Review Article

Obstet Gynecol Sci 2018;61(4):431-442
https://doi.org/10.5468/ogs.2018.61.4.431
pISSN 2287-8572 · eISSN 2287-8580

Obstetrics & Gynecology Science

Ovarian tissue cryopreservation and transplantation in patients with cancer

Sooyoung Kim*, Younji Lee*, Sanghoon Lee, Tak Kim

Department of Obstetrics and Gynecology, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Korea

Chemotherapy and radiotherapy improved survival rates of patients with cancer. However, they can cause ovarian failure and infertility in women of reproductive age. Infertility following cancer treatment is considered a major quality of life issue. Ovarian tissue cryopreservation and transplantation is an important option for fertility preservation in adult patients with cancer who need immediate chemotherapy or do not want to undergo ovarian stimulation. Ovarian tissue freezing is the only option for preserving the fertility of prepubertal patients with cancer. In a recent review, it was reported that frozen-thawed ovarian transplantation has lead to about 90 live births and the conception rate was about 30%. Endocrine function recovery was observed in 92.9% between 3.5 and 6.5 months after transplantation. Based on our review, ovarian tissue cryopreservation and transplantation may be carefully considered before cancer treatment in order to preserve fertility and endocrine function in young cancer survivors.

Keywords: Fertility preservation; Ovarian tissue cryopreservation; Ovarian tissue transplantation; Neoplasms; Therapeutics

Introduction

Many women in their reproductive age are diagnosed with cancer each year. Approximately 843,820 women were diagnosed with cancer in the United States in 2016 and over 89,000 cases were under 45 years old [1]. In Korea, the number of female patients with cancer was 104,175 in 2014. The 5-year survival rate of all patients diagnosed with cancer between 2011 and 2015 was 70.7%, and has been steadily improving [2]. The development of medical technology in the diagnosis and treatment of cancer, particularly of chemotherapy and radiotherapy, has increased the survival rate of these patients [3]. Both chemotherapy and radiotherapy cause loss of ovarian function due to follicular depletion [4,5]. Especially alkylating agents such as cyclophosphamide are gonadotoxic and cause premature ovarian failure [6].

According to the social trends of postponing the childbearing for professional or personal reasons, many patients with cancer have not yet begun or completed their family planning [7]. For women, cancer treatment-related infertility may be associated with a loss of self-esteem and can lead to psychosocial distress [8]. Therefore, efforts should be made to provide with opportunities for young patients with cancer to preserve their fertility potential. The recovery of ovarian function, which means recovery of endocrine function and fertility, will improve the quality of life of women in their reproductive age after they have survived cancer [9].

Cancer treatment and ovarian damage

Due to improvements of chemotherapy and radiotherapy, the effect of cancer treatment and survival rate of patients with cancer are greatly improved compared to the past, but unfortunately gonadal injury remained a major complication.

Received: 2017.09.07. Revised: 2017.10.11. Accepted: 2017.10.20.
Corresponding author: Sanghoon Lee
Department of Obstetrics and Gynecology, Korea University Anam Hospital, Korea University College of Medicine, 73 Inchon-ro, Seongbuk-gu, Seoul 02841, Korea
E-mail: mdleesh@gmail.com
https://orcid.org/0000-0002-5546-0763
*Sooyoung Kim and Younji Lee equally contributed in this manuscript.

Table 1. Estimated risk of gonadal damage according to chemotherapy treatment

High risk	Intermediate risk	Low risk
Cyclophosphamide	Cisplatin	Methotrexate
Ifosfamide	Adriamycin	5-Fluorouracil
Chlorambucil		Vincristine
Melphalan		Bleomycin
Busulfan		Actinomycin D
Nitrogen mustard		
Procarbazine		

Chemotherapy-induced amenorrhea has been reported in literature and its incidence ranges from 53% to 89% in patients with breast cancer [10].

