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FERTILITY PRESERVATION

A transportation network for human ovarian tissue is indispensable to success for fertility preservation

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Abstract
Purpose The purpose of this study was to examine the efficacy of an ovarian tissue transportation network for fertility preservation (FP) for cancer patients in Japan.
Methods PubMed was searched for papers on transportation of human ovarian tissue for FP. We analyzed population, area, number of cancer patients for ovarian tissue cryopreservation (OTC), quality control/assessment and safety, cost of a cryopreservation center for the building for 30 years, and medical fees of cancer patients (operation, cryopreservation, and storage of ovarian tissue).
Results More than twenty babies have been born in Denmark and Germany through a transportation system. Up to 400 new patients a year need OTC. The fees for removal, cryopreservation, and storage for 5 years, and transplantation of ovarian tissue are around €5,000, €4,000, and €5,000, respectively. It costs more than €5 million to establish and maintain one cryopreservation center for 30 years. If we have a few cryopreservation centers in Japan, we can cryopreserve 400 patients' ovarian tissue per year by safer slow freezing and maintain quality control/assessment. We need to lighten the patients' burden for easy to use FP by a government subsidy and medical insurance coverage.
Conclusions This model has been termed the Danish model ("the woman stays - the tissue moves"). This is truly patient-centered medicine. We can have maximum effects with the minimum burden. A transportation network like those of Denmark and Germany is the best strategy for FP in Japan. It may be the best system for cancer patients, medical staff, and the Ministry of Health, Labor, and Welfare.

Keywords Fertility preservation · Transportation · Human ovarian tissue · Cryopreservation · Network

Introduction

Approximately 95 children have been born from ovarian tissue cryopreservation (OTC) all over the world, and 93 out of the 95 children were derived from slow freezing, whereas only two were from vitrification [1].

More than 20 babies have been born in Denmark and Germany through the use of transportation networks [2, 3].

A transportation network has been completed in Denmark, and another, FertiPROTEKT, includes Germany. The first birth was reported in Belgium [4], the second was in Israel [5], and the third in Denmark [6]. These three countries started OTC between 1997 and 2000. To centralize an appropriate number of cancer patients for fertility preservation (FP) to a limited number of excellent centers may be the key to success.

The areas and populations of these countries are small. There were only 1–5 cryopreservation centers, and around 800 patients have had tissue frozen in each country. On the other hand, Germany's area and population are larger than those of the three countries. The "FertiPROTEKT" network (four cryopreservation centers and 101 operation hospitals) was established in 2006. More than 2500 cryopreserved tissue samples were obtained in four centers (1400 in Bonn, 500 in Erlangen, 170 in Innsbruck, and 100 in Berne). These have achieved great pregnancy and delivery outcomes. Japan's area and population are almost the same size. We think we need only a few cryopreservation centers using a transportation

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network for FP in Japan. We investigated the efficacy of a transportation network, safety of cryopreservation protocol, and high-quality control and assessment in Japan.

Materials and methods

PubMed was searched for transportation of human ovarian tissue using the terms "cryopreservation of ovarian tissue," "transplantation of ovarian tissue," and "transportation." We also manually searched the reference lists of the identified articles for other references, which had not been identified in the PubMed search.

We calculated the number of patients per year, cost of building and maintenance of cryopreservation centers for 30 years, patients' medical fees (resection of one ovary, transplantation, and cryopreservation 5 years' storage of ovarian tissue), quality control/assessment, and safety. We obtained information by means of questionnaires from 13 centers registered with the Japanese Society for Fertility Preservation (JSFP) for a presentation of the 34th annual meeting of the Japan Society of Fertilization and Implantation. One hundred percent of those responded.

