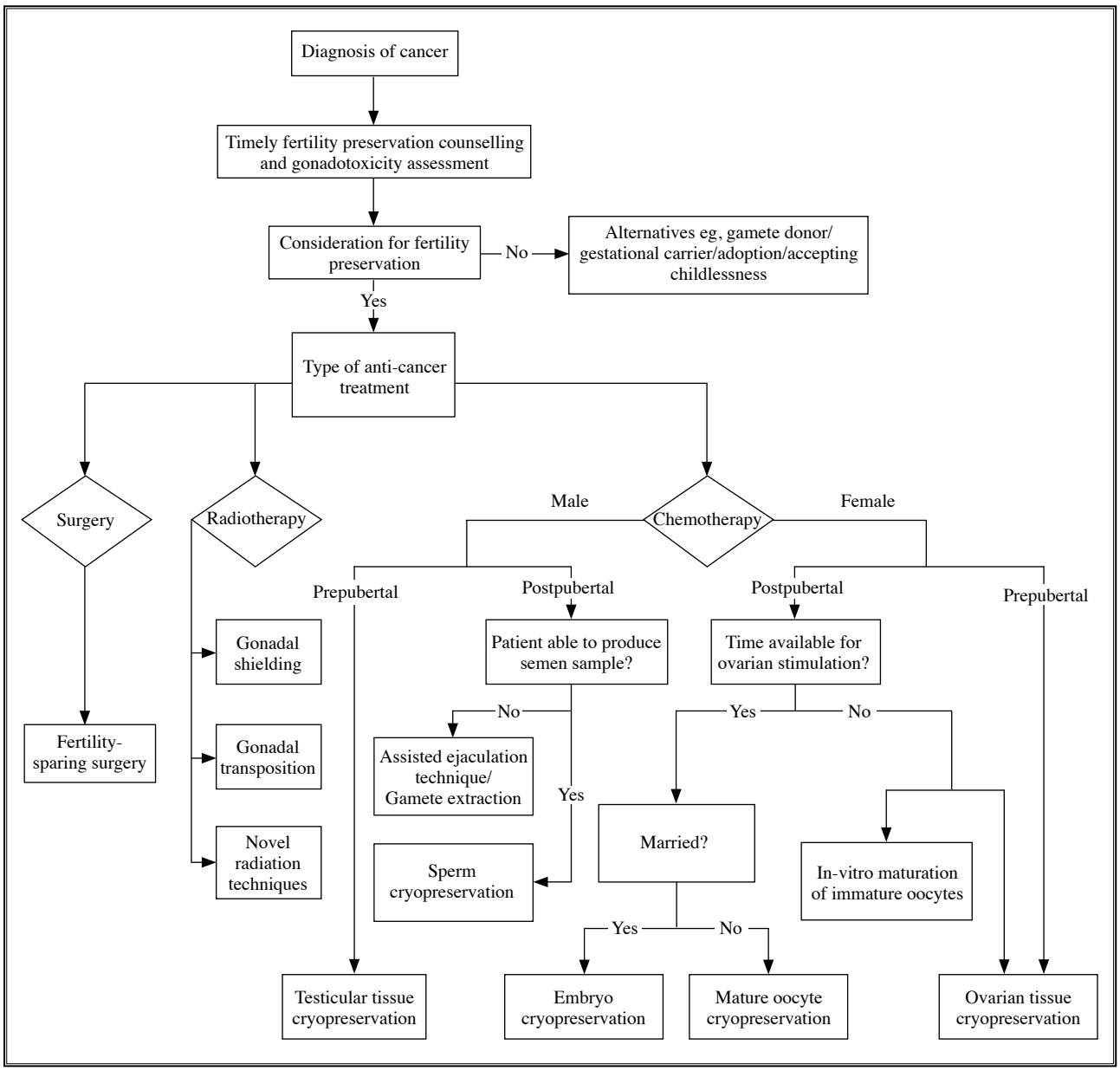

Figure. Fertility preservation strategies

radiation field. However, women with reduced ovarian reserve and risk of ovarian metastasis are not suitable for ovarian transposition. As radiation scatters, ovaries are not completely protected from radiation. There is also a risk of remigration of ovaries; thus, ovarian transposition should be performed close to the time of radiotherapy[6]. In testicular transposition, the spermatic cord is moved up to the external inguinal ring, the gubernaculum attachments at the scrotum are released, and the testes are transposed under the abdominal skin. Testicular transposition can lower the radiation dose received by the testes during scrotal or pelvic irradiation[33]. After radiotherapy, the testes are relocated back to the scrotum[34].

Intensity-modulated radiation therapy and proton radiotherapy

In conventional radiotherapy, the X-ray passes the body, through the tumour, and comes out at the other side. This 'exit dose' of radiation affects healthy tissue in the field. In contrast, intensity-modulated radiation therapy manipulates proton beams to precisely irradiate the target tumour, minimising radiation dose to neighbouring healthy tissue. Proton radiotherapy can deliver energy more precisely to the tumour. Protons release more energy within the tumour and cease to penetrate healthy tissues, reducing radiation exposure and potential damage to healthy tissue[35,36].

Strategy for chemotherapy

For women, gonadotropin-releasing hormone agonist (GnRHa) is used to create a state similar to menopause. However, GnRHa can cause hypo-estrogenic symptoms and irreversible bone loss after long-term use. Although a meta-analysis reported a benefit of GnRHa in the prevention of chemotherapy-induced premature ovarian failure, the American Society of Clinical Oncology and the European Society of Medical Oncology do not recommend GnRHa as a sole FP strategy[6]. The former suggests GnRHa in young women with breast cancer only when other FP strategies are not feasible. For men, GnRHa shows efficacy in animal models only but not in humans[37]. Therefore, chemical shielding is not recommended in male patients.