Anti-cancer drugs for gonadal damage are generally classified into low risk, intermediate risk, and high risk groups (Table 1) [6,11]. With conventional chemotherapy, there are differences in ovarian failure rate according to type, dose, duration of chemotherapy drug, and age of patient [12]. Gonadotoxic treatment at any reproductive age can lead to subsequent infertility. The primordial follicles are lost with increasing age, and the risk of gonadal damage and infertility is higher in older patients than in younger patients [13]. In addition, most patients with cancer are treated with multiagent chemotherapy protocols, and it is not easy to assess the degree of gonadal damage caused by each specific agent [14].

The primordial follicles are very sensitive to radiation and the extent of damage to the ovaries depends on the total dose, the field of treatment, fractionation schedule and age at the time of treatment [15]. Radiotherapy-induced follicular damage resulting in a high risk of prolonged amenorrhea can occur when pelvic or whole abdominal areas are exposed to a radiation dose ≥6 Gy in adult women, ≥10 Gy in postpubertal girls, and ≥15 Gy in prepubertal girls [16-20]. As the number of primordial follicles is proportional to the oocyte pool, younger patients who receive radiotherapy have the later onset of premature menopause [21].

Awareness of health-care providers regarding fertility preservation

The American Society of Clinical Oncology (ASCO) guidelines recommended that oncologists should inform patients with cancer about potential treatment-related infertility and make appropriate referrals for interested patients [22]. In one survey, 61% of oncologists always or usually discuss the impact of potentially gonadotoxic treatments on patient's future fertility. Of interest, nearly half (45%) never referred women to reproductive specialists, with only 15% was routinely referring [23]. Another study reported that there have been sex differences in access to fertility-related information and the use of fertility preservation treatment. Compared to female patients with cancer, males received more information about treatment impact on fertility (80% vs. 48%) and fertility preservation (68% vs. 14%). More than half of men banked frozen sperm whereas only 2% of women underwent fertility preservation [24]. For women with breast cancer, factors favoring early referrals were older age, early-stage cancer, family history of breast cancer, and academic center involvement. Those seen before cancer treatment were more likely to receive an intervention [25].

Physician's knowledge about efficacy of fertility preservation and the referral of patients is one part of communication barrier regarding fertility preservation. One survey reported that only half of physicians (53.3%) in pediatric hematology/oncology were aware of knowledge of current research and technology in fertility preservation and 64.3% of physicians answered that there are difficulties in finding proper referral site and specialists for their patients with cancer [26].

Most physicians know about the adverse effects of cancer treatment with chemotherapy and radiotherapy on reproductive potential. However, gaps exist between knowledge and practice, therefore, more readily available and accessible information is needed.

Options on fertility preservation in women

Fertility preservation options for women take into account patient's age, the presence of partner, the treatment method, and the possibility of treatment delay. Several options for fertility preservation in females have been introduced, including embryo and oocyte cryopreservation, ovarian tissue cryopreservation, ovarian suppression, ovarian transposition, and conservative gynecologic surgery (Table 2) [22,27].

Both embryo and oocyte cryopreservation require a period of approximately 10–14 days from the onset of menstruation for ovarian stimulation. Therefore, if it is difficult to delay che-

Table 2. Fertility preservation options in women with cancer

Standard
Embryo cryopreservation
Oocyte cryopreservation
Gonadal shielding during radiation therapy
Ovarian transposition (oophoropexy)
Other conservative gynecologic surgery
Investigational
Ovarian tissue cryopreservation and transplantation
Ovarian suppression with GnRH analogs or antagonists

GnRH, gonadotropin-releasing hormone.

motherapy, it is advisable not to wait for the next menstrual cycle to start the stimulation protocol and random start stimulation protocol is recommended [6,28]. Embryo cryopreservation is known as the best-established technique and has been widely used around the world. In a recent retrospective cohort study, frozen embryo transfer protocols had higher implantation rate (46.8% vs. 42.0%) and ongoing pregnancy rate (52.0% vs. 45.3%) than fresh transfer protocols [29]. It was estimated that more than half million of babies have been born worldwide using frozen-thawed embryos [30].

