Received: 6 November 2018 | Revised: 25 February 2019 | Accepted: 8 March 2019

DOI: 10.1002/rmb2.12268

MINI REVIEW

Reproductive Medicine and Biology

WILEY

Current state and future possibilities of ovarian tissue transplantation

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Funding information
This work was supported by JSPS KAKENHI Grant Number JP17H04342.

Abstract

Background: As a result of recent developments in cancer treatment, cancer survivorship and survivors' quality of life have been emphasized. Although ovarian tissue cryopreservation (OTC) is an experimental technique, it would be the sole technique for fertility preservation treatment for girls with malignant disease. Indeed, OTC requires ovarian tissue transplantation (OTT) for conception. As for OTC, there is room to investigate OTT. The present review focused on the current state and progress of OTT.

Method: The literature regarding OTT, which is currently under development, was reviewed.

Main findings: To improve the outcome of OTT, both efficacy and safety are important. Good surgical technique and the optimal site are important surgical factors, with orthotopic transplantation increasing. Treatment of growth factors, gonadotropins, antioxidants, apoptosis suppression factors, and cell therapy may improve the efficacy of OTT by inducing neo-angiogenesis and preventing damage. Artificial ovaries, complete in vitro primordial follicle culture technique, and non-invasive ovarian imaging techniques, such as optical coherence tomography, to select the best ovarian tissue are future possibilities.

Conclusion: Improving neo-angiogenesis and preventing damage with optimization, as well as investigation of future techniques, may bring us to the next stage of a fertility preservation strategy.

KEYWORDS

fertility preservation, in vitro oocyte maturation techniques, investigative techniques, tissue and organ harvesting, transplantation

1 | INTRODUCTION

With the dramatic developments in cancer treatments, "cancer survivorship" is regarded as an important issue in cancer therapy. "Fertility" has been a particular concern among cancer survivors and medical practitioners.[1,2] Furthermore, facilitation of pregnancy and delivery after cancer treatment is one solution to recovering the reduced birthrate of leading countries that have a low total fertility rate. Therefore, fertility preservation is an attractive field, not only in reproductive medicine, but also from a social perspective. Based on the guideline that was revised by the American Society of Clinical Oncology (ASCO), only oocyte and embryo cryopreservation are endorsed as an "established method" for fertility preservation for patients who face a threat to their own fertility due to cancer treatment.[4] Meanwhile, many experts

believe that ovarian tissue cryopreservation (OTC) fulfills the criteria for an "established method" rather than an "experimental method".[5]

The indications for OTC are specifically fertility preservation for child and adolescent patients and patients who do not have enough time to receive another fertility preservation treatment.[4,5] Therefore, the number of cases who underwent OTC is much fewer than the number of cases who underwent oocyte and embryo cryopreservation. However, more than 4500 cases underwent OTC in Europe,[7] and more than 200 cases underwent OTC in Japan (2006-2016, unpublished data). In addition, the numbers of cases who underwent ovarian tissue transplantation (OTT) were less than the number of OTC cases. Of the few cases of OTT (185 in Europe between 2010 and 2014[7]; 29 in the United States[8]; 3 in Japan until 2016, unpublished data), there were more than 130 live birth as of June 2017.[5] Hence, 3%-4% of OTC cases have ultimately undergone OTT, and <1% ultimately generated pregnancies and deliveries.[9]

Consequently, how to develop the procedure of OTT remains unknown. This review focuses on the current state and future possibilities of OTT to become an "established method" for fertility preservation.

2 | SEARCH METHODS

Using PubMed, the English-language literature on OTT, which is currently under development, was reviewed. The specific focus of the literature review was the surgical procedure and additives to accelerate the effectiveness of OTT, as well as the methodology to ensure the safety of OTT, by avoiding the re-implantation of malignant cells.

