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A Study on the Legal and Ethical Issues of Uterus Transplantation*

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Abstract

The first uterus transplant for humans was attempted in Saudi Arabia in 2000, but it failed. In 2014, a 30-year-old woman in Sweden with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome who was born without a womb gave birth to a baby after receiving a uterus transplant from her mother. Since then, many studies have been conducted on uterine transplants. The uterus is similar to the hands, arms, and legs in terms of being non-vital, but it has a special function of pregnancy and childbirth, making it difficult to see the success of transplantation as a stable "engraftment" of the uterus and aims to achieve healthy childbirth with the transplanted uterus. However, it is questionable whether uterus transplantation can guarantee the health of a child born this way. Korea's legal system does not stipulate that the uterus is a transplantable organ. However, symposiums related to uterus transplantation were held in Korea in 2020 and 2021, and the possibility of uterus transplantation is being discussed. In nearby Japan, a report by the Japanese Medical Association on uterus transplantation ethics was prepared for a clinical study plan submitted by a research team at Keio University, and a clinical study on uterus transplantation was approved in 2021. However, since the uterus is bound to be limited to a specific gender, social consideration must precede the establishment of criteria for selecting donors in the law. In addition, recipients are also different from the medical indications for general organ

transplants, so it is necessary to closely review the selection of recipients for donation and receipt.

Although uterus transplantation is still being researched with a small number of specialized medical staff and limited facilities, ethical standards must also be considered for proper research to proceed. The ethical criteria to be considered in uterus transplantation differ from those required in general clinical studies because transplantation studies and procedures for pregnancy and childbirth are performed together. Therefore, in this study, the current status and characteristics of uterus transplantation will be examined, and legal and ethical issues will be reviewed for uterus transplantation as a clinical study and medical procedure. In addition, we would like to propose appropriate management measures, such as legitimate standards for conducting ethical clinical studies and monitoring required to secure safety and effectiveness.

Keywords

Uterus transplantation, organ transplantation, living donors, brain-dead (deceased) donors, in vitro fertilization, pregnancy and childbirth

I. Introduction

Organ transplantation began in Korea with the first successful kidney transplant in 1969, followed by kidney and liver transplants from brain-dead patients in 1979 and 1988, respectively.[1] Since then, the need for fair and efficient management of the increasing number of organ transplants and the reporting of legal organ transplants for humanitarian purposes to eradicate illegal trafficking has been raised.[2] The [Act on Organ Transplantation] (hereinafter referred to as the "Organ Transplantation Act") was enacted in 1999[3] as transplantation has been activated in earnest since the 1990s, thereby establishing a full-scale foundation on which to carry out organ donation and transplantation procedures within the public system. Although organ transplantation is an indispensable treatment for patients who have organ failure and for whom transplantation is the only solution as

1 Ha Jong-Won, "Proposal for activation of organ transplantation," *Medical Policy Forum* 11(3), 2013, pp. 97-103.

2 Reasons for enactment of the Act on Organ Transplantation [Law No. 5858, enacted on Feb. 8, 1999], National Legal Information Center.

3 Kwon Bok-Kyu, Kim Hyun-Chul, *Bioethics and Law* (Revised Edition), Ewha Womans University Press, 2009, p.103.

the recipient,[4] it is important to establish ethical donation procedures since the organs required for transplantation are derived from other human beings. In addition, since the supply of organs is always insufficient compared to the demand for transplantation, prudence needs to be exercised for the distribution method. However, due to advances in transplantation techniques and the development of effective immunosuppressive drugs, the range of transplantable organs is expanding, including kidneys, liver, pancreas, heart and lungs, which are directly related to the recipient's life in terms of function, as well as organs that are not directly related to the recipient's life, such as hands, arms and legs, which are aimed at the improvement of the quality of life of the recipient. An arm transplant was first performed in 2017 in Korea using an arm donated by a brain-dead person,[5] and there have been attempts to include the uterus as a transplantable organ.

