



Fertility preservation for female cancer patients

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Abstract

An improvement in the survival rates of cancer patients and recent advancements in assisted reproductive technologies have led to remarkable progress in oncofertility and fertility preservation treatments. Currently, for adults and postpubertal girls, oocyte or embryo cryopreservation is an established method. If their cancer treatment cannot be postponed for 2 weeks, ovarian tissue cryopreservation is offered as an experimental technique. For prepubertal girls, ovarian tissue cryopreservation is the only option. As for ovarian protection, there is insufficient evidence regarding the effectiveness of GnRH agonist in fertility preservation. In the past decade, the concept of fertility preservation for cancer patients has been rapidly spreading, but at present only a small part of young cancer patients receive fertility preservation services. It is partly because of the lack of adequate provision of information on fertility preservation and the lack of referral from oncology to the fertility clinic. In Japan, the clinical practice guidelines for fertility preservation in childhood, adolescent and young adult cancer patients was issued last year by the *Japan Society of Clinical Oncology* (JSCO). It would help Japanese health care providers, including oncologists and reproductive specialists, to increase their knowledge on fertility preservation for cancer patients and move forward the fertility preservation services. For further progress, it is also needed to establish a national registration system of fertility preservation for cancer patients to evaluate the safety and efficacy of the current management.

Keywords Fertility preservation · Embryo cryopreservation · Oocyte cryopreservation · Ovarian tissue cryopreservation · Ovarian protection · Gonadotropin-releasing hormone (GnRH) agonist

Introduction

The survival rates of cancer patients have greatly improved over the past two decades with advances in early detection and therapy. Consequently, more than 80% of children and adolescents with cancer become long-term survivors [1, 2]. However, cancer treatments including chemotherapy and radiotherapy can compromise ovarian function and future fertility of cancer survivors. Accordingly, the demand for fertility preservation for the childhood, adolescent and young adult cancer patients has greatly increased [3], which is reflected in the most recent clinical practice guideline issued by the *American Society of Clinical Oncology* (ASCO). ASCO recommends in its guideline that as part of education and informed consent before cancer therapy,

health care providers should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss fertility preservation options and/or to refer all potential patients to appropriate reproductive specialists [4].

When we discuss fertility preservation for cancer patients, the most important point is that cancer treatment should take top priority, without being delayed or interfered with by fertility preservation. Another key point is that the age of the patient is an important determinant of the risk of premature ovarian insufficiency (POI) caused by cancer therapy, as well as the outcomes of fertility preservation. Ovarian damage is drug and dose dependent, but the same dose of a highly ovotoxic agent, such as cyclophosphamide, exerts less severe effects when it is administered to younger women [4]. Younger women exhibit better outcomes of fertility preservation as well. Among women who cryopreserved ten oocytes with non-oncologic reasons, the cumulative live birth rate was twofold higher (60.5 vs. 29.7%) in the younger group of women, who were 35 years of old or younger when oocytes were cryopreserved, compared to the older group

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[5]. Lastly, another key issue to keep in mind is that the outcomes of fertility preservation for cancer patients are just estimated at present based on the results obtained from cryopreserved embryos, oocytes and ovarian tissues for non-oncologic reasons, by assuming that the outcomes of cancer patients are comparable to non-cancer patients. However, it is still controversial whether this assumption is true [2, 3, 6].

With developments in assisted reproductive technologies (ART), several fertility preservation options have been developed for the cancer patients confronting the cancer treatment-induced POI [7, 8]. This topic review summarizes these currently available options, as well as gonadotropin-releasing hormone (GnRH) agonist therapy for fertility preservation and then discusses the future perspectives in this field.

The currently available options for fertility preservations

A current algorithm for female fertility preservation is as follows [7]. For adults and postpubertal girls, oocyte or embryo cryopreservation is an established method. If their cancer

treatment cannot be postponed for 2 weeks, ovarian tissue cryopreservation is offered as an experimental technique. For prepubertal girls, ovarian tissue cryopreservation is the only option. Currently, there is insufficient evidence regarding the effectiveness of GnRH agonist in fertility preservation [4]. The techniques for fertility preservation described in this review are summarized in Table 1.