Oocyte cryopreservation was newly accepted as a standard method for fertility preservation in 2013 ASCO guideline update. For a long time, oocyte cryopreservation was based on slow freezing protocols, which made it harder for zona pellucida. This drawback could only be overcome after the development of intracytoplasmic sperm injection [31]. Oocyte freezing by vitrification can avoid intracytoplasmic ice crystal formation as well as cytoskeleton damage. With these methods, high survival and pregnancy rates were obtained [32]. An implantation rate of 40% and clinical pregnancy rate of 55% with vitrified oocytes have been reported similar to fresh oocytes [33].

Gonadal shielding during radiotherapy is used as a treatment protocol in female cancer. If shielding of the gonadal area is not feasible, ovarian transposition, in which the ovaries are surgically fixed away from the radiation field, should be considered. Gynecologic oncologists should consider the radiation field, which is usually extents to the upper field border of the forth/fifth lumbar vertebra [34]. It is widely accepted that surgical transposition should be performed at least 3 cm above the upper border of the radiation field [35].

Ovarian suppression with gonadotropin-releasing hormone agonist (GnRHa) or antagonist treatment during chemotherapy is still a controversial method of fertility preservation. This method is based on the theory that ovarian follicle destruction is prevented by maintaining the ovarian follicle dormant by suppressing ovarian function transiently during chemotherapy. In a recent study performed on 218 premenopausal patients with breast cancer, the outcomes of standard chemotherapy with a GnRHa were compared with standard chemotherapy alone [36]. The ovarian failure rate was 8% in the GnRHa group and 22% in the chemotherapy alone group. Pregnancy rates were higher in the group with GnRHa than in the chemotherapy alone group (21% vs. 11%), and a total of 12 babies were born in the chemotherapy alone group versus 18 babies were born in the GnRHa group. However, there was no significant difference between the 2 groups when pregnancy rates were recalculated for women attempting to conceive. In addition, they used follicle-stimulation hormone (FSH), estradiol, and inhibin B as the indicator of ovarian reserve therefore their concentration varied according to the menstrual cycle. Previous studies, using an anti-Müllerian hormone (AMH) or antral follicular count that are independent indicators of fertility in a physiological cycle, no benefit of GnRHa was reported [37]. Further studies are required to confirm the efficacy and safety of ovarian suppression using GnRHa to prevent gonadal damage during chemotherapy. Another study showed that treatment with AMH during chemotherapy can significantly protect the ovarian reserve in mice [38]. AMH also known as müllerian inhibiting substance is produced by granulosa cells of growing follicles, which act as a negative regulator of primordial follicle activation. Unlike current hormonal contraceptives that interfere with the hypothalamus-pituitaty-gonadal axis, AMH directly affects the first step of folliculogenesis, allowing it to spare the pool of quiescent primordial follicles. The inhibition of primordial follicle activation by AMH was found to be reversible. It demonstrated that AMH is an effective contraceptive in mice during chemotherapy and expected to open up many clinical possibilities in other conditions. The other study conducted to evaluate the effects of sphingosine-1-phosphate (S1P) on human ovarian tissue implanted in mice during chemotherapy [39]. S1P is an anti-apoptosis agent, which is an inhibitor of ceramide-induced death pathway of follicular cells. They treated with S1P co-treatment and evaluated an expression of activated caspase 3 to confirm the activation of apoptotic cell death pathways. S1P co-treatment with chemotherapy was associated with the significant decrease in the percentage of apoptotic follicles compared with

chemotherapy only group (32.7±4.4% vs. 62.0±3.9% in cyclophosphamide; 27.1±7.6% vs. 76.7±7.4% in doxorubicin). It demonstrated that S1P can block human apoptotic follicles death induced by chemotherapy agents and suggested pharmacological strategies to preserve ovarian function in human undergoing cancer treatments.