Uterus transplantation was first attempted in Saudi Arabia in 2000,[6] and the efficacy, safety and social implications of uterus transplantation are still being debated. From the perspective of the transplantation procedure, the uterus may be similar to a hand, arm or leg in that it is not directly related to the recipient's life but has the special function of pregnancy and childbirth. Therefore, unlike other organ transplants, the measure of success in uterus transplantation may not be simply the "engraftment" of the uterus. Current research related to uterus transplantation also involves the implantation of embryos using in vitro fertilization following stable engraftment of the uterus, implantation of the embryo, maintenance of the pregnancy, childbirth and even the follow-up examination of the health of the child born this way.

The introduction of a new transplant procedure always involves the need to bear the burden of significant risks in its implementation since it involves the intensive use of the cutting-edge technologies of the corresponding era. Organ transplantation is not only associated with physical risks, such as various complications and sequelae of surgical procedures, immune rejection and the side effects of immunosuppressive drugs, but also with built-in mental anxiety such as psychological rejection of the transplanted site and the sense of loss associated with organ extraction. Therefore, the advancement of organ transplantation has always been accompanied by various clinical, social, ethical and legal controversies. Currently, although the laws of Korea do not specify the uterus as a

4 Generally, the person who receives an organ (recipient) in an organ transplant is referred to as the beneficiary, because organ transplantation is a "benefit" in itself for patient whose life is directly related to it. However, to avoid overemphasizing the benefits of organ donation, this paper will refer to them as donor and recipient, respectively.

5 Choi Gwang-seok, "[Outskirt News ①] Arm transplant succeeded for the first time in Korea, what is next?," *Youth Doctor*, 2017.12.26. https://www.docdocdoc.co.kr/news/articleView.html?idxno=1050697 (accessed on May 24, 2022.)

6 Grady. D., "Medical first: A Transplant of a Uterus," *The New York Times*, 2002.03.07. https://www.nytimes.com/2002/03/07/world/medical-first-a-transplant-of-a-uterus.html (accessed on May 22, 2022.)

transplantable organ, "hand, arm, foot and leg" were explicitly included as transplantable organs in Clause 1-C of Article 4 of the Act with the amendment of the Organ Transplantation Act in January 2019. In accordance with Clause 1-D of Article 4 of the Act, the Minister of Health and Welfare determines and announces the scope of organs, etc. after deliberation on related matters by the Organ Transplantation Ethics Committee based on Item 4 of Clause 2 of Article 8 of the Act, or it is stipulated that other human organs or tissues can be extracted and transplanted for functional recovery by Presidential Decree in accordance with Clause 1-E of Article 4 of the Act, thereby enabling the transplantation of new organs that are not specified under Clause 1-D of Article 4 of the Act. However, although it is appropriate to assume that all organs can only be obtained from the brain dead unless specified as an organ that can be obtained from a living person in accordance with Clause 5 of Article 11 of the Organ Transplantation Act,[7] this may be controversial since many studies include obtaining organs from living, functioning individuals. Since it is unavoidable that the donor of a uterus is limited to a specific gender, the issue of whether the law should allow uterus donation by living persons needs to be subjected to more prudent social considerations. This is particularly true in Korea, because unlike other countries where donations are mainly made by the brain dead following their death, organs that can be obtained from living persons account for a greater proportion of organ donation than that from brain-dead donors.[8] Discussions that focus on the function of the uterus should be taken with a grain of salt, particularly in the current circumstance of low birthrates emerging as a serious social issue and encouraging childbirth.

Meanwhile, since not only the selection of donors but also the scope of recipients may differ from the medical indications for general organ transplantation, it seems necessary to review the selection of recipients. The Montreal Criteria for the Ethical Feasibility for Uterus Transplantation (hereinafter referred to as the "Montreal Criteria") announced by Canada in 2012 proposed that recipients should be limited to genetic women of childbearing age who have been diagnosed with absolute uterine factor infertility (UFI), either congenital or acquired, and have not received a medical opinion that uterus transplantation is not possible. While the known cases of uterus transplantation until now have only been performed on genetic women, there is controversy regarding the expansion of the category of recipients. In addition, the ethical legitimacy of organ transplantation is based on the altruistic voluntariness of the donor as the key premise, and when the benefits to the recipient of the transplant outweigh the risks to the donor, and

7 According to Clause 5 of Article 11 of the Organ Transplantation Act, only one out of two normal kidneys, liver, peripheral blood, bone marrow, lungs and organs prescribed by Presidential Decree (pancreas, small intestine and peripheral blood) can be donated by a living person, that is, a living donor.