3 | CURRENT STATE OF OVARIAN TISSUE TRANSPLANTATION

The first live birth case was reported in 2004,[10] and the numbers of live births from transplanted ovaries have increased logarithmically since 2013.[5] Ovarian activity after OTT varies, and its duration is around 4-5 years (maximum > 10 years).[11,12] Generally, the duration depends on follicular density at the time of OTC.[13] Although the pregnancy rate after OTT is reported to be 29%-41%, with a live birth rate of 23%-36%,[13,14] as with oocyte cryopreservation, this outcome may vary depending on the age of the patients who undergo OTC.

As mentioned before, OTC-OTT is still an "experimental method" for fertility preservation from the viewpoint of the ASCO (United States). However, it is already considered a non-experimental method in some countries.[4] Additionally, confirmation of the safety of OTT (especially for patients with leukemia) is needed to increase the use of OTC-OTT.[4]

4 | SELECTING THE SITE FOR OTT AND SURGICAL TECHNIQUES

Transplanted ovarian tissue does not serve to restore long-term ovarian function,[16] because 50%-90% of follicles disappear due to ischemia and hypoxia before revascularization.[17] Indeed, revascularization after OTT may take up to 48 hours in rodents and up to 5 days in humans.[18] Therefore, the OTT procedure is an extremely important step to achieve graft survival and pregnancy.

Generally, the ovarian tissues are transplanted orthotopically (into the remaining ovary, ovarian fossa, or broad ligament) by laparoscopic surgery,[16,19] because most live birth cases were from orthotopically transplanted ovarian tissue.[5] Furthermore, von Wolff et al suggested and explained orthotopic transplantation into three sites (pelvic peritoneum, into the ovary, and onto the ovary). In particular, they consider that "onto the ovary" transplantation needs the greatest laparoscopic-microsurgical expertise to finish the transplantation with 5-0 PDS (Johnson & Johnson, NJ, USA) suturing within 1-2 hours.[16] Now, *Ferti*PROTEKT is conducting an open international multicenter study to determine the most suitable site for OTT.[16] As for heterotopic transplantation, the candidate sites are subcutaneous, abdominal wall, forearm, beneath the peritoneum, rectus muscle,[19] and fallopian tube and omentum which we have suggested.[20,21]

To induce neovascularization before OTT, two-step laparoscopy has been performed by pioneers of OTT.[10,23,24] The first-step laparoscopy was performed to create a peritoneal pocket aimed to induce angiogenesis 1 week before OTT. Although some researchers tried to confirm the efficacy of two-step OTT using an animal model, it remains unclear.[25]

Additionally, the safety of OTT is also important in terms of laparoscopic surgery. Unfortunately, there are no large clinical studies of postoperative complications, though it seems that complication rates after OCT and OTT are <1%.[26,27]

5 | ADDITIVES FOR IMPROVING OVARIAN TISSUE GRAFT SURVIVAL

Revascularization and preventing apoptosis are key factors to ensure ovarian tissue graft survival, because ischemia and hypoxia have been reported as major obstacles to successful OTT. Some additives and cell therapies have been investigated for clinical application to achieve effective OTT (Table 1).

5.1 | Growth factor treatments

After OTT, vascular endothelial growth factor (VEGF) transcription in the graft is upregulated due to hypoxia. Controlled VEGF infusion from biomaterials has been effective to promote angiogenesis. OTT with fibrin encapsulation, consisting of fibrin-heparin-binding peptide (HBP)-VEGF hydrogels, demonstrated that it could accelerate angiogenesis and primordial follicle survival, based on investigating follicle counts and blood vessel density.[18] In addition, the fibrin hydrogel containing basic fibroblast growth factor (bFGF) could increase the number of surviving follicles by decreasing follicle apoptosis. This outcome was verified by CD31 expression and microvascular density.[28]

TABLE 1 Candidates of options for improving ovarian tissue transplantation outcomes

