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REVIEW ARTICLE

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Uterus transplantation: Toward clinical application in Japan

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Abstract

Background: In recent years, uterus transplantation (UTx) has been applied as the treatment for patients with uterine factor infertility worldwide. Thus, the clinical application of UTx in Japan should be considered through both the history of UTx technology development in the world and future prospects.

Methods: Recent information on UTx was collected via a literature survey and the Internet.

Results: Basic research using various animals has been done mainly since 2000. In 2014, the world's first UTx baby was born in Sweden. In total, 24 UTx procedures have been performed at 10 institutes in nine countries and five births were obtained (as of May, 2017). In Japan, the "Project Team for Uterus Transplantation" initiated UTx experiments in 2008 and the "Japan Society for Uterus Transplantation" was organized in March, 2014. In the rest of the world, the "International Society for Uterus Transplantation" was established in January, 2016.

Conclusion: Uterus transplantation is still under development as a reproductive medicine tool and organ transplant procedure. A collaborative system that is not limited by facilities and specialties should strive to build an "all-Japan" team.

KEYWORDS
ethical issues, Mayer–Rokitansky–Küster–Hauser syndrome, surrogacy, uterine factor infertility, uterus transplantation

1 | INTRODUCTION

In recent years, assisted reproductive technology (ART) procedures, such as in vitro fertilization (IVF), intracytoplasmic sperm injection, and embryo cryopreservation, have led to successful pregnancy and childbirth in many infertile couples worldwide. In Japan, 47 322 babies were born in 2014 by using ART, which constituted one-in-21 newborns. However, in some cases, it is not possible to achieve conception with this technology. This is primarily related to uterine factor infertility (UFI).[1] The acquired gynecologic causes of UFI are uterine leiomyoma, endometrial polyposis, chronic endometritis, Asherman's syndrome, severe adenomyosis,[2] intractable endometriosis, and uterine malignancy[3,4] that requires a hysterectomy. Obstetric causes of UFI include intractable post-partum hemorrhage and malplacentation, wherein a hysterectomy is required following the failure of standard therapy. A congenital absence or anatomical defect of the uterus, such as uterine hypoplasia, Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome,[5] uterine malformations, and Müllerian anomalies[6] also can contribute to UFI. It is estimated that there are between 60 000 and 70 000 patients in Japan with UFI of reproductive age (20-40 years old).

For ART treatment in patients with UFI, IVF surrogacy has been applied recently.[7] However, in this third-party ART, the following problems regarding ethical, legal, and social issues (ELSI) exist: (i) ethical: handover and takeover refusal; (ii) legal: custody and childcare rights; and (iii) social: commercialization and medical tourism. In a 2016 survey,[8] only 38% of countries permitted gestational carrier arrangements

and 56% did not. In recent times, strong restrictions on surrogacy have been placed by countries on patients who are not citizens of that country. Additionally, a notice from the Japan Society of Obstetrics and Gynecology (JSOG, Opinion for Surrogacy; http://www.jsog.or.jp/about_us/view/html/kaikoku/H15_4.html (Japanese)) states that "It is not permitted to implement surrogate pregnancy."

In October 2014, a significant news report about a new successful treatment for UFI was issued in Sweden: "Birth of the world's first uterus transplantation (UTx) baby."[9] In this review, the clinical application of UTx in Japan through the history of UTx technology development in the world and the present situation and future prospects in Japan are considered.

2 | BASIC ANIMAL RESEARCH

The first clinical implementation of UTx was performed in Saudi Arabia in April, 2000.[10] The recipient was a 26 year old woman whose uterus was excised due to post-partum hemorrhage and the donor was a third-party 46 year old woman who was hysterectomized with a resection of bilateral ovarian cysts. Although the transplant surgery itself succeeded, the transplanted uterus had to be removed due to uterine necrosis, with thrombus formation on the 99th postoperative day. The insufficiency of basic studies in this field was pointed out,[11] and since then, basic research using animal species was started. The animal experiments regarding UTx have been conducted on small animals, such as mice,[12-16] rats,[17-22] and rabbits,[23-26] large animals (including pigs[27-31] and sheep[32-40]), and non-human primates like monkeys[41-48] and baboons.[49-52] Many results regarding transplantation techniques, postoperative management, immunosuppression methods, and so on have been obtained.[53-59]

However, the significance of basic research using animals might be attenuated because the case number of human UTx is increasing steadily in the world and clinical knowledge has been accumulating.[60-70] Although the animal experiments might be useful for developing adequate surgical techniques that are associated with UTx, the implementation limits from the viewpoint of animal welfare should be considered further.