Assisted reproductive technology

Sperm cryopreservation can be offered to post-pubertal patients. Ejaculation through masturbation does not delay cancer treatment. Phosphodiesterase type-5 inhibitors can be used to facilitate ejaculation in those with or without ejaculating difficulty or erectile dysfunction[38]. Assisted ejaculation techniques (vibratory or electro-ejaculatory stimulation) can be used in pre-pubertal patients or patients unable to ejaculate. For azoospermic patients, urological procedures (percutaneous epididymal sperm aspiration, microsurgical epididymal sperm aspiration, and testicular sperm extraction) can be used for sperm acquisition[39]. For patients with testicular cancer who failed to ejaculate, oncological testicular sperm extraction can be performed immediately after orchiectomy[40], followed by intracytoplasmic sperm injection (injection of a single sperm into an oocyte using a micropipette under the microscope), which is beneficial for those with oligospermia or cryopreserved sperms in whom in vitro fertilisation may be less effective.

Testicular tissue and spermatogonial stem cells cryopreservation through biopsy is performed under general anaesthesia for pre-pubertal boys who have no mature sperm or cannot ejaculate. In patients aged 13 to 14 years, sperm cells might be present and thus can be cryopreserved[41]. For younger patients, only spermatogonial stem cells can be isolated and cryopreserved. As spermatogenesis originates from spermatogonial stem cells, auto-transplantation of these stem cells into the testes may restore fertility[17]. This technology also preserves other testicular cells, including Sertoli cells, which is postulated to maintain crucial cell-cell interactions and account for improved spermatogonial stem cell survival. It can be performed in patients in whom chemotherapy cannot be delayed. However, success has been reported in animal model only but not yet in humans[42]. Similar to ovarian tissue cryopreservation (OTC), testicular tissue cryopreservation carries both surgical risk and the risk of reseeding malignancy during auto-transplantation.