Treatment		Donor	Recipient	Graft site	Effect	References
Growth factor	VEGF (with fibrin-HBP)	Mice	Mice	Bursa	Survival primordial follicles↑ Blood vessel density↑ The average time until the first deliverly↓	Shikanov[18]
	bFGF (with fibrin)	Mice	Mice	Under the skin	Survival and proliferation of follicles↑ Apoptosis of follicles and stromal cells↓ Revascularization↑	Gao[28]
Horomone	HMG	Mice	Mice	Kidney capsule	Number of surviving follicles↑ Revascularization↑ VEGF expression↑	Wang[33]
	AMH	Human	Mice	Gluteus maximus	Percent of primordial follicle↑	Man[43]
Antioxidant	Vitamine E	Human mice	Mice	Kidney capsule	Rate of survival rate↑ lipid peroxidation↓	Nugent[44]
	Melatonin Oxytetracycline	Rat	Rat	Intraperitoneal	Malondialdehyde (ovarian necrosis)↓	Sapmaz[45]
Protection of ischemia-reperfusion injury	Amlodipine (antioxidant)	Rat	-	-	Ovarian tissue damage↓	Halici[46]
	Tadalafil (PDE-5 inhibitor), L-arginine (NO precursor)	Rat	No OTT (Adnexal or testicular torsion model)		Ovary and testis tissue damage↓	Arikan[47] Ozmerdiven[48]
Apoptosis suppression factor	S1P	Human	Mice	Dorsal muscle	Apoptotic follicles↓ Vascular density↑ Proliferation of ovarian stromal cells↑ Necrosis and tissue hypoxia of ovarian stromal cells↓	Soleimani[50]
Cell therapy	MSC	Human	Mice	Subcutaneous	Number of surviving follicles↑ Revascularization↑	Zhang[57]
	ASC	Rat	Rat	Retroperitoneum	Earlier resumption of the estrous phase Enhanced estrogen receptors	Damous[60]
	ExEC	Human	Mice	Fascia of the Gluteus Maximus	Number of surviving follicles↑ Ovarian function↑ Revascularization↑	Man[43]

OTT, ovarian tissue transplantation; VEGF, vascular endothelial growth factor; HBP, heparin-binding peptide; bFGF, basic fibroblast growth factor; HMG, human menopausal gonadotropin; AMH, Anti-Müllerian hormone; PDE-5, phosphodiesterase type-5; NO, nitric oxide; S1P, Sphingosine-1-phosphate; MSC, Mesenchymal stem cell; ASC, Adipose tissue-derived stem cell; ExECs, exogeneous endothelial cell.

5.2 | Hormonal factors

Vascular endothelial growth factor gene expression is regulated by various factors, not only hypoxia, but also cytokines and growth factors as well.[29,30] Moreover, it has been reported that follicle-stimulating hormone (FSH) and luteinizing hormone (LH)/human chorionic gonadotropin (hCG) modulate the expression of VEGF in the ovary.[31,32] Although the efficacy of FSH treatment for OTT was investigated, it continues to be a controversial issue. OTT into the kidney capsule using ovaries that were cultured in medium containing human menopausal gonadotropin (HMG) demonstrated enhanced VEGF expression (1.6-6.5 times) and increased survival of follicles after OTT (1.2-1.5 times).[33] Meanwhile, OTT into the rat skin of the back auto-transplantation model, which received intraperitoneal injection (IP) of pregnant mare's serum gonadotropin (PMSG) 10 IU every other day, demonstrated only a slight increase of VEGF mRNA expression in the early stages of angiogenesis. There were no significant differences in terms of number of follicles and VEGF protein expression between control- and PMSG-treated rats.[34] As one hormonal factor, androgens are suggested as additives to improve follicular survival of OTT.[25] Based on a study of OTT into male mice, androgens were not harmful, because normal pups were born in the male OTT groups. However, it was insufficient to conclude that androgen treatment was effective for OTT, although it may alter follicle responsiveness to FSH stimulation.[35] As a result of reviewing the articles,[35,36] we have concluded that it

is difficult to determine the effect of androgens on improving follicular survival of OTT.