3 | CLINICAL DEVELOPMENT

Based on the fundamental research results mentioned above, the clinical application of UTx again was initiated abroad. In August, 2011, a Turkish team (Akdeniz University Hospital, Antalya, Turkey) reported a UTx from a brain-dead woman.[71-74] The donor was a 22 year old multi-organ donor who died in a traffic accident and the recipient was a 21 year old woman with MRKH syndrome. A successful pregnancy was achieved by cryopreserved-thawed embryo transfer (ET) in April, 2013, which resulted in a spontaneous abortion. The pregnancies did not result in the birth of babies, even after two trials of ET.

In September, 2012, a UTx between a mother and a daughter was performed at Sahlgrenska University Hospital in Gothenburg, Sweden.[75,76] Ultimately, UTx procedures from nine living donors were performed. Eight of the recipients had MRKH syndrome (27-38 years old) and one had postoperative cervical carcinoma (33 years old). As donors, five cases were mothers, and a sister, an aunt, a mother-in-law, and a friend of the mother were involved. The average age of the donors was 53 years (37-62 years), five were postmenopausal (three of them had been postmenopausal for ≥5 years). The mean time of the hysterectomy for the donors was 11 h, 37 min (10 h, 17 min to 13 h, 8 min) and the average bleeding volume was 920 mL (300-2400 mL). The mean time that was required for transplantation to the recipient was 4 h, 46 min (4 h, 10 min to 5 h, 56 min) and the average bleeding volume was 670 mL (250-1600 mL). A bladder–vaginal fistula occurred as a postoperative complication in a donor, but it was repaired. Two of the transplanted uteri had to be removed due to thrombosis and repetitive intrauterine infections.

In the postoperative course, menstruation was observed in all patients and rejection was observed in five patients, but it was relieved by steroid administration.[77] From March, 2014, cryopreserved embryos were thawed and transferred sequentially and the first infant was born in September, 2014.[9,78] In the recipient of this case with MRKH syndrome, pre-eclampsia occurred at 31 weeks of gestation and a 1775 g boy was born via an emergency Cesarean section. Since then, five births have been officially reported to date as of April, 2017.

4 | ETHICAL, LEGAL, AND SOCIAL ISSUES REGARDING UTERUS TRANSPLANTATION

Uterus transplantation is a medical treatment with two aspects: reproductive medicine and an organ transplant. When discussing the ELSI for UTx, it must be remembered that the concepts of third-party ART and organ transplantation are different from culture to culture due to diversified philosophical and religious traditions[79] and that the feelings toward reproduction are different from person to person, even within the same culture. In addition, the ELSI for progressive medical performance will change over time. Furthermore, uterine tissue engineering has been tried in rat models.[80-82] If the artificial uterus or placenta is able to regenerate, UTx might become unnecessary for the treatment of UFI.

Although many articles from various regions around the world have been published so far,[83-90] the ELSI of UTx discussed here are applicable to the present situation in Japan.

4.1 | Ethics

From the standpoint of reproductive medicine involving a third party, UTx is comparable with surrogacy.[91-94] As a kind of organ transplant, the problem of transplantation that is unrelated to life-threatening organ use is faced. Although many ethical problems exist regarding the clinical application of UTx, ~80% of Japanese general citizens have accepted UTx ethically, which was higher than the acceptance rate of surrogacy,[95-97] similar to other countries.[98,99]

4.2 | Legislation

Japan is a unique country, in which no law is available for reproductive medicine. This medicine is regulated only by a notice of JSOG that consists of doctors belonging to a special medical field. Organ transplantation involves hearts, lungs, livers, pancreases, kidneys, and small intestines from deceased donors and is regulated by the Organ Transplant Law that went into effect in 1997. However, the transplant implementation from living donors is only regulated by the ethical guidelines of The Japan Society for Transplant (JST). In other words, UTx from a living donor can be performed without it being illegal today in Japan. Of course, it goes without saying that comprehensive legal development should be necessary.

4.3 | Social consensus

In order to obtain the social consensus for UTx, the authors organized a society concerning UTx and underwent several meetings, as mentioned below. However, the recognition rate of UTx by general citizens was 10%-15%, even after the successful UTx and live birth in Sweden was reported.[96,97] Compared to this, the term "surrogacy" was well known to >80% of them.

Although three other guidelines than those indicated below have been proposed (those of the International Federation of Gynecology and Obstetrics Committee,[100] The Montreal Criteria,[1] and The Indianapolis consensus[101,102]), they must be revised in order to adapt to the current conditions of clinical UTx research.[103]

5 | CURRENT SITUATION IN JAPAN

5.1 | Project Team for Uterus Transplantation

Six individuals belonging to the Department of Obstetrics and Gynecology, Keio Gijuku University School of Medicine, Tokyo, the Department of Plastic, Reconstructive and Aesthetic Surgery, The University of Tokyo Hospital, Tokyo, or the Department of Human Health Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan, organized the "Project Team for Uterus Transplantation" (PTUTx) (www.pt-ut.org) in 2008 and started autografting experiments by using cynomolgus macaques in January 2009.[41,42] As a result, a natural pregnancy was achieved in the sixth case and the child was acquired in March, 2012.[43,44] Even after that, allogeneic transplant experiments have been carried out as a clinical approach to UTx.[45-48]

Furthermore, because ethical and social problems could be important for actual clinical application,[104,105] in September, 2012, an ethics committee with seven outside parties was established in the PTUTx. This committee includes not only obstetricians and gynecologists, doctors in other departments, and health professionals, such as a midwife, a nurse, and a clinical psychologist, but also specialists in research ethics and bioethics and a representative of the infertility patients' association. After eight discussions over 2 years, in December, 2014, the "Guidelines for Clinical Research on Uterus Transplantation" was published (Appendix 1). This guideline was sent to JSOG, the Japan Society for Reproductive Medicine (JSRM), and JST for review. At JSOG, a subcommittee on UTx was established within the Ethics Committee and discussions were made. The JSRM replied that the society would follow JSOG's policy.

In addition, because the authors thought that it was necessary to provide information to the society in general, to discuss the UTx situation, to investigate the consciousness of donors, recipients, and general citizens, and to obtain social consensus, a specific academic society was organized, as stated below.

5.2 | Japan Society for Uterus Transplantation

As a place to deepen the social understanding and discussion of UTx, the "Japan Society for Uterus Transplantation" (JSUTx) (www.js-ut.org) was established in March, 2014. The executive committee of JSUTx consists of experts in each field that is related to UTx as four advisers, 23 directors, three secretaries, and one auditor. Six board

TABLE 1 Clinical application of uterus transplantation worldwide (n=24 cases, as of May 2017)

Year	Country	Donor (N)	Recipient (N)
2000	Saudi Arabia	Living (1)	Post-partum hemorrhage (1)
2011	Turkey	Deceased (1)	MRKH syndrome (1)
2012-2013	Sweden	Living (9)	MRKH syndrome (8)/ cervical cancer (1)
2015	China	Living (1)	MRKH syndrome (1)
2016	USA (Cleveland)	Deceased (1)	MRKH syndrome (1)
2016	USA (Baylor)	Living (4)	MRKH syndrome (4)
2016	Czech Republic	Living (2)/deceased (2)	MRKH syndrome (4)
2016	Germany	Living (1)	MRKH syndrome (1)
2017	Serbia	Living (1)	MRKH syndrome (1)
2017	India	Living (1)	MRKH syndrome (1)
Total	10 institutes in 9 countries	Living: 20 Deceased: 4	MRKH syndrome: 22 Others: 2

MRKH, Mayer–Rokitansky–Küster–Hauser.

meetings already have been held, consisting of academic and public lectures. At the fourth meeting on November 3, 2015, four women with MRKH syndrome themselves stated the intention for UTx as recipients. At the sixth meeting on April 9, 2017, a woman with MRKH syndrome and a hysterectomized survivor of cervical cancer as recipient candidates and a man with gender identity disorder (female-to-male) as a donor candidate also talked about their mental troubles and expectations of UTx.

6 | TRENDS IN THE REST OF THE WORLD

6.1 | Trends in foreign countries

Following the success in Sweden, the clinical application of UTx is planned and performed in many countries in the world. In September, 2015, planned UTx using deceased donors to 10 recipients (18-36 years old) was revealed at Imperial College, London, UK.[106] Likewise, in November of the same year, for eight recipients (25-35 years old) at Limoges Hospital, Limoges, France,[107] and 10 recipients (21-39 years old) at Cleveland Clinic, Cleveland, OH, USA, UTx was planned by using deceased donors.[108]

Furthermore, in November, 2015, Xijing Hospital in Xi'an, China, announced that a UTx was performed successfully between a 43 year old mother and a 22 year old daughter.[109] The UTx procedures involved 38 doctors with 11 areas of expertise and took 14 h with the help of robotic surgical tools. In 2016, the Cleveland Clinic performed its first UTx in February, but the transplanted uterus was removed 2 weeks after surgery due to complications.[108] In September, four UTx procedures using living donors were performed at Baylor University Medical Center, Dallas, TX, USA, but three procedures

TABLE 2 Founding members of the International Society for Uterus Transplantation

Country	Gynecology	Reproductive medicine	Transplantation surgery	Others (N)
Sweden	④	2	3	Obstetrics (1) Nephrology (1) Anesthesiology (2) Phycology (1) Pathology(1) Medical film photography (1)
Argentina	1	①		
Australia	①			
Belgium	①		1	Nephrology (1)
China	②			Nursing (1)
Colombia	③			
Czech Republic	2		①	
France (Limoges)	③			Nephrology (1)
France (Paris)	③	1		
Germany	1		①	
India		①		
Japan	①	1		
Mexico	②			
Singapore	②			Plastic and reconstructive surgery (3)
Spain	②			
Turkey		1		Plastic and reconstructive surgery (②)
UK	②			Phycology (1)
USA (Boston)			①	
USA (Cleveland)		2	①	
USA (Dallas)	1		②	Obstetrics (1)
USA (Omaha)		1	②	Nursing (1)
Total [number of team leaders]	31[12]	10 [2]	12 [6]	18 [1]

○, the field to which the team leader belongs, according to the institute.

were unsuccessful.[110] Furthermore, UTx procedures from two living and two deceased donors in the Czech Republic (Motol University Hospital, Prague, Czech Republic)[111] and a UTx from a living donor in Germany (Tübingen University Hospital, Tübingen, Germany)[112] were performed in October, 2016. A team in Serbia also completed a UTx in March, 2017 (M. Brännström, 2017, personal communication). Most recently, an Indian team (Galaxy Care Hospital, Pune, India) performed a UTx procedure between a mother and a daughter in May, 2017.[113]

Table 1 shows the summary of clinical UTx procedures that were performed before May, 2017. In total, 24 procedures were performed from 20 living and four deceased donors. Twenty-two (92%) of the recipients were women with MRKH syndrome. Eight (33%) uteri had to be removed due to failure; therefore, it is hard to state that UTx is a reliable procedure.

6.2 | International Society for Uterus Transplantation

With the call of Professor Mats Brännström of Sahlgrenska University in Sweden, a founding meeting of the "International Society for Uterus Transplantation" (ISUTx) (www.isutx.org) was held in Gothenburg on January 8-9, 2016. Seventy researchers from 20 institutions in 17 countries gathered together. After reporting the circumstances of each country, the articles of by laws, membership, global case registration system, and schedule of academic congresses were discussed. For the executive committee of ISUTx, Professor Brännström as President, Dr. Suganuma as Vice-President, two secretaries, and two treasurers were chosen. The names of 12 board members from all over the world and two advisory members also were suggested.

The specialized medical fields of the 71 founding members of ISUTx differ widely (Table 2). Although most are gynecologists, transplantation surgeons, reproductive medical doctors, and specialists in other fields are involved. The team leader in each institute or country also is distributed. This means that UTx includes different medical aspects for third-party ART and organ transplantation.

It was decided that the first international meeting would be held in Gothenburg on September 18-19, 2017, with a precongress course to demonstrate the techniques of live-donation UTx on September 17. The program will consist of symposia that discuss several relevant topics of UTx: (i) the surgical techniques of organ procurement in live-donor UTx; (ii) the surgical techniques of organ procurement in deceased-donor UTx; (iii) venous outflow options; (iv) the surgical technique of UTx for the recipient; (v) immunosuppression at UTx; (vi) rejection diagnosis and grading; (vii) IVF before and after UTx; (viii) obstetric monitoring after UTx; (ix) psychology regarding UTx; and (x) the ethics around UTx. These items seem to involve actual issues for the clinical application of UTx.

7 | FUTURE PROSPECTS FOR CLINICAL APPLICATION IN JAPAN

For patients with UFI, there is no doubt that UTx can be an alternative to surrogacy and adoption. However, this medical treatment requires not only gynecologists and transplant surgeons, but also many medical staff members (Figure 1). Psycological support for the recipients and donors of UTx is essential.[114-118]

Of course, even in Japan, UTx cannot be carried out only by the authors' team. The facility that will actually perform UTx needs to form a UTx group therein. At that time, PTUTx will join as an advisory board on the surgical procedures that have been obtained through animal experiments, clinical management, and ethical considerations so far. In doing so, approval of each institutional ethics committee is necessary. Additionally at that time, because JSUTx consists of many occupational types and experts involved in UTx, its ethics committee can suggest the approach for technical problems and ELSI through discussion among the committee members, as well as consultation with various academic societies, such as JSOG, JSRM, and JST through JSUTx.

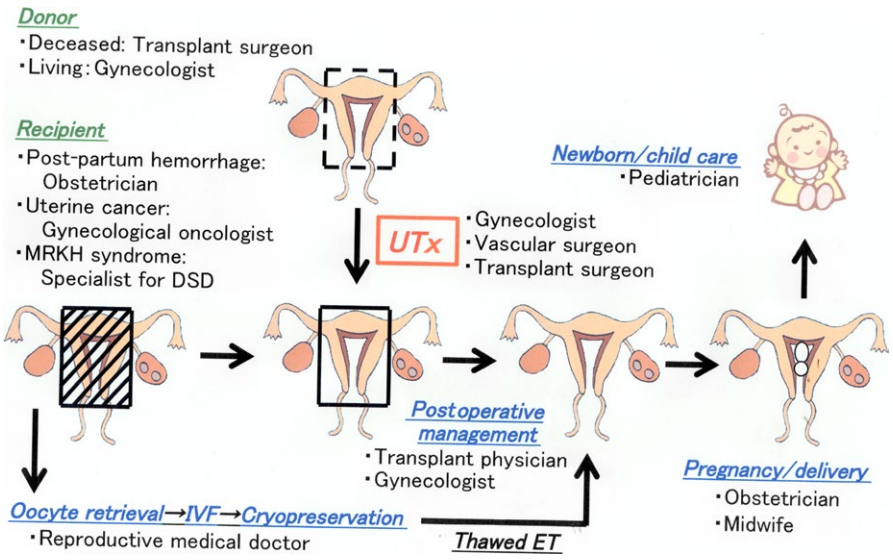

FIGURE 1 Medical fields and staff members that are involved in the clinical process of uterus transplantation. DSD, disorders of sexual development; ET, embryo transfer; IVF: in vitro fertilization; MRKH, Mayer–Rokitansky–Küster–Hauser; UTx, uterus transplantation

8 | CONCLUSION

The present situation and prospects of UTx have been outlined. Based on these, it cannot be denied that UTx is still under development as a reproductive medicine and organ transplant procedure. Future efforts will be required to treat patients with UFI successfully.[101,119-126] Additonally, in Japan, a collaborative system that is not limited by facilities and specialties should strive to build an "all-Japan" team.

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APPENDIX 1

Guidelines For Clinical Research On Uterus Transplantation (By the Project Team for Uterus Transplantation, December 17, 2014.)

1. Uterus transplantation, unlike the transplantation of traditional life-sustaining organs, in view of the reproductive health and rights of women, is positioned as organ transplantation for the purpose of the improvement of quality of life by allowing pregnancy and childbirth.
2. Any living and deceased donors are considered as UTx candidates, as well as for other organ transplants. Their dignity, rights, and safety must be prioritized above anything else. In a living donor, any intimidation must be eliminated and the provision of voluntary decisions must be ensured. Also, in order to relieve any mental burden, a support system of continued counseling is required.
3. The recipients of UTx are women with UFI who are absolutely unable to get pregnant medically and who strongly hope to bear children. Noting their physical risk and burden, it is necessary to provide sufficient information to them. In addition, a support system is required to relieve any mental burden through counseling of the recipients, as well as of the donors.
4. The rights and welfare of the children who are born by UTx must be guaranteed to the maximum.
5. Before UTx implementation, the treatment procedures, including the problems and disadvantages to be expected, should be explained in advance to the recipient and the donor by using a document that fully describes these risks, sufficient understanding of the participant to voluntarily consent should be obtained, and the ability to store the consent document should be possible.
6. Regarding the costs involved in UTx, it is necessary to obtain an agreement between the patient and the practitioner in advance. Additionally, mediation of commercial uterus provision or a similar action should never be taken.
7. In clinical studies of UTx, in addition to compliance with the laws and regulations, guidelines, and ethical principles, compliance with the guidelines of various medical societies needs to come into force with the approval of the implementation facility's ethics committee.
8. Basic experiments on animals, including non-human primates, are needed to train to achieve adequate surgical techniques for the implementation of UTx.
9. It is recognized that the UTx procedure uses medicine across different fields. A medical team that includes a wide range of professionals must be enforced.
10. In order to obtain a social consensus on the clinical application of UTx, information provision and opinion collection must be performed in addition to continuous research.