Embryo cryopreservation

Embryo cryopreservation is a well-established technique in ART field for infertile patients, with a pregnancy rate per cryopreserved embryo of 30–35% according to the 2015 data from the *Japan Society of Obstetrics and Gynecology* (JSOG). For embryo cryopreservation, multiple oocytes are picked up either transvaginally or transabdominally following controlled ovarian stimulation (COS), then fertilized with sperm, and the resulting embryos are cryopreserved at either cleavage or blastocyst stage by vitrification [9]. When a patient wants to use her cryopreserved embryos, they are thawed and transferred into her uterus.

Adverse effects of embryo cryopreservation which might delay the start of cancer treatment would be ovarian

Table 1 Summary of the techniques for fertility preservation

Name of method	Contents
Embryo cryopreservation	Oocytes are picked up either transvaginally or transabdominally, fertilized with sperm, and the resulting embryos are cryopreserved An established technique COS dependent Takes at least 2 weeks Only for adults and postpubertal girls
Oocyte cryopreservation	Oocytes are picked up either transvaginally or transabdominally and cryopreserved Sperm is not necessary at cryopreservation An established technique COS dependent Takes at least 2 weeks Only for adults and postpubertal girls
Ovarian tissue cryopreservation	Ovarian tissue is harvested laparoscopically and cryopreserved Sperm is not necessary at cryopreservation An experimental technique COS independent Takes a few days For adults and post- and prepubertal girls A potential risk of MRD
COSTLES	A COS protocol combined with an aromatase inhibitor, to prevent an increase in serum estradiol levels following COS
Random-start COS	A COS protocol in which COS is initiated in either the follicular or the luteal phase, while it is initiated at the early follicular phase in conventional COS
DuoStim	A COS protocol in which COS is initiated both in the follicular and luteal phase within a single menstrual cycle
GnRH agonist therapy	Considered as a pharmacologic protection of the ovary during chemotherapy Insufficient evidence regarding the effectiveness in fertility preservation

COS controlled ovarian stimulation, MRD minimal residual diseases, COSTLES COS with letrozole supplementation, DuoStim double stimulation, GnRH gonadotropin-releasing hormone

hyperstimulation syndrome (OHSS) following COS and massive bleeding or intraperitoneal infection after oocyte pickup (OPU). To reduce the risk of OHSS, GnRH-antagonist protocol for COS is recommended [10]. In addition, triggering final oocyte maturation with GnRH agonist, instead of routinely used human chorionic gonadotropin (hCG), can reduce the risk of OHSS [11, 12].

It is still controversial whether COS, which increases serum estradiol levels, is safe for patients with estrogen-sensitive cancer including hormone receptor-positive breast cancer. For these patients, a COS protocol combined with an aromatase inhibitor such as letrozole is applied to prevent a rise in serum estradiol levels [10, 13]. The numbers of mature oocytes and embryos obtained with COS with letrozole supplementation (COSTLES) are comparable to those with a protocol without letrozole [13]. As for safety, Kim et al. recently reported the long-term safety of COSTLES, showing no increase in recurrence risk in breast cancer during the 5 years after diagnosis by comparing the patients who underwent COSTLES and those who did not undergo COS at all [14].

COS is conventionally initiated at the early follicular phase and requires approximately 2 weeks before mature oocytes are harvested. For a patient who cannot wait for her next menstrual period, but still has 2 weeks before her cancer treatment, random-start COS is applied. Random-start COS means initiating COS in either the follicular or the luteal phase. Random-start COS is as effective as conventional-start COS for fertility preservation for cancer patients in terms of the number of oocytes recovered, maturation rates and fertilization rates [15, 16]. No difference was noted in the pregnancy rates of frozen–thawed embryos for non-oncologic reasons retrieved by random- versus conventional-started COS [17].

Double stimulation (DuoStim), another innovative protocol, is also applicable, especially for patients with reduced ovarian reserve [18]. In DuoStim, COS is initiated both in the follicular and luteal phase within a single menstrual cycle. In DuoStim cycles applied for non-oncologic patients with poor ovarian reserve, no differences were found in the number of oocytes recovered and maturation rates between COS initiated in the follicular and luteal phase, indicating that DuoStim may double the number of oocytes recovered in a single menstrual cycle although it takes around 30 days. DuoStim can maximize the number of oocytes recovered in the shortest possible time [19].