Anti-Müllerian hormone (AMH), a member of the transforming growth factor beta (TGF-β) super-family of growth factors, is one of candidates for improving the efficacy of ovarian tissue transplantation. It was demonstrated that AMH could suppress the primordial follicle activation with AMH null mutation mice and in vitro ovarian culture model.[38,39] The suppression of follicle activation after OTT is important to maintain ovarian function, because follicle activation may be caused immediately after OTT.[41] Indeed, co-transplantation of AMH with cell therapy (after-mentioned) and exogenous AMH for ovarian tissue transplantation demonstrated the retention of follicular reserve following ovarian tissue transplantation.[42,43]

5.3 | Antioxidants and protection of ischemia-reperfusion injury

Ischemia-reperfusion injury, which is caused by oxygen free radicals, is a representative harmful factor for grafted ovarian tissue. Endogenous antioxidant factors can neutralize oxygen free radicals produced in excess during ischemic stress.[25] As exogenous antioxidants, ascorbic acid, mannitol, vitamin E, melatonin, and oxytetracycline are candidates for improving the follicular survival rate after OTT.[44,45] However, antioxidants have demonstrated only limited beneficial effects for OTT, and they are very controversial.[25] In terms of protection from ischemia-reperfusion injury, amlodipine,[46] tadalafil (long-acting phosphodiesterase type-5 (PDE-5) inhibitor),[47,48] and L-arginine (NO precursor)[48] have been investigated in ovarian and testicular torsion model animals.

5.4 | Apoptosis suppression factor (sphingosine-1-phosphate)

Recently, sphingosine-1-phosphate (S1P) has been noted as an apoptosis suppression factor that induces cell growth and proliferation.[49] It is also the ligand for a family of G protein-coupled receptors, and five types of S1P receptor have been cloned: s1p1 (EDG-1), s1p2 (EDG-5), s1p3 (EDG-3), s1p4 (EDG-6), and s1p5 (EDG-8). Its biological functions are related to the type of receptor, because different G proteins act as downstream second messengers.[49] It also acts as a modulator of angiogenesis in non-human non-reproductive tissues, and cross-talk between S1P and angiogenesis-related growth factor receptors (platelet-derived growth factor and/or VEGF) has also been demonstrated.[50] Researchers have found that S1P increases vascular density, accelerates the angiogenic process and the significant proliferation of ovarian stromal cells, and reduces necrosis and tissue hypoxia. These processes could result in a lower percentage of apoptotic follicles on xenografted models of human ovarian tissue.[19,50] In fact, S1P could inhibit cell apoptosis caused by chemotherapy and radiotherapy.[51,52] Additionally, inclusion of S1P in the vitrification solution during transplantation of vitrified-warmed ovaries prevented apoptosis of the primordial follicular pool.[56]

5.5 | Cell therapy

Co-transplantation with stem cells or other types of cells is also a new approach for improving graft survival in OTT. In particular, mesenchymal stem cell (MSC),[57] adipose tissue-derived stem cell (ASC),[58,59] and exogenous endothelial cell (ExEC)[43] co-transplantation could promote angiogenesis in a xenograft OTT model. As for the mechanisms of co-transplantation treatments, one of the main mechanisms for precipitating angiogenesis is differentiation of MSCs into endothelial cells and pericytes, thereby providing the necessary cellular components to stabilize newly formed vessels.[58,61,62] Furthermore, MSCs promote vascular formation through secretion of growth factors such as VEGF, fibroblast growth factor (FGF) 2, hepatocyte growth factor (HGF), bFGF, platelet-derived growth factor subunit B (PDGFB), TGFβ, and angiogenin, among others.[64] ASCs may play a part in modulating inflammation in the innate immune response, because a low degree of inflammation in implants containing ASC was demonstrated.[58,65] As a result of these mechanisms, co-transplantation treatments with ASCs, MSCs, and ExECs show high pO_2 levels and CD34 expression, improvement of viability, and preservation of the follicular pool.[43,57,58]