Conservative gynecologic surgery intends to spare the reproductive organs as much as possible for subsequent fertility. Trachelectomy is a surgical procedure used to treat eligible women with early stage cervical cancer who wish to preserve their fertility. In one study, 125 patients underwent vaginal radical trachelectomy and reviewed fertility and obstetrical outcomes. The recurrent rate of cervical cancer after trachelectomy was 4.8% and the death rate was 1.6%. A total of 58 women were pregnant from 106 cases, and 75% of them had full term delivery. Overall, 13.5% of patients had problems associated with fertility [40]. In ovarian cancer, according to the National Comprehensive Cancer Network guidelines, unilateral salpingo-oophorectomy preserving the uterus and contralateral ovary can be considered for patients with apparent early stage invasive epithelial tumors, or low malignant potential lesions who wish to preserve their fertility [41,42]. In endometrial cancer by stage 1 grade 1, fertility-preserving therapy can be performed when there is no invasion into the myometrium [43]. Following continuous progestin-based therapy, endometrial sampling must be performed every 3–6 months. If a patient shows complete remission after 6 months, she may attempt a pregnancy while being carefully monitored in every 3–6 months, and undergo surgical staging surgery, including total hysterectomy and/or bilateral salpingo-oophorectomy, upon pregnancy completion [44].

Ovarian tissue cryopreservation is an experimental method of fertility preservation. It has advantage of requiring neither a sperm donor nor ovarian stimulation. Therefore, it is the only option available for prepubertal girls and patients who cannot delay their cancer treatment for ovarian stimulation. Unlike freezing individual oocytes or embryos, ovarian tissue cryopreservation can preserve hundreds of primordial follicles more effectively at once [45].

There are 2 methods of ovarian tissue cryopreservation: slow freezing and vitrification. Slow freezing is known as equilibrium freezing and results in safe freezing without serious osmotic and deforming effects to cells [46]. Samples are frozen slowly in a programmable freezer to approximately –140°C, and then the tissue is put into liquid nitrogen at –196°C for storage. Vitrification is a non-equilibrium method and is developed to minimize the risk of ice crystal formation in ovarian tissue [47,48]. Vitrification requires much higher concentrations of the cryoprotectant and extremely high cooling rate compared to slow freezing [49]. The frozen-thawed ovarian tissue can be transplanted orthotopically to the pelvis or heterotopically to subcutaneous areas such as the forearm or abdomen. As transplantation of ovarian tissue is performed without vascular reanastomosis, the ovarian graft is exposed to ischemia and potential follicular depletion during the time before tissue revascularization. Therefore, an adequate time is necessary for new blood vessels growth [50].

Whole ovarian transplantation with vascular anastomosis allows an immediate revascularization of the ovarian cortex, and significantly reduces the probability of ischemic injury [51]. To avoid ischemic injury, transplantation of a whole cryopreserved ovary may be a better option. However, cryopreserving a large sized intact ovary is problematic because of the difficulty of adequate diffusion of cryoprotective agents into large tissue masses and vascular injury caused by intravascular ice formation [52]. Nevertheless, successful cryopreservation and autotransplantation of whole ovaries have been achieved in a number of experimental animal studies [53-55]. The viability of the human whole ovary after cryopreservation and transplantation are encouraging and further research should allow the utilization of this option in the future.

Recently, *in vitro* ovarian follicle maturation is being studied for preservation of fertility. One serious and legitimate concern is the possibility of reimplanting malignant cells from the primary tumor back into women who have overcome their cancer [56]. Isolation of individual ovarian follicles from ovarian tissues and subsequent *in vitro* culture may minimize the risk of transmission and reimplantation of malignant cells. The goal of these methods are to retrieve fully developed oocytes from cultured follicles that could be matured *in vitro* and fertilized, producing viable embryos for transfer to the uterus [57]. These techniques have been successfully used to culture follicles from mice to human [58,59].