FP is more complicated in females than in males and depends on pubertal stage, time availability before anti-cancer treatment, and marital status. False reassurance should not be given[43]. Women should attempt to conceive soon after remission of disease when they are physically fit for pregnancy, as their fertility decreases with age.

Embryo cryopreservation is the optimal choice of FP for married women with adequate time for ovarian stimulation[44]. It involves ovarian stimulation to produce mature oocytes for retrieval and then in vitro fertilisation. Embryos are cryopreserved and thawed for use when the patient is ready for a pregnancy. Embryos are more resistant to cryo-damage than oocytes, as oocytes have a higher susceptibility to meiotic spindle damage[44]. However, ovarian stimulation takes at least 2 to 3 weeks, rendering a delay in anti-cancer treatment. There is also a risk of a transient increase in oestradiol levels, leading to regrowth of tumour cells in hormone-sensitive cancer.

Mature oocyte cryopreservation is the most common strategy and is used for post-pubertal women who are single and have adequate time for ovarian stimulation. It involves controlled ovarian stimulation, harvesting of mature oocytes, and freezing of unfertilised eggs. Vitrification is a relatively new cryopreservation technology; it rapidly freezes the oocyte using a high concentration of cryoprotectant to prevent crystallisation of water content, thus lowering the cryo-damage. Slow freezing is the conventional cryopreservation technique; it freezes the oocyte at a lower rate (2°C/minute) with a low cryoprotectant concentration. A systemic review reported that vitrification is superior to slow-freezing in terms of post-thaw viability of the oocyte and clinical pregnancy[45,46]. Intracytoplasmic sperm injection is suggested to increase the success rate, as cryopreservation of the oocytes leads to hardening of the outer shell (zona pellucida) and potentially reduces the fertilisation rate[47]. Mature oocyte cryopreservation provides greater flexibility and autonomy on fertility decision. It is an alternative to married women, especially in case of potential change of future marital status[48]. Women can decide the timing and partner to start a family[48]. Legally, women are prohibited to use cryopreserved embryos in situations such as divorce and decease of the partner. Mature oocyte cryopreservation is also an alternative for patients with religious or ethical

concern over embryo cryopreservation. However, it temporarily increases oestradiol level and thus the risk of hormone-sensitive cancer progression. The rate of a cryopreserved oocyte translating to live birth is about 5% to 7% in well-established units. 15 to 20 oocytes are needed to secure a 70% to 80% probability of having one live birth in women under 38 years old[49]. As only 8 to 12 oocytes can be harvested in each ovarian stimulation cycle, more than one cycle is needed to harvest adequate oocytes, and the anti-cancer treatment may be further delay[48].

Conventional ovarian stimulation starts during the follicular phase of the menstrual cycle. For patients with limited time between diagnosis and commencement of anti-cancer treatment and those who seek FP consultation during non-follicular phase, random-start ovarian stimulation (initiation of ovarian stimulation at any point of the menstrual cycle) enables harvesting oocytes in a short time[50]. Its effectiveness is similar to conventional protocols in terms of oocyte yield and fertilisation rate[51]. Double stimulation combines conventional stimulation at the follicular phase with luteal phase stimulation; thus, oocyte can be retrieved twice in the same cycle[52]. For breast cancer sensitive to oestrogen, protocols that lower the circulating oestrogen level increase the safety margin of ovarian stimulation and prevent recurrence and progression. Letrozole is an aromatase inhibitor that suppresses circulating oestrogen level. It releases the negative feedback by oestrogen on the hypothalamic-pituitary axis, promoting the follicle-stimulating hormone secretion. During ovarian stimulation, co-administration of letrozole suppresses oestradiol levels without significantly affecting the oocyte yield or shortening the disease-free survival rates[53]. Tamoxifen is a selective oestrogen receptor modulator used in hormone-sensitive breast cancer. In addition to the anti-oestrogen effect on the breast tissue, its antagonist effect on the central nervous system releases the negative feedback of oestrogen on the hypothalamic-pituitary axis, resulting in increased GnRH secretion and hence follicle-stimulating hormone for follicle development[21,54]. Co-administration of tamoxifen lowers the ovarian stimulation dose, but a comparable or larger number of oocytes can still be collected[54].