Oocyte cryopreservation

Oocyte cryopreservation is also an established technique in the ART field for infertile patients [20]. The only difference between the embryo and oocyte cryopreservation procedure is that unfertilized mature oocytes are cryopreserved

in oocyte cryopreservation, while fertilized embryos are cryopreserved in embryo cryopreservation. Accordingly, the patient who undergoes oocyte cryopreservation does not need a partner at OPU. When a patient wants to use her cryopreserved oocytes, they are thawed and fertilized with the sperm and the resulting embryos are transferred into her uterus.

A pregnancy rate per cryopreserved oocyte is 4.5–12% [20], which suggests that one live birth requires at least ten cryopreserved oocytes. This estimation is supported by the results recently reported by Cobo et al. that the cumulative birth rates of 10 and 15 oocytes cryopreserved for non-oncologic reasons were 60.7 and 85.2%, respectively, even in young women who were 35 years of age or younger [5]. Given that the pregnancy rate per embryo is far superior to that per oocyte, embryo cryopreservation is recommended to a patient with her partner, rather than oocyte cryopreservation.

Ovarian tissue cryopreservation

Ovarian tissue cryopreservation is still an experimental, but rapidly progressing technique [3, 21]. For ovarian tissue cryopreservation, ovarian tissue is harvested laparoscopically and cut into cortical strips which contain many primordial follicles. The tissue is then cryopreserved either by slow freezing or vitrification [3]. Ovarian tissue can be harvested from any female patient irrespective of their age, while mature oocytes required for embryo or oocyte cryopreservation can be harvested only from adults or postpubertal girls. Moreover, ovarian tissue cryopreservation can be conducted within a few days because it is COS independent, while COS-dependent embryo or oocyte cryopreservation requires at least two weeks. Furthermore, ovarian tissue cryopreservation can be combined with embryo or oocyte cryopreservation [3]. Ovarian tissue cryopreservation followed immediately by COS and oocyte retrieval for cancer patients did not impair the number or quality of the retrieved oocytes [22]. This combined procedure may increase fertility preservation potential. When a patient wants to use her cryopreserved ovarian tissues, they are thawed and transplanted usually in the pelvic cavity, either on the ovarian medulla or inside a peritoneal window [2, 3, 8].

After transplantation of ovarian tissue in the pelvic cavity, ovarian endocrine activity is restored in more than 95% of cases [3, 23]. As of January 2018, more than 130 live births after transplantation of ovarian tissue, cryopreserved either for oncologic or non-oncologic reasons, has been reported [8]. A pregnancy rate after transplantation of ovarian tissue is not established since the number of transplantations performed worldwide is not known. However, a pregnancy rate and live birth rate are estimated, based on the results of several case series as 30–40% and 25–35%, respectively

[3, 24–27]. Pregnancies after ovarian tissue preservation resulted either from natural conception or from in vitro fertilization [28].

It is the biggest concern on transplantation of cryopreserved ovarian tissue for oncologic reasons that the risk of reintroducing malignant cells contaminating in ovarian tissue, which is called minimal residual disease (MRD). The relative MRD risk for most types of cancer is still unknown, but the risk of MRD is considered to be high in leukemia patients [29, 30]. The risk of MRD is estimated to be high for leukemia, moderate for gastrointestinal cancer and low for breast cancer, sarcomas of the bone and connective tissue, and Hodgkin's and non-Hodgkin's lymphoma [31]. In addition, the methods to evaluate MRD in ovarian tissue is not established. Accordingly, ovarian tissue cryopreservation and transplantation is not recommended for leukemia patients at present [4].

GnRH agonist therapy for fertility preservation

Administration of GnRH agonist has been considered as a pharmacologic protection of the ovary during chemotherapy. The proposed mechanisms of action include hypogonadotropism-induced ovarian quiescence and reduction of ovarian blood flow. Although GnRH agonist may have some medical benefits such as prevention of menorrhagia induced by thrombocytopenia following chemotherapy, there is insufficient evidence regarding the effectiveness of GnRH agonist in fertility preservation [4]. A number of papers with conflicting results have continued to be published [32–34], but to confirm the protective effect of GnRH agonist, it would be necessary to show that administration of GnRH agonist is effective not only in the recovery of menses, but also in achieving pregnancy. A recent report of prospective randomized trial, with a median follow-up time of five years, showed that the GnRH agonist is not efficient in preventing chemotherapy-induced POI and has no influence on the future pregnancy rate [35].