6 | SAFETY MANAGEMENT TO PREVENT RE-IMPLANTATION OF MALIGNANT CELLS

When considering improvement of the quality of OTT, we cannot avoid the "safety" of OTT. It is well known that there are risks of re-introducing cancer cells from the transplanted ovarian tissues. The ovarian metastasis potential of cancers has been categorized based on systematic studies. In high-risk disease, in terms of a high risk of metastasis to the ovary, OTC should be considered as highly experimental, and the patient should be informed that the tissue might not be used or can only be used after further establishment of the techniques.[16] Indeed, leukemia is one of the major diseases which OTC can be applied for child cancer patients. In addition, neuroblastoma, Burkitt's lymphoma, and ovarian carcinoma have the same risk of re-introducing cancer cells from the transplanted ovarian tissues, although some live birth cases have been reported from OTT of patients with such diseases.[66,67] Based on the literature review, preoperative imaging, histological studies (standard and immunohistochemistry: IHC), and polymerase chain reaction (PCR) of ovarian tissue are used to search for malignant cells. Some authors have transplanted the ovarian tissue to animals (xenografting) to assess the potential of malignant cells to nest and reproduce in the host animal. Although preoperative imaging may be helpful in screening large ovarian masses, it is unable to detect small metastases. Histological studies including IHC are sensitive methods and can detect clusters of malignant cells, but they cannot detect very small malignant cells. Reverse transcriptase (RT)-PCR is a more highly sensitive method to detect small quantities of genetic material, but it requires a specific and known sequence in the examined material.[68] Indeed, some cases are ineligible for RT-PCR before OTT.[69,70] Though RT-PCR could

confirm the presence of the malignant cells, it cannot confirm the viability or malignant potential of the cells if transplanted. Also, these procedures (IHC and RT-PCR) must destroy the examined tissues to detect the malignant cells, and therefore, the examined tissues cannot be used for OTT. Finally, it is unclear how many malignant cells are required to cause recurrence of the cancer; it may vary among individuals and malignancies.[68] Although there are some limitations, xenotransplantation into other animals may be a valuable method to assess the risk of disease transmission. Immune incompetent host mice or cultured ovarian tissues (bovine and human) may act as bio-incubators to propagate potential malignant cells.[68,71] This procedure can assess the recurrence risk of malignant disease without specific antibodies or the sequence for the malignant disease. In fact, long-term (5 months) xenografting into immunodeficient mice was performed to detect malignant cells in borderline ovarian tumors.[72] Indeed, three times xenografting with 6-month follow-up, combined with fluorescence in situ hybridization and next-generation sequencing, resulted in a healthy newborn in a patient with leukemia.[73]

However, these procedures cannot assure that the ovarian tissues are not contaminated with malignant cells. The possibilities of contaminating malignant cells in another fragment of ovarian tissues remain, even though the probability and the amount may be small. Therefore, more investigation focused on high-quality procedures to detect malignant cells non-invasively is needed to achieve safe OTT.

7 | FUTURE POSSIBILITIES OF OVARIAN TISSUE TRANSPLANTATION

7.1 | Artificial ovary

An artificial ovary is one solution for malignant cell contamination of OTT. This is constructed from two parts. The first part is follicle isolation (mainly primordial and primary follicle), and the second part is transferring them into/onto a scaffold to create the artificial organ.[5] As a matter of course, the recovery rate of transplanted secondary follicles into artificial ovary is superior to that of primordial-primary follicles.[74] Recently, the safety of follicle isolation from patients with leukemia without malignant cells appears to have been achieved with a triple-wash.[75] Although a few leukemic cells inside an artificial ovary may not lead to recurrent leukemia in an animal model,[76] we need to reduce contamination of malignant cells to the utmost limits to ensure safety. The candidate basic materials for creating the scaffold are fibrin with thrombin and gelatin.[77,78] Also, aimed to improve the outcome of OTT (not for artificial ovary), decellularized human extracellular tissue matrix (ECTM) was reported as scaffold.[79] The recent advances in the artificial ovary have demonstrated that an artificial ovary could cause puberty and obtain live birth litters in a murine model.[77,80]

7.2 | Complete in vitro growth of primordial follicles

For several decades, complete in vitro growth of primordial follicles to mature follicles has been one of the biggest themes for researchers. If we could establish this procedure, we could use OTC for ovarian cancer and patients with leukemia, because OTT would then not be compulsory for fertility preservation treatment.