Immature oocyte cryopreservation is used for women requiring immediate anti-cancer treatment or those with polycystic ovarian syndrome who are not candidates for embryo or mature oocyte cryopreservation. It does not require mature oocyte or ovarian stimulation. This alternative has shown success and may be the standard of treatment in future. The collected immature oocytes are matured inside the culture medium, ie in vitro maturation. The matured oocytes can then be preserved or fertilised with sperms to form embryos for cryopreservation. Immature oocyte cryopreservation with in vitro maturation has a lower risk of ovarian hyperstimulation syndrome than does conventional ovarian stimulation[55]. However, compared with conventional IVF, in vitro maturation has a lower live birth and cumulative ongoing pregnancy rate[56].

Ovarian tissue cryopreservation (OTC) uses cortical biopsies to obtain multiple primordial follicles from each ovary. The tissue is then reimplanted in the orthotopic region (eg, pelvis) or heterotopically in the subcutaneous space of the forearm or abdomen when the patient desires for pregnancy[57]. The first live birth after OTC is reported in 2004, and >170 live births have been reported since then[58]. OTC is no longer considered experimental according to the American Society for Reproductive Medicine[59,60]. It is the only FP strategy for pre-pubertal girls. OTC is beneficial to patients with limited time before anti-cancer therapy such as those with leukaemia. Without the need for ovarian stimulation, cortical biopsies can be performed immediately before anti-cancer therapy. Risks related to ovarian stimulation are avoided. The live birth rate in patients with OTC after anti-cancer treatment is comparable to that in patients with OTC before the treatment[61]. OTC restores not only fertility but also gonadal function. OTC and reimplantation can act as a physiological hormone replacement therapy after menopause; this is known as cell/tissue-based hormone replacement therapy[62]. However, this may be limited by the lifespan of graft tissue and thus requires repeated implantation[63]. It is unknown whether OTC itself leads to earlier menopause[64]. However, OTC involves both surgical biopsy for cryopreservation and auto-transplantation. The transplanted tissue may carry malignant cells, particularly in cancers with high gonadal metastasis risk such as haematological cancers (leukaemia and non-Hodgkin lymphoma) and paediatric cancers (neuroblastoma and Ewing sarcoma)[65]. The risk of reintroduction of malignant cells at the time of auto-transplantation can be minimised by meticulous examination of a representative biopsy in terms of histology, immunohistochemistry, and molecular biology[66]. Optic coherence tomography can also be used to screen malignant cells in the ovarian tissue before transplantation[67].

Future trends

Artificial ovary can solve the potential malignancy implantation risk of OTC. Preantral follicles are obtained through an ovarian tissue biopsy and are subsequently

isolated and cryopreserved. Other non-germ cells of the ovaries are then harvested from the pre-treatment ovarian tissue or from a second biopsy after cancer remission, which minimises the risk of carrying cancerous cells[68]. The follicles and other ovarian cells are contained by using a scaffold made from biological or synthetic materials[69]. The artificial ovary remains at a primitive stage of development; more studies are warranted.

In-vitro growth and maturation of primordial follicles and immature oocytes from cryopreserved ovarian tissue is an alternative to mature oocyte cryopreservation. This method is useful in whom ovarian auto-transplantation is not possible or in women with blood-borne leukaemia or cancers with high risk of ovarian metastasis[70].