Ovarian tissue cryopreservation and transplantation

The first ovarian transplant with cryopreserved ovarian tissue was performed by Oktay et al. in 1999 and 2010 [60,61].

Eighty pieces of tissue were thawed and sutured to 2 triangular frames composed of an absorbable cellulose membrane. They were then sutured underneath the left pelvic peritoneum laparoscopically [60]. In 2004, Donnez et al. [62] reported the first successful live birth after ovarian tissue transplantation by using slow freeze technique. Since then, there have been many human studies reporting successful pregnancies after ovarian tissue cryopreservation and transplantation [62-66]. Recently, robot-assisted transplantation approach that may have several advantages over laparoscopic transplantation, which include precision, more delicate graft handling, and reduced time from tissue thawing to transplantation, has also been reported [67].

Ovarian tissue has been xenotransplanted from human to immunodeficient mice, with subsequent ovulation for experimental purpose [68-70]. High rates of follicular survival after transplantation of cryopreserved human ovarian tissue in mice have been demonstrated with the reservation of a large pool of dormant primordial follicles [71]. However, aberrant microtubule organization and chromatin patterns that occur during the maturation process may result in abnormal oocytes [72,73]. The risk of trans-species infections, caused by pathogens including retroviruses and prions also needs to be evaluated before clinically addressing this experimental approach.

Ovarian function recovery and longevity after ovarian tissue transplantation

A review of 3 centers reported 60 cases of re-implantation [74]. All ovarian tissues were frozen using the slow freezing method and the ovarian activity was restored in 92.9% of cases. Approximately 3.5 to 6.5 months after transplantation were necessary for a rise in estradiol and a decrease in FSH levels.

Silber et al. [75] reported orthotopic ovarian isotransplantation between a series of monozygotic twins discordant for ovarian failure in 2008. Normal FSH levels and menstrual cycles resumed 77–142 days after fresh and cryopreserved ovarian tissue transplantation. Subsequently, 11 live births were reported following fresh ovarian tissue transplantation and 3 live births after cryopreserved one [76,77]. The tissues had been frozen for 14 years at most. Most patients conceived naturally and 3 of them conceived twice or 3 times from the same graft. Modest portion of ovarian tissue grafts have survived more than 7 years indicating minimal oocyte loss from ischemic period.

Donnez et al. [78] reported 3 cases of ovarian transplantation between genetically non-identical sisters in 2010. The recipients received chemotherapy and radiotherapy resulting in premature ovarian failure. All donated ovarian tissue were human leukocyte antigen-compatible with the recipients. The donor's ovarian cortex was sutured to the recipient's decorticated ovarian medulla. The biopsies taken during transplantation showed atrophic ovaries of the recipient with lack of follicles. It was the first successful recovery of ovarian function after allo-transplantation.

Kim [79] reported the longevity of heterotopic auto-transplantation of frozen-thawed ovarian tissue in 5 patients with cancer from 2001 to 2011. The patients were aged between 30 and 40 years and received stored ovarian tissue (for 1–10 years). A total of 8 to 10 slices of rapidly thawed thin ovarian cortex were threaded onto a 3-0 Vicryl suture for re-implantation between the rectus sheath and muscle. Monthly hormone levels were monitored until the cessation of endocrine function had been confirmed. Endocrine function was recovered between 12 and 20 weeks after transplantation. Four patients underwent the second transplantation 1 to 2 years after the first one. The duration of endocrine function after the second transplantation was much longer (9–84 months) and the longest one lasted for 7 years. The patient had 3 *in vitro* fertilization cycles resulting in 4 embryos.

