LETTER TO THE EDITOR

Concerns Associated with Uterus Transplantation in Japan

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Uterus transplantation (UTx) has seen increasing global adoption as an alternative for women with uterine factor infertility to achieve pregnancy. However, several medical, ethical, and social issues need to be addressed before UTx can be applied clinically. Since 2009, Japan has amassed a large database of basic research on UTx in non-human primates, but clinical application has not been realized because of conservative attitudes and prudent concerns. Nonetheless, UTx may be viable in Japan after comprehensive resolution of the concerns associated with this medical technology.

Keywords: Japan, quality of life, surrogacy, uterine factor infertility, uterus transplantation

To the Editor:

After the first successful delivery following uterus transplantation (UTx) by Brännström et al. in Sweden in 2014, UTx has become a treatment alternative for women with uterine factor infertility (UFI). To date, more than 70 UTx procedures have been performed worldwide, and more than 20 healthy babies have subsequently been born. Although UTx is still in the experimental stage and there are several medical, ethical, and socio-economic issues to be resolved, the technology associated with UTx is now being standardized.

In Japan, approximately 60,000 women of reproductive age with UFI cannot have biological children because gestational surrogacy is forbidden. Consequently, basic research on UTx using non-human primates has been performed since 2009 under the assumption that the findings may be applicable to this group of women. At that time, UTx had not been performed in humans, except for one failed operation in Saudi Arabia in 2000. Subsequently, Japanese and Swedish researchers pioneered UTx research.

However, despite the extensive data gathered in non-human primates and ethical discussions concerning the procedure, UTx has not been clinically applied in Japan. Herein, we describe the concerns associated with UTx in Japan.

Concerns Associated with UTx in Japan

The clinical application of UTx requires basic research and a full discussion of the issues related to reproductive ethics. We have performed basic experiments in cynomolgus monkeys for more than a decade and gathered extensive data. Consequently, our approach has been deemed suitable for UTx in humans by academics and specialists in obstetrics and gynecology, transplant surgery, and ethics. However, conservative opinion in Japan poses an obstacle to the clinical application of UTx. We have approached various experts, academic societies, and the general public to determine the acceptability of applying UTx in clinical practice. We have reached the following conclusions regarding the challenges to the clinical application of UTx in Japan.

Resistance to the transplantation of non-vital organs

UTx is a procedure that is performed for the improvement of quality of life (QOL) rather than survival, which is the case in vital organ transplantation. The burden of not only surgery but also immunosuppressant use and subsequent complications are major factors in organ transplantation and sometimes lead to fatal consequences. Vital organ transplantation is regarded as an inevitable means for saving lives, whereas UTx facilitates significant improvement in the QOL of UFI patients. Therefore, some academic experts on bioethics insist that organ
transplantation should not be conducted solely for the improvement of QOL. Additionally, there is some concern regarding the application of UTx as a scientific technology for creating new life. Specifically, questions regarding the ethics of allowing transplantation therapy to fulfill a woman’s desire for childbirth, despite the threat to her life, rather than to improve a patient’s QOL or treat a physical disorder, have been debated. Nonetheless, transplantation of non-vital body parts, such as the hand, arm, larynx, face, and abdominal wall, has been performed in humans to improve QOL. Moreover, renal and pancreatic transplants may be considered to target improvements in QOL because alternative treatments such as hemodialysis and insulin therapy have progressed markedly and can achieve similar prognoses to these transplantations. However, it is questionable whether UTx has been prioritized to the same extent as renal and pancreas transplantations or vascularized composite allotransplantation in Japan.

**Risks for donors and recipients**

The greatest concern held by Japanese experts is the risk faced by donors in UTx. In the first Swedish trial that resulted in UTx in nine patients, blood loss was high and the mean operative time for donors was 11.5 h, whereas the operative time for recipients was 4.5 h. Studies in other countries have also reported times of 5–13 h for donor surgery. This is because extremely precise surgical procedures are required to remove a part of the deep uterine vein located in the pelvic floor and the internal iliac veins that drain it. Moreover, perioperative complications including ureter laceration, ureterovaginal fistula, leg/buttock pain, vaginal cuff dehiscence, and fecal impaction have been reported in donor surgery. Recently, robot-assisted surgery has been performed to achieve less invasive procedures in living donors, and novel operative procedures using the ovary or utero-ovarian vein as a drainage vein in place of the uterine vein have been developed. Although less-invasive UTx surgery in living donors has been developed, the organ should ideally be collected from a deceased donor, which clearly has a great advantage over a living donor in terms of the elimination of surgical stress. However, living donors are more frequently used in UTx operations than deceased donors, although this varies depending on the background and culture of individual countries. In Japan, organ transplantations from living donors greatly outnumber those from deceased donors. Moreover, the uterus cannot be transplanted from a deceased donor in Japan as long as the current laws concerning organ transplant prevail because the uterus is not included in the list of potential transplant organs. Therefore, UTx using a living donor would be the only possibility in Japan. Although Japan has a cultural background of organ procurements from deceased donors, the number is extremely small compared with that of the United States. As a result, Japan appears to be falling behind in this discussion and is therefore struggling to arrive at a conclusion. The risks for the recipients shown in Table 1 should also be considered.

**Comparison with surrogacy**

As an alternative treatment for UFI, gestational surrogacy is often compared with UTx. Both of these therapeutic approaches use the uterus from a donor and the gametes from the couple. However, these methods also differ in various aspects (Table 2). The prime consideration in reproductive ethics is the utmost respect for the welfare of newborns. In Japanese civil law, the person who delivers the baby is regarded as the mother. Consequently, surrogacy may cause complications in family relationships. Problems related to breach of contract, such as refusal of a baby, may also occur in surrogacy because pregnancy and delivery are entrusted to a third party. Furthermore, maternal behavior, the mental basis of nursing behavior, is formed by involvement of the endocrine system throughout the gestational period. Therefore, children born to a surrogate mother may not experience maternal behavior that fully respects the child’s wellbeing. Consequently, surrogacy is not permitted in Japan according to the guidelines established by the Japan Society of Obstetrics and Gynecology; however, the guidelines rely on self-regulation and are not enshrined in law. In contrast to surrogacy, UTx may resolve problems related to the welfare of the child. UTx differs markedly from gestational surrogacy because the parent gives birth to a child carrying her genes. However, there are opinions that prefer surrogacy because of the extensive risks associated with UTx and stringent legal regulations for UTx to maintain the social order. The risk of fetal anomalies caused by

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**Table 1. Risks faced by donors and recipients**

| Living donor | Recipient |
|--------------|-----------|
| Surgical complications | Surgical complications |
| Graft loss | Graft loss |
| Mental health issues | Mental health issues |

**Table 2**

| IVF-ET: in vitro fertilization and embryo transfer. |
Table 2. Comparison between surrogacy and UTx in Japan

|                                                                 | Surrogacy                      | Uterine transplantation |
|-----------------------------------------------------------------|-------------------------------|-------------------------|
| Uterus                                                           | Third party                   | Third party             |
| Gamete                                                          | Married couple\(^a\)          | Married couple          |
| Delivery                                                        | Third party                   | Recipient               |
| Risks for third party                                          | Yes (surrogate mother)        | Yes                     |
| Transplant surgery                                              | No                            | Yes                     |
| Use of immunosuppressants                                      | No                            | Yes                     |
| Risks of pregnancy and delivery                                 | Yes (surrogate mother)        | Yes (recipient)         |
| Risk of fetal anomaly                                          | No                            | Unclear                 |
| Maternal behavior                                              | May be hard to develop        | Should be easy to develop|
| Mother by law                                                   | Surrogate mother              | Recipient               |
| Respect for welfare of newborn                                  | Not fully respected           | May be respected        |
| Possibility of contract breach                                  | Yes                           | Rare                    |
| Regulation in Japan                                            | No                            | No                      |

\(^a\)Donated semen is used for traditional surrogacy.

immunosuppressants is thought to be equal to the risks associated with a normal pregnancy, based on reports of pregnancy after organ transplantation; however, this is still uncertain for UTx. Moreover, the transplanted uterus is removed after successful delivery of a child because the objective of UTx is to deliver a newborn; the removal of the uterus represents a physical and mental burden on the recipient. UTx is a very different process to that of surrogacy, although comparisons between the two have been much debated. Nevertheless, the discussion of surrogacy itself has not yet made its way to Japan. Furthermore, there is an absence of legal regulations concerning assisted reproduction technology despite long-term discussions having been conducted since 2003 by the Government and Science Council of Japan.\(^5\)

Public awareness and social needs

Given the importance of addressing social needs, consideration of social values, such as whether UTx is truly required for UFI patients to bear children, is warranted. Alternative methods including surrogacy and adoption should be evaluated in terms of their advantages and disadvantages. According to two large surveys of public attitudes toward UTx in Japan,\(^4,11\) UTx is favored over surrogacy and is likely to be socially and personally more acceptable to most people. However, surrogacy is not currently well known in Japan, and it is important that medical professionals present correct information, including the advantages and disadvantages of UTx, to the public and discuss whether UTx is the best course of action.

Costs

Even though UTx is a temporary transplantation procedure, it involves major costs for both the donor and recipient. It is estimated that the whole process would cost ¥25 million, including pre- and post-operative examinations, donor and recipient surgery, immunosuppressants and other drugs, in vitro fertilization and embryo transfer, follow-up during pregnancy, cesarean section, and hysterectomy after the delivery. In Japan, medical expenses associated with infertility treatment are not generally covered by health insurance. Therefore, if this technology is deemed to be an infertility treatment and not an organ transplantation, only the wealthiest patients would be able to afford such treatment.

Conclusion

Progress toward the clinical application of UTx in Japan has seen steady but slow advancement as a result of conservative and prudent attitudes deeply rooted in Japanese culture. Although the clinical practice of UTx still requires technology and knowledge acquisition through basic experiments, discussions in institutions and academic societies, and consensus-building among the general public, this promising procedure could bring about a major improvement in the QOL of patients with UFI in Japan.
Conflicts of Interest

The authors declare that no conflict of interest exists.

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