8 Choi Eun-Gyeong, Kim Myeong-Hee, Kim Bo-Bae, *A Study on Medical Screening Criteria for Living Liver Donors*, Korea National Institute for Bioethics Policy, 2018.

when the risks to the donor are objectively acceptable. However, if the birth of a healthy child is considered the success of uterus transplantation, the ethical justification of uterus transplantation must be verified against the possible risks to the child born through the transplanted uterus. Accordingly, this paper examines the current status of uterus transplantation, related systems and guidelines, and the ethical issues to be considered when introducing uterus transplantation under the current legal system in the future.

II. Current Status of Uterus Transplantation

The first animal experiment involving uterus transplantation was reported to have taken place around 1950.[9] Later, in the 1960s, animal experiments involving uterus transplantation were mostly performed on puppies.[10] The first modern human uterus transplant was performed in Saudi Arabia in 2000. A 46-year-old woman's uterus was transplanted into a 20-year old woman whose uterus had been damaged after childbirth. However, the transplanted uterus necrosed shortly after surgery and the recipient had to undergo another hysterectomy.[11] Although a 21-year-old woman born without a uterus in Turkey received a uterus from a brain-dead donor 11 years later with successful implantation, the woman was unable to conceive and give birth.[12] Then, in 2013, a 30-year-old woman in Sweden with Rokitansky syndrome (also known as Mayer-Roskitansky-Küster-Hauser (MRKH) syndrome) born congenitally without a uterus gave birth to a child in 2014 at Sahlgrenska University Hospital after having undergone transplantation of uterus donated by a 61-year-old woman as part of a clinical study.[13] A woman in Brazil in her 30s born with Rokitansky syndrome gave birth to a child in 2017 after receiving a donated uterus from a brain dead woman in her 40s in 2016.[14] This corresponds to the first case in the world of a woman giving birth to a baby using a transplanted uterus donated by a brain-dead person.

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9 Zaami S, Marinelli E, Luca NM Di, "Ethical and medio-legal remarks on uterus transplantation: may it solve uterine factor infertility?," *European Review for Medical and Pharmacological Sciences* 21(22), 2017, p. 5290.

10 Akouri R, Maalouf G, Abboud J. "First live birth after uterus transplantation in the Middle East," *Middle East Fertility Society Journal* 25(1), 2020, p. 2.

11 Grady. D., op. cit.

12 AFP TV reports, "Turkish woman has world's first womb transplant," *Times of MALTA*, 2011.10.11. https://timesofmalta.com/articles/view/turkish-woman-has-world-s-first-womb-transplant.388596(accessed on May 22, 2022.)

13 Brännström M, Johannesson L, Bokström H, "Livebirth after uterus transplantation," *The Lancet* 385(9968), 2015, pp. 607-616.

14 Ejzenberg D, Andraus W, Mendes LRBC, "Livebirth after uterus transplantation from a brain-dead donor in a recipient with uterine infertility," *The Lancet* 392(10165), 2018, pp. 2697-2704.

It has been more than 20 years since the first human uterus transplant was performed in 2000, and while the number of cases and demand for transplants is not high, they have been attempted steadily. Although the International Society of Uterus transplantation (ISUTx), which was founded in 2016, is an internationally recognized authority on uterus transplantation and officially surveys the status of uterus transplantation in each country, it is too early to review the relevant statistical data. Nonetheless, in the [Report by the Review Committee on the Ethics of Uterus transplantation of the Japanese Society of Physicians (hereinafter referred to as the "Japanese Society of Physicians Report")] published by the Japanese Society of Physicians in July 2021, the Review Committee on the Ethics of Uterus transplantation summarized the current status of uterus transplantation as of April 2019,[15] announced with 木須伊織 (Kisu Iori) adding issues that have been additionally organized as of March 2021. According to the report, 85 cases of uterus transplantation (63 from living donors and 22 from brain-dead donors) were performed at 19 facilities in 16 countries. Of these, only 70 cases resulted in confirmed pregnancies and 40 cases resulted in confirmed births. These countries included the United States reporting 17 cases, while Sweden reported 11 cases, the Czech Republic three cases, Germany three cases, and one each for China, Brazil, Serbia, India, Turkey, Lebanon and France.[16]

When these statistics are examined by country, the United States has the highest number of cases at 17 (20%) out of 85 cases worldwide as of March 21 according to the Japanese Society of Physicians Report since there is no requirement for research to confirm the safety and efficacy of surgical procedures, thereby enabling them to be necessarily conducted in the form of research. It is estimated that one in every 500 women of childbearing age are infertile due solely to uterine factors and that the total number is approximately 85,000 in the United States.[17] A uterus transplant was first performed in the United States in 2015 at the Cleveland Hospital in Florida for a woman in her 20s with a uterus donated by a brain-dead woman. However, the transplanted uterus had to be re-extracted due to complications following the transplant surgery.[18] Since then, in 2016, a

15 There have been 58 cases of uterus transplantation reported from 11 countries, and 15 countries, including Korea (and Japan), have reported that they are making preparations for it. Of the 58 cases, 30 were able to confirm pregnancy and 14 went on to give birth. Of the 14 cases, eight were in Sweden, two in the United States, and one each in China, Brazil, Serbia and India. In 44 cases, the uterus was donated by a living donor and in 14 cases, the uterus was donated by brain-dead patients. Japanese Society of Physicians, *Report by the Review Committee on the Ethics of Uterine Transplantation of the Japanese Society of Physicians*, 2021, pp. 2-3. https://jams.med.or.jp/news/059_2.pdf.

16 Ibid.

17 Bruno B, Arora KS, "Uterus Transplantation: The Ethics of Using Deceased vs. Living Donors," *Am J Bioeth* 18(7), 2018, p. 6.

18 Feltman R, "Cleveland Clinic announces first successful uterus transplant in the U.S.," *The Washington Post*, 2016.02.26. https://www.washingtonpost.com/news/speaking-of-science/wp/2016/02/26/cleveland-clinic-announces-first-successful-uterus-transplant-in-the-u-s/?wprss=rss_health-science(accessed on May

20-year-old woman with Rokitansky syndrome received a uterus from a 30-year-old living donor who had given birth to two children, and , gave birth to her first child in 2017 with a uterus transplant in the United States. It has been reported that the corresponding case is an institutional review board-approved study after having undergone a thorough medical and psychological evaluation of the recipient prior to transplantation.[19]

A total of 10 uterus transplantation studies were also approved by the National Health Service Health Research Authority (NHSHRA) in the UK in 2015. Uterus donations were from brain-dead individuals, and the recipients were all women between the ages of 25 and 38 years who had been born without a uterus but had functioning ovaries and eggs.[20] Before transplantation can be provided as a medical procedure, it is necessary to verify its safety and effectiveness with clinical studies. Accordingly, a total of 10 uterus transplantation clinical studies were approved by the relevant regulatory authorities in 2015. In 2018, it was announced that the corresponding studies would include five additional transplants from living donors.[21] It was confirmed that a study sponsored by Womb Transplant UK began in January 2017 but not whether recruitment was conducted.[22] It is confirmed that a study on the transplantation of the uteruses of brain-dead persons into 10 women and making observation of it began in 2019 and that the recruitment of subjects is currently ongoing.[23] While there is no confirmation of successful transplants or births for any specific individual, it can be presumed that the study is still ongoing since the limited number of subjects and indications identified in accordance with the approved research protocols have been confirmed.

In 2018, a team of researchers from Keio University in Japan[24] submitted a clinical study plan to the Japan Society of Obstetrics and Gynecology and the Japan Society of Transplantation to transplant a uterus donated by a relative, such as a mother or sister, in patients with Rokitansky syndrome.[25] Although the Japanese Medical Society, which

22, 2022.)

19 Testa G, Mckenna GJ, Gunby Jr RT, "Five live births after uterus transplantation in the United States," *Am J Transplant* 18, 2018, pp. 1270-1274.