The longevity of grafted ovarian tissue is still being evaluated. Jensen et al. [80] reported 53 transplants maintaining endocrine function up to 10 years and a pregnancy rate of 31% for those who wish to conceive (10 of 32). This result after freezing-thawing transplantation would be beneficial for young patients with cancer and premature ovarian failure.

Table 3. Factors affecting the longevity of ovarian tissue graft

1. Age at the time of cryopreservation
2. Baseline ovarian reserve
3. History of cancer treatment
4. Techniques of ovarian tissue preparation
5. Freezing-thawing protocols
6. Number of cortical sections grafted
7. Transplantation techniques and graft sites
8. Degree of ischemia after transplantation
9. Number of follicles survived in ovarian grafts

Follicles may be cryopreserved for future use, and some patients may require repeated transplantation to maintain ovarian hormonal function [81].

Many factors that may affect the length of time the grafts function (Table 3) [79,82]. One of the most important factors is the number of survived eggs during the freezing-thawing and revascularization. The graft needs 4–5 days to be reoxygenated [83,84]. To increase the chance of fertility preservation, one-half to two thirds of the cortex from one ovary is harvested in most cases [85]. During revascularization, about one third of the immature eggs survived the ischemic damage [86]. Subsequently, the number and the likelihood of the immature eggs' survival may be estimated during freezing-thawing to ensure transplant of more than 1,000 non-growing follicles (the number in a menopause women) [87,88]. In experiment, to improve the angiogenesis, the site of transplantation could be prepared by encapsulated vascular endothelial growth factor (VEGF) [89] and stromal cells enriched in CD 34 cells [90]. Patient treatment with melatonin or ovarian tissue incubation with hyaluronan-rich biological glue, plus VEGF-A and vitamin E may improve graft survival [91].

Pregnancy outcomes from cryopreserved and re-implanted ovarian tissue

To date, 87 live births and 9 ongoing pregnancies have been reported from ovarian tissue cryopreservation and transplantation worldwide (Fig. 1) [92,93]. The data from 5 centers where the information concerning the number of transplantations was known was collected [94]. Overall, 29% women conceived after tissue cryopreservation and transplantation (32 of the 111 recipients). Except for 2 births achieved by vitrification method reported by Migishima et al. [54] and few births, slow freezing was used mostly although the results of vitrification in experimental models are increasingly promising. Two women delivered 3 babies each, demonstrating the possibility of natural conception several times after one procedure [95]. According to Donnez et al. [94], orthotopic transplantation allowed more than 50% of women to conceive naturally. The patient's age at the time of cryopreservation is a predictive factor, as the majority of pregnant women were under age of 30. In general, age of 35 is regarded as upper limit for cryopreservation of ovarian tissue, because during the procedure, follicle preservation mainly occurs in primordial follicles, but their number significantly decreases with age [96]. There are a few recommendations to select candidates most likely to benefit from ovarian tissue cryopreservation (Table 4) [97,98].

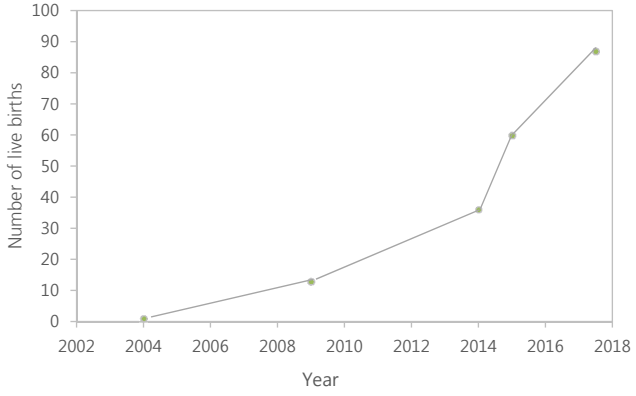

Fig. 1. Cumulative live births after ovarian tissue cryopreservation and transplantation. The number has increased in recent years, resulting in a total of 87 live births until May 2017.