Alternatives to FP such as donor gametes and gestational carriers can be discussed with suitable patients who are in clinical remission and fit for parenting. Donor gametes are suitable for those who are not suitable for gamete retrieval, including those with ovarian malignancy or those who cannot produce gametes after anti-cancer treatments (eg, bilateral oophorectomy or orchiectomy). Gestational carrier, or gestational surrogacy, refers to a woman who gestates an embryo with no biological relationship for a couple or an individual and has to relinquish the child to them after its birth[71]. Gametes are from the couple with fertility needs and form an embryo in vitro before transplantation into the gestational carrier's uterus. Gestational carrier differs from traditional surrogacy, in which the woman has a biological link to the foetus, as the fertilisation is completed with the oocyte from the surrogate mother. These solutions are suitable for those who cannot have intrauterine pregnancy such as those with hysterectomy.

Adoption is another solution that does not require ART. Medical social workers can be referred to those who are interested. If all the above options fail, the patient may have to be counselled to accept the fact of not having children.

Current situation in Hong Kong

In Hong Kong, fertility-sparing surgeries and pelvic shielding are frequently practised. Oocyte cryopreservation and embryo cryopreservation are widely used. Ovarian and testicular tissue cryopreservation are not currently available. Hopefully, they will be FP options for pre-pubertal patients and those in need in future. Although FP is an essential part of cancer treatment, the awareness and utilisation of FP in Hong Kong are low. In a cross-sectional study of clinicians, only 45.6% were familiar with FP[72]. In a study of medical students, 77.8% did not know where to seek FP service providers in Hong Kong[73]. The awareness of FP among the general public is inadequate, with about 50% of respondents not aware of any FP strategies and about 80% not knowing where to seek FP advice or service[74]. Respondents with higher education and income have significantly higher awareness and knowledge of FP[74]. Inadequate understanding and awareness of FP result in low utilisation of FP in Hong Kong. Between 1995 and 2012, only 125 cases of sperm cryopreservation were performed in a university hospital in Hong Kong[75]. Both medical students and the general public (64.3%) acquire the FP knowledge mainly from the traditional and/or social media, followed by medical schools (among medical students) and healthcare providers (among the general public). The mass media has a major role in promoting FP. Medical professionals should provide correct concepts of FP during teaching to medical students or consultation with patients and through mass media, especially social media. Other channels for patient education include public talks, television programmes, newspaper articles, and printed information/pamphlets. All these help promote awareness and knowledge of FP among the general public.

In Hong Kong, ART is regulated by the Human Reproductive Technology Ordinance (Cap. 561). The Council on Human Reproductive Technology sets up the Code of Practice on Reproductive Technology and Embryo Research. Cryopreserved oocytes and sperms can only be used when the patient is married at the time of using ART. The storage duration for frozen gametes is limited to 10 years or until the patient reaches the age of 55 years, whichever longer. The storage duration for frozen embryos is also limited to 10 years. The cryopreserved gametes and embryos can only be used when the patients have sufficiently recovered from illnesses and are legally married. It is a clinical judgement made by the appropriate experts of the relevant discipline. In addition, posthumous use of the cryopreserved gametes and embryos is prohibited in order to protect the welfare of the future child[76].

Conclusion

Anti-cancer treatment adversely affects one's fertility. FP is a vital component of quality of life in cancer survivors, especially those with fertility wish. Oncofertility is an emerging field aimed at preserving gonadal function and fertility among oncological patients. This review discussed the risks of fertility impairment after anti-cancer therapies and the FP strategies to enable live birth after gonadotoxic procedures. Each FP strategy has certain

limitations and is not suitable for all patients; the FP plan should be customised for each patient. FP counselling should be conducted promptly after the diagnosis to shorten the time between diagnosis and treatment. In Hong Kong, FP services are underutilised, owing to technological limitations and financial concerns as well as lack of awareness and understanding of FP among the public, even among medical students and physicians. Patient education, research, and campaigns are required to promote the awareness and utilisation of FP, as are establishment of FP centres to provide medical professionals training, FP management, and comprehensive bio-psycho-social care to patients.

Declaration

The authors have no conflicts of interest to disclose.

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