Two decades ago, in vitro growth (IVG) from primordial follicles and production of live young were only achieved in a murine model.[81,82] Recently, IVG from primordial germ cells (PGCs) has been established in a murine model.[83,84] On the other hand, several studies demonstrated that preantral follicle culture could lead to the production of embryos in several species (sheep, porcine, and bovine).[83]

To induce follicle development from the primordial/primary stage, non-isolated follicle culture is appropriate.[83,86] A tailored culture system is also needed for primordial/primary follicle culture of human in vitro growth.[83] Based on the research, it has been concluded that a multiple-step culture system could support development of each stage of the follicles.[87] A multistep approach could sustain primordial follicle activation and initiation of early follicular growth and support the growth and differentiation of the early preantral to antral stage.[83] According to the latest findings, metaphase II oocytes have been retrieved from human ovarian tissue provided by patients (mean age 30.7 ± 1.7 years) who underwent Cesarean section. A multistep culture system of four steps was constructed. The first step was ovarian tissue culture for 8 days. The second step was secondary follicle culture with activin A for 8 days, the third step was cumulus -oocyte complex (COC) culture with activin and FSH for 4 days, and the final step was in vitro maturation (IVM) with IVM medium.[88] This finding would be beneficial and could become one of the solutions for the issue of contamination of OTT.

7.3 | Ovarian tissue selection for transplantation

The amount of ovarian tissue for OTT differs among the reports. The average amount of transplanted tissue at the first OTT was around 46% of the total amount of frozen tissue. At the second OTT, the average amount was around 37%, while the third transplantation used an average amount of 38%.[8] Indeed, the strategy for deciding the amount of tissue for OTT is not established. In general, the duration may depend on the amounts of primordial follicles contained in the ovarian tissues for OTT. Based on the literature, there are differences in the duration of function as viable ovarian tissue after OTT, and it is up to 10 years.[11,12] To plan contraception after OTT exactly, it is better to know the duration how long ovaries may work after OTT. However, there are no suitable procedures to count the numbers of follicles non-invasively.

Optical coherence tomography (OCT), which is a non-invasive and well-established high-resolution imaging technique using near-infrared ray (NIR) examination, is one answer for this issue. We have demonstrated the efficacy and accuracy of this technique to detect and count the number of primordial follicles with murine and human models.[89,90] Although optimization and developments for clinical application are needed, OCT may lead to a plan based on the numbers of primordial follicles that are contained in ovarian tissue for OTT. There is also the possibility that OCT may detect malignant cells in ovarian tissue for OTT.[91]

8 | CONCLUSION

OTT is still a developing technique, but many studies from diverse standpoints may move this technique forward to an established method for fertility preservation. In addition, we need to seek a way to establish an in vitro follicle culture system from primordial follicles or to accurately detect malignant cells on ovarian tissue. Progress in these areas will be extremely valuable for high-risk OTT patients with ovarian cancer or leukemia.

DISCLOSURES

Conflict of interest: None of the authors have any commercial or financial involvement in connection with this work that represent or appear to represent any conflicts of interest. *Human/Animal rights statements and informed consent*: This article does not contain any studies with human and animal subjects performed by any of the authors.

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How to cite this article: Takae S, Suzuki N. Current state and future possibilities of ovarian tissue transplantation. *Reprod Med Biol*. 2019;18:217–224. https://doi.org/10.1002/rmb2.12268