Future perspectives

In the past decade, the concept of fertility preservation for cancer patients has been rapidly spreading and several guidelines have been issued [4, 10, 36]. Currently, however, only a small part of young cancer patients receive fertility preservation services. For example, a Canadian survey on 188 women, who were diagnosed with cancer between the ages of 18–39 after the year 2000 and had finished active cancer treatment, reported that only 17 (9%) patients received fertility preservation services [37]. The process of decision-making on fertility preservation is not easy for cancer patients, partly because of the lack of adequate

provision of information on fertility preservation (lack of information, timing of the information and patient–provider communication) and the lack of referral from oncology to the fertility clinic [38]. In the above-mentioned Canadian survey, 45 (23.9%) patients did not recall having a fertility discussion with their oncologists, which is comparable with the percentages reported in two other Web-based surveys [39, 40]. Of the remaining 143 (76.1%) patients who had a fertility discussion, discussions were equally initiated by oncologists ($n = 71$) and patients ($n = 72$), and eventually 49 women (26%) were referred to a fertility specialist. Interestingly, they also found a link between the quality of the oncologist–patient fertility discussions and the subsequent receipt of fertility preservation consultation [37]. In a survey on Japanese breast cancer specialists, fair knowledge had a strong impact on physicians' positive behavior toward discussing fertility issue with patients [41]. A survey on adult and pediatric oncology providers in the USA showed that the majority of them felt discomfort while discussing on fertility preservation, partly because of the lack of knowledge about options or places to refer, and this discomfort hindered referrals to specialists [42]. In Japan, the clinical practice guidelines for fertility preservation in childhood, adolescent and young adult cancer patients was issued last year by the *Japan Society of Clinical Oncology* (JSCO). It would help Japanese health care providers, including oncologists and reproductive specialists, to increase their knowledge of fertility preservation for cancer patients and move the fertility preservation services forward.

Although the number of the patients who receive fertility preservation services has been increasing in Japan, the precise data on the national status of fertility preservation for cancer patients are not available because of the lack of a national registry (e.g., the number of cryopreserved embryos, oocytes and ovarian tissues, diagnosis for the patients who received fertility preservation services, and pregnancy and oncologic outcomes of these patients). To promote fertility preservation services, we definitely need to evaluate the pregnancy and live birth rates of each fertility preservation option, as well as an obstetric outcome and a long-term oncologic prognosis of a patient. Furthermore, newborns' short- and long-term health should be addressed. Our national survey supported by the *Japan Agency for Medical Research and Development* (AMED) revealed that more than 1000 embryos or oocytes and more than 100 ovarian tissues were already cryopreserved for cancer patients between January 2011 and December 2015 (unpublished data). It is urgently needed to establish a national registration system to evaluate the safety and efficacy of the current management.

Lastly, we briefly introduce several new approaches under development for fertility preservation [7]. In vitro growth and maturation of follicles is a promising technique.

Immature follicles, such as secondary, primary, or even primordial follicles, are harvested from ovarian tissue and cultured in vitro to produce mature oocytes [43]. This technique would overcome the risk of MRD following ovarian tissue cryopreservation. Generating germ cells in vitro from pluripotent stem cells is another approach and successful in rodents [44], although many technical and ethical issues need to be addressed for humans. Novel strategies for gonadal protection are also under investigation [45]. One is the drug delivery system (DDS) to enhance the site selectivity and reduce the exposure of ovary, a non-targeted organ, to anticancer agents. The other is to administer the agents which reduce gonadal damage, including sphingosine-1-phosphate (S1P), imatinib (Gleevec) and ammonium trichloro(dioxoethylene-o,o')tellurate (AS101). S1P and imatinib inhibit a specific apoptotic pathway and protect follicles from apoptosis [46, 47]. AS101 affects the activation of the PI3K/PTEN/Akt pathway and attenuates 'burn out' which involves the activation of dormant follicles by anticancer agents, resulting in the depletion of ovarian reserve [48].

Conclusion

Fertility preservation for cancer patients is steadily progressing in Japan. The recently published clinical practice guidelines issued by JSCO would promote its progress. In addition, it is urgently needed to establish a national registration system to evaluate the safety and efficacy of the current management.

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Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest.

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