Results

There are 47 prefectures in Japan. One system produces 47 cryopreservation centers (one prefecture has one cryopreservation center), whereas the other requires only a few cryopreservation centers for ovarian tissue in Japan. It is possible to cryopreserve oocytes and embryos for FP in around 600 existing assisted reproductive technology (ART) outpatient centers in 47 prefectures in Japan. However, OTC requires a laparoscopic operation under general anesthesia and hospitalization for 3 to 4 days in Japan. Thirty-four cryopreservation centers are already registered with the JSFP at present. In our survey on April 30, 2016, we found around 141 patients have had tissue frozen in 13 cryopreservation and operation hospitals in Japan since 2006 (Table 1) [7]. There were 15,333 new female cancer patients under the age of 40 in Japan in 2011 [8]. A maximum of five cryopreservations per million (a maximum of 400 ovarian tissue cryopreservation procedures per year) in Germany and a maximum of 13 per million (70 cryopreservations per year) in Denmark were carried out each year [3]. Extrapolated to the population of 126.5 million, this would represent 633–1644 cryopreservations of ovarian tissue per year in Japan. Around 10–84% of counseled patients used FP [9–16]. Furthermore, FP is divided into oocytes, embryos, and OTC. Breast cancer is a common disease in women and a good indication for cryopreservation of oocytes and embryos, because we have 8 weeks to cryopreserve them at least twice, a lower rate of premature ovarian failure (breast cancer vs. hematological diseases = 11 vs. 34.5%) [17], and a higher rate (24.2%)

Table 1 Data of ovarian tissue cryopreservation: Result of questionnaire to the facilities in Japan belonged in Society for Fertility Preservation (JSFP) on April 30, 2016

Facility	Number of practice	Cryopreservation method	Since	Age	Cancer cell examination	Number of transplantations	Days of hospitalization	Fee (€)			
								Excision of tumor	Cryopreservation	Renewal	Transplantation
A	66	V	2010/10	14–41	HD	1	4	5000	0	420	5000
B	18	V	2013/1	9–36	HD	0	5	1300	800 (incl. IVM: 1250)		Undecided
C	16	V	2014/6	14–41	HD	0	3	4200	0		
D	14	SF	2008/9	14–45	HD	0	4–5	5000 (all)			
E	9	V	2012/12	13–35	HD 1 others 7	0	5–7	3300	0		2500
F	6	SF	2006/9	15–28	HD	0	5	5000		100	
G	5	Cell sleeper	2008/5	12–18	None	0	3–4	2500	500		
H	5	NA	2014/2	18–36	HD	0	3	5500			
I	1	V/SF	2014/10	31	HD	0	NA	Study			
J	1	V	2015/10	34	HD	0	6	2300	710		2800
K–G	0										

SF slow freezing, *V* vitrification
(Kyono K. JSFI, 2016)

of metastasis in the ovary [18]. For women who require urgent cancer treatment such as neo-adjuvant chemotherapy, cryopreservation of ovarian tissue should be considered [19]. Two-thirds of women under 40 years of age at diagnosis will have a tumor over 2 cm in size and/or involving axillary lymph nodes (stage II or higher). Triple negative or HER2 positive incidence is around 20% in breast cancer patients under 35 years of age in Japan [20–22]. Neo-adjuvant therapy is given before surgery for women with clinically positive nodes or a tumor of 2 cm or greater as these women are likely to harbor micro-metastases. It is up to the oncologist [23]. According to selection criteria, patient choice, treatment urgency, tumor progression, medical insurance coverage, and financial resources, it is estimated that the number of new patients of FP using ovarian tissue is around 400 at most in Japan each year [2–5, 9–16].

Quality control and assessment is very important for higher pregnancies and deliveries and safer FP following frozen-thawed ovarian tissue [24–30]. Transportation network systems have been established, achieved a great success, and spread worldwide [1–3, 6, 7, 31–43]. There have been at least 18 studies about the issue, since 2003 from four different countries. Among the models studied, we judge the German and Danish systems to be the most suitable for Japan as Japan's area and population are almost the same size as in those systems.

We estimated that it costs more than €5 million for one cryopreservation center's establishment and maintenance for 30 years. This includes labor cost of only two experts, microscopes, LN_2 tanks, transportation boxes, lamina flow, a fluorescence microscope, a programmed freezer, maintenance of medical instruments, and periodic replenishment of LN_2. (Table 2). It would cost more than 235 million€ (5 million€ times 47 prefectures) to build cryopreservation centers in each prefecture in Japan for 30 years.

In Japan, the fee for removal of one ovary, cryopreservation and storage for 5 years, and transplantation of frozen-thawed ovarian tissue was around 5000, 4000, and 5000€, respectively.