As previously mentioned, re-implantation can be classified as orthotopic or heterotopic [99]. Endocrine function recovery has been described consistently after heterotopic ovarian transplantation [100]. The strengths of heterotopic ovarian tissue re-implantation are: 1) avoidance of invasive procedure; 2) easy accessibility of the graft; 3) cost-effective technology, if the procedure is required more than once; and 4) feasibility even in cases of severe pelvic adhesions that hinder orthotopic transplantation [79,100,101]. However, natural conception cannot be expected, and *in vitro* fertilization is required. To date, there are 2 reported cases of pregnancy after heterotopic grafting worldwide [102,103]. This result may provide optimism for women who had prior pelvic surgery or radiotherapy without an appropriate orthotopic site for transplantation.

Table 4. Selection criteria for ovarian tissue cryopreservation

1. Age below 35 years (flexible depending on AMH level and biological age)
2. A high risk of premature ovarian failure (>50%) gonadotoxic
3. A realistic chance of surviving for 5 years
4. No previous chemotherapy or radiotherapy if aged 15 years or older at diagnosis, but mild, non-gonadotoxic chemotherapy is acceptable if younger than 15 years
5. No disseminated disease
6. No contraindications against operation or anaesthesia
7. Informed consent (parent and patient when possible)

AMH, anti-Müllerian hormone.

The current and future perspective of ovarian tissue transplantation

In Korea, to our knowledge, the first successful ovarian tissue transplantation was performed in 2016 [104]. A 23-year-old patient with cervical cancer underwent pelviscopic partial resection of both ovaries for ovarian tissue cryopreservation using vitrification. As a result of concurrent chemoradiation therapy, she developed iatrogenic premature ovarian failure with no tumor recurrence observed during 5 years after treatment. The patient requested ovarian tissue transplantation, and it was performed in both pelvic lateral walls via Pfannenstiel incision. Monthly hormonal levels were monitored after transplantation, and a rise in estradiol and a decrease in FSH levels were measured 5 months after. The radiotherapy to the uterus with ovarian transposition significantly and irreversibly damages the uterus and its function. Thus, one of possible clinical scenarios is that she may undergo ovum retrieval under ultrasound guidance from the relocation site, and the eggs can be fertilized with sperm. This may allow the patient to have a child through a surrogate mother [105].

Ovarian tissue cryopreservation and re-implantation in women diagnosed with cancer before cancer treatments is an effective option to preserve their fertility and to restore gonadal endocrine function. For cryopreservation, most of the births were derived from slow freezing [74]. Considering the expense and complexity of slow freezing, vitrification requires further investigation to be chosen as an alternative. Except for 2 pregnancies, all reported pregnancies resulted from orthotopic transplantation [102]. Despite steady functional recovery, heterotopic sites may not provide an optimal environment for pregnancy [103]. After ovarian tissue transplantation, endocrine function restoration has been observed consistently with increasing number of successful live births. Transplantation of ovarian tissue for fertility preservation is yet experimental, but as Donnez et al. [94] suggested, time may have come for the technique to move on from experimental studies to clinical application.

Conclusion

Progress in the diagnosis and treatment of cancer has increased the number and prognosis of cancer survivors. Early referral to reproductive specialists is crucial for patients with cancer of pre-pubertal and childbearing age [27]. Embryo or oocyte cryopreservation is the standard method for fertility preservation, while ovarian tissue cryopreservation and transplantation is yet investigational. The latter is the only fertility preservation option for prepubertal girls diagnosed with cancer. The recovery of endocrine function after re-implantation is well established and the live birth rate has been substantially increasing. Based on our review, ovarian tissue cryopreservation and transplantation may be carefully considered before cancer treatment in order to preserve endocrine function and fertility in young patients with cancer.

Acknowledgements

This work was supported by the national research foundation of Korea grant funded by the Korean government (NRF-2016R1C1B3015250) and Korea university grant (K1609791).

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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