20 "UK Womb Transplant Research Team receives go-ahead to begin operations," *Womb Transplant UK*, 2015.09.29. https://wombtransplantuk.org/uk-womb-transplant-research-team-receives-go-ahead-to-begin-operations (accessed on May 22, 2022.)

21 Testa G et al., op. cit., p. 20.

22 "Human Clinical Trial of Uterine Transplantation in the United Kingdom," ClinicalTrials.gov, 2016.11.08. https://clinicaltrials.gov/ct2/show/NCT02388802 (accessed on January 16, 2022.)

23 "Investigational Study Into Transplantation of the Uterus (INSITU)," ClinicalTrials.gov, 2020.01.28. https://clinicaltrials.gov/ct2/show/study/NCT04244409?term=Womb+Transplant+UK&draw=2&rank=2 (accessed on January 16, 2022.)

24 Keio Uterus Transplantation Research, https://keio-utx.org/index.html (accessed on May 22, 2022.)

25 Kim Byung-Gyu, "Japan, pushes to allow 'surrogate birth by transplanting uterus,' medical community discusses," *Yonhap News Agency*, 2018.11.08.http://www.yonhapnews.co.kr/international/2018/11/08/06190

organized a review committee at the request of these societies, presented a conditional opinion in July 2021 that the clinical study could be conducted in a small number of cases,[26] no actual recruitment and transplantation cases have been confirmed as of 2022.

Korea held the first uterus transplantation symposium in January 2020, centered on the Department of Obstetrics and Gynecology at Seoul Asan Medical Center, to formally discuss the indications for uterus transplantation and the medical aspects of uterus acquisition and transplantation.[27] In June 2021, a multidisciplinary uterus transplantation team consisting of obstetrics, gynecology, transplantation and plastic surgery personnel held the first online uterus transplantation symposium at Samsung Medical Center to further discuss the issue in detail.[28] Although the symposium reflected the characteristics of the multidisciplinary team and discussed relatively specific issues such as indications needing uterus transplantation, considerations to be made for uterus transplantation surgery, in vitro fertilization for pregnancy and future revisions to related laws, etc., there was no confirmation of the submission or deliberation of a report of an actual clinical study protocol for uterus transplantation.

III. Review of Legislation Related to Uterus Transplantation

1. Review of legislation in each major country

1) United States

In the United States, the National Organ Transplant Act (NOTA, Public Law 98-507, 1984), which was enacted as a federal law in 1984, provides the basis for the establishment of the Organ Procurement and Transplantation Network (OPTN) and stipulates the establishment of a private nonprofit organization to operate it under a federal contract (hereinafter, Sec 274). Currently, the OPTN is a public-private partnership that connects all professionals involved in the U.S. donation and transplantation system and has been managed by the United Network for Organ Sharing (UNOS) with a contract since

00000AKR20181108064900073.HTML (accessed on May 22, 2022.)

26 "「子宮移植」条件付きで容認の報告書を公表 日本医学会 検討委," NHK, 2021.07.14.https://www3.nhk.or.jp/news/html/20210714/k10013139531000.html (accessed on April 22, 2022.)

27 1st uterus Transplantation Symposium, Asan Medical Center, Seoul, Korea, 2020, https://amc.seoul.kr/asan/academy/event/eventDetail.do?eventId=1146&arisSeq=&pageIndex=1&deptTabIndex=2&hpCds=D019&searchKeyword=&searchCondition= (accessed on May 22, 2022)

28 2017 Organ Transplantation Center Symposium, Center for Organ Transplantation of Samsung Medical Center, 2017, https://www.instagram.com/uterus.transplant/ (accessed on May 22, 2022.)

September 1986. The U.S. Department of Health and Human Services (HHS) has 42CFR121 regulations to support and implement the OPTN.

According to the NOTA regulations, an organ signifies the human kidney, liver, heart, lung, pancreas, and any other human organ (with the exclusion of corneas and eyes) prescribed by the Secretary by statute for purposes of sec. 274a of this chapter (Sec. 274b.(d)(2)), and includes bone marrow. The phrase "any other human organ as prescribed by the Secretary under the Act" means organs defined in 42CFR121.2 and refers to the human kidney, liver, lung, pancreas, intestine (including the esophagus, stomach, small intestine, or large intestine, and any part of the stomach), or vascularized composite allograft (VCA). In addition, blood vessels including extra blood vessels extracted from an organ donor during the removal of the above organs may be used, but only "for organ transplantation."[29] For the purposes of the statute, a VCA is a body part that is (1) vascularized and requires blood flow through the surgical connection of blood vessels to function after transplantation, (2) contains multiple tissue types, (3) is extracted as an anatomical/structural unit from a human donor, (4) is transplanted as an anatomical/structural unit into a recipient, (5) is minimally manipulated (processing that does not alter the original characteristics of the organ that are relevant to its usefulness for reconstruction, treatment, or replacement), (6) is for allogeneic use (replacing or supplementing the recipient's organ with an organ that performs the same basic function or functions in the recipient as it did in the donor), (7) is not combined with something else such as a medical device, (8) is susceptible to ischemia and stored only temporarily and not cryopreserved and (9) is susceptible to allograft rejection, thereby generally requiring immunosuppressive medications that may increase the recipient's risk of infectious disease.[30]

In 2014, the OPTN identified "VCA transplantation" as falling within the scope of management of OPTN, and in 2016 listed VCA organs and genitourinary organs as part of VCA(s), with the view that genitourinary organs include "uterus," internal and external male and female genitalia, and the urinary bladder,[31] thereby managing and monitoring uterus transplantation with application of OPTN bylaws and policies.[32] Currently, the OPTN requires that living donors undergo (1) a psychosocial evaluation, (2) an independent living donor advocate consultation (ILDA), (3) informed consent based on

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29 PART 121 - ORGAN PROCUREMENT AND TRANSPLANTATION NETWORK, Code of Federal Regulation [Apr. 2, 1998], https://www.ecfr.gov/current/title-42/chapter-I/subchapter-K/part-121#121.13 (accessed on May 22, 2022.)

30 Ibid.

31 OPTN Policy 1, pp. 3-4, https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf (accessed on February 10, 2022.)

32 Johnson N, Wall A, Johannesson L, "Implementing regulations and policies for uterus transplantation," *Current Opinion in Organ Transplantation* 26(6), 2021, p. 660.

sufficient information and (4) a medical evaluation. Since uterus transplantation has also been subject to the application of OPTN bylaws and policies since 2016, living uterus donors are also subject to these assessments prior to donation.[33] Accordingly, psychosocial and financial risks must be explained to genitourinary VCA living donors in order to obtain their informed consent based on sufficient information. At this time, it must be disclosed that although such risks could be temporary, they could also be permanent. Moreover, information on potential surgical risks including bowel damage, the need for hormone replacement therapy, pain or discomfort during intercourse, the possibility of partial or complete loss of certain functions including reproductive function, physical damage, and urinary tract damage or dysfunction must be provided. In addition, potential psychosocial risks should be explained, including the potential for emotional distress or grief, if the recipient does not experience a successful functional and cosmetic outcome, or reproduction. They should also be informed that some procedures may not be covered by health insurance due to potential financial implications, including but not limited to it.[34] For medical evaluation, all VCAs living donors must undergo an infectious disease screening (toxoplasma immunoglobulin G (IgG) antibody test). This screening must be performed by a CLIA-certified laboratory or a laboratory that meets the requirements set forth by CMS using FDA-licensed, approved, or cleared tests. In the case of uterus donation, additionally required tests, such as bacterial vaginosis, must be performed,[35] and past gynecologic and obstetric history including previous childbearing history must be examined with the addition of a Pap smear. A radiologic evaluation (pelvic exam) must also be performed to determine if the uterus is anatomically suitable for transplantation.[36] Since 2015, the OPTN has also imposed data collection and reporting obligations on VCAs, requiring organizations to report on the hospital that provided the transplant surgery, etc. and submit recipient information annually after the transplant until the death of the recipient. In addition, other relevant information such as infectious diseases, information about living donors and other patient safety information must be submitted as standardized data.[37] When these transplant outcomes are reported, the OPTN generally

33 OPTN Policy 14, https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf (accessed on February 10, 2022.)

34 Ibid.

35 Additional tests that OPTN may order for living uterus donors include bacterial vaginitis (Gardnerella Vaginalis), chlamydia by nucleic acid test (NAT), gonorrhea by nucleic acid test (NAT), herpes simplex virus (HSV) 1/2 immunoglobulin G (IgG) antibody test, human papillomavirus (HPV) cervical specimen by DNA or mRNA, trichomoniasis, and fungal testing including vaginal candidiasis (at evaluation and donation). OPTN Policy 14, pp. 283-284, https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf (accessed on February 10, 2022.)

36 OPTN Policy 14, p. 283, https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf (accessed on February 10, 2022.)

37 OPTN Policy 18, p. 311-319, https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf (accessed

defines success as the survival of the recipient,[38] which differs from the United States Uterine Transplant Consortium, which defines the success of uterus transplantation as the health of the mother and of the child born.[39]

2) United Kingdom

The United Kingdom has established and been managing regulations on relevant materials such as organs, tissues and cells as human-derived substances (human materials)[40] that can be removed, stored and used for the purpose of transplantation from deceased or living persons under the Human Tissue Act (hereinafter, HT ACT) since 2004. The Human Tissue Authority (HTA), a governing body established under the HT ACT, serves as the regulatory authority for organ transplantation.

In addition, after 2019, issues related to consent for the purpose of transplantation in the HT ACT have been subject to the opt-out system under the Organ Donation Deemed Consent Act (hereinafter, ODDC Act). On the other hand, the National Health Service (hereinafter, NHS) supports the work of the HTA by managing the donation and transplantation of organs and blood at the National Health Service Blood and Transplant (hereinafter, NHSBT) under its umbrella. This means that dualization in the management of relevant issues with the supply and demand for transplantable organs is managed with the HTA playing the key role, while the actual medical practice of donation and transplantation is managed by the NHS as the principal. Although the HT ACT does not stipulate the organs that are covered by specifically listing them, the HTA website posts a list of human-derived substances that can be considered under the HT ACT, which includes organs.[41] If the product is not included in the list of human-derived substances provided on the HTA website, the relevant person must make their own determination as to whether it may correspond to a human-derived substance under the HT ACT, and if

on February 10, 2022.)

38 Johnson N et al., op. cit., pp. 662-663.

39 Johannesson L, Testa G, Flyckt R, "Guidelines for standardized nomenclature and reporting in uterus transplantation: an opinion from the United States Uterus Transplant Consortium," *Am J Transplant* 20(12), 2020, p. 3321.

40 The category of human materials under the HT ACT of the UK is broader than the category of human derivatives under the Korean Bioethics Act, and is defined to include organs other than cells, tissues, etc. as well as the body itself. Accordingly, in this report, "human materials" will be described as "human derived materials, etc."

41 "List of materials considered to be 'relevant material' under the Human Tissue Act 2004," Human Tissue Authority(HTA), 2021.06.23. https://www.hta.gov.uk/guidance-professionals/hta-legislation/relevant-material-under-human-tissue-act-2004/list-materials (accessed on December 28, 2021.)
※ The list provided in the corresponding website is not inclusive of all human-derived substances under the HT ACT and will be reviewed regularly and updated as necessary.

necessary, request a determination from the HTA for advice.[42]

With the enactment of the ODDC Act in 2019, the UK introduced an "opt-out" system for organ donation, which stipulates excepted adults and permitted material exceptions that cannot be donated under the opt-out system even if a donation is received under the HT Act. Accordingly, the relevant regulations (Human Tissue (Clauses 2 to 5 of Article 2 of the Permitted Material: Exceptions) Regulations 2020, (hereinafter referred to as the "HT Regulations")) define the body: arms, brain, face, fingers, feet, forearms, hands, legs, calves, mouth, nose, spinal cord, thighs, toes, trachea, upper arms, cervix, and clitoris, embryos, fallopian tubes, fetuses, labia, ovaries, penis, perineum, placenta, prostate, testicles, umbilical cord, uterus, vagina, vulva