There are several other fertility preservation system models, and they have a good network; however, we believe that the Danish-model is the best model. Limiting the number of cryopreservation centers to two centers, for instance, to lighten patients' burden and improve the quality of cryopreservation centers would enable us to reduce costs by 225 million€ over 30 years. On a broader view, this plan is ideal for the development of research into minimal residual disease and cost effective for medical fees for cancer patients. In Japan, it is suggested we should adopt a transportation network like those in Denmark and Germany.

Discussion

Safety and quality control/assessment are very important. In Japan, 21 cases of OTC have been cryopreserved by slow freezing and 121 cases by vitrification with the freezing method since 2006. However, no pregnancy has been reported in FP using ovarian tissue of cancer patients.

Ninety-three out of 95 babies were born following slow freezing [1–6, 17, 29, 37–39], and only two babies have been born after vitrification [44, 46].

In slow freezing, 1.5 M dimethyl sulfoxide (DMSO) [3–5, 24, 26–30], 1.5 M propanediol (PROH) [25] or 1.5 M ethylene glycol (EG) [1, 2, 6, 31, 39] have been used as cryoprotectants. In vitrification, a high concentration of cryoprotectants (5.64 M EG in Ova Cryo Kit [46], 2.81 M DMSO, and 3.58 M EG in cryotissue [45]) have been used, and warming time was four times shorter.

In successful cases of vitrification for premature ovarian insufficiency, grafts were performed following culture with Akt stimulating drugs for 2 days after warming of vitrified ovarian tissue [44]. We assume the residual EG was washed out for 2 days culture.

Obata et al. and Nakamura et al. reported the residual cryoprotectants (around 30 mg/g in Ova Cryo Kit [46]) and around 10 mg/g DMSO and 10 mg/g EG in cryotissue [45] in ovarian tissue just before transplantation into human body [47, 48]. Iwanani et al. [49], Larman et al. [50], and Cordeiro et al. [51] reported cryoprotectant toxicity from gene expression

Table 2 Minimum cost of establishment and maintenance of one cryopreservation center for 30 years

Labor cost of two embryologists	110,000€ cost of two embryologists (one leading expert with an embryology and/or cell culture background plus one additional person with a bio-medical technical background)*30 = 3,300,000€
Medical equipment	LN_2 tank*3, transportation box*10, lamina flow*2, microscope, fluorescence microscope, programmed freezer, incubators, refrigerator, thermo plate with circulating cooler, laboratory ice maker, nitrogen supply tank, plate-shaker, analytical calibrated scale, micro pipette, dewar-container, dry shipper: 200,000, T = 600,000
Research and test	Reagent etc., 1000,000€
Periodic replenishment of LN_2	10,000€
Electricity, water, sewage, and gas cost	100,000€
Total	5,010,000€

profiling. We could not find residual cryoprotectants in ovarian tissue following slow freezing. So, we adopted a slow freezing protocol in our cryopreservation center giving primary consideration to the safety of patients.

Dolmans MM et al., Von Wolff M et al., Liebenthron J et al., Bastings L et al., Bittinger S et al., Meirow D et al., and Rodriguez-Iglesias B. et al. [24–30] reported the importance of quality control and assessment of FP (follicular viability test, follicular density, and maximal safety measures including search for malignant cells).

On transportation systems, Schmidt et al. (2003) [31] reported the efficacy of transport of ovarian tissue cooled on ice for a period of up to 4 h from local hospitals without facilities and expertise to cryopreserve ovarian tissue to a cryopreservation center. Andersen et al. (2008) reported two successful births (February 2007 and January 2008) following transportation of ovarian tissue 4–5 h prior to cryopreservation [6]. Dittrich et al. (2012) reported the first successful birth following autotransplantation after overnight transportation of ovarian tissue using special transportation containers with precise temperature documentation from a local area to a center for 18–24 h before freezing [37]. Kyoya et al. confirmed the transportation system (6 vs. 18 h) from Osaka to Sendai was effective using human ovarian tissue [32].

About transportation medium, the Denmark group [1, 2, 6, 31, 39] used IVF culture medium at 4 °C for 4–5 h and the FertiPROTEKT group [3, 26–28, 34–38] used special preservation medium to preserve the viability of the tissue by maintaining a stable temperature of 4–8 °C for 36 h. It is clear that in the short time that ovarian tissue transport protocols have been employed in Europe, there have been multiple live births following autotransplantation. Kamoshita K et al. suggested that prolonging ovarian storage time (≧ 8 h) using culture medium reduces fertility in mice. Ovaries should be frozen immediately after harvesting or transported as rapidly as possible to minimize damage using culture medium. We should select medium in humans depending on the purpose and transportation time. A US group (Laronda MM et al. [41] and Duncan FE et al. [42]) reported for human ovarian tissue; cold temperatures favor the preservation on preantral follicles but may not be optimal for antral follicles. Addition of anti-apoptotic agents in the transport, processing, and cryopreservation media improved the quality of primordial follicles post-thaw as assessed by culture and histological evaluation [43]. Tissue transportation has the potential to increase the number of patients and local medical staff who are in geographic areas that lack an oncofertility program to have ovarian tissue preserved for their later use for transplantation or other emerging fertility preservation options.

The FertiPROTEKT network was founded in 2006, and more than 2500 cryopreserved tissue samples have been stored in the four central cryobanks. This has achieved great pregnancy and delivery results. Belgium, Israel, and Denmark

Table 3 Comparison of patient's fee, cost of operation, and cryopreservation of human ovarian tissue in six different-sized countries [1–3, 7, 44–47]

Country	Area ($\times 10^4 km^2$)	Population ($\times 10^6$)	Fee					No. of cryopreservation	Since	No. of transplantations	No. of births (ongoing pregnancy)
			Cryopreservation		Removal	Transplantation	Transport				
Belgium	3.1	10.4	Insurance 3	SF	Insurance 3	Insurance		800 70/year	1997		11 (1)
Israel	2.1	8.0	Free 5	SF	Free 5	Free	Free				8
Denmark	4.3	5.7	Free 1	SF	Free 3	Free	Free	800 70/year	2000	25	8
Spain	50.7	47.7	Free public	SF	Free public	Public free				33	7 (3)
Germany	35.8	81.5	500€ 2	SF	Covered by insurance up to 1000€	1000€	100–150€	2500–400/year	2006	95	12
			300–400€	VF	5000€ 3 hospitalization	5000€ 3 hospitalization	200–500€ 3 hospitalization	150	2012 (2006)	4	0
Japan	37.9	126.5	800€ incl. 1 year storage fee								

SF slow freezing, *V* vitrification personal communications with several doctors (Prof. MM Dolmans, Prof. Dror Meirow, and Prof. M. Montag)

achieved birth following FTOT in 2004, 2005, and 2007. They have 3/3, 5/5, and 1/3 cryopreservation/operation centers of human ovarian tissue, respectively. In these three countries, around 800 patients have had tissue frozen, with success in the early stages. In Japan, the number of patients using OTC is around 400 per year at most [2–5, 9–16]. The main indications for FP using OTC are hematological malignancy and breast cancer [1–7, 19, 52].

FP is free of charge in Denmark and Israel or covered by government insurance in most countries (Germany, Spain, and Belgium), except for Japan (Table 3). The fees in Japan are the data from a questionnaire to the facilities in JSFP and the rough estimate of the establishment of HOPE, which includes labor costs and equipment fee. [1, 7, 53–55].

The key to success was concentrating cancer patients in a few high-quality centers and lightening the cancer patients' fee burden through government subsidies and medical insurance coverage. A transportation network would also be useful in big countries like the USA, China, or India by devising [42].

A transportation network is an ideal strategy for development of FP using ovarian tissue in Japan. To lighten medical fees of cancer patients is the biggest challenge we are facing now. In conclusion, a few cryopreservation centers using the slow freezing method and transportation system is an ideal number for Japan. This plan surely will lead to long-term success and safety. Minimum burden leads to maximum values. We established the safer Human Ovarian Tissue Preservation Enterprise (HOPE) using a transportation system for cancer patients in Tokyo, Japan on November 1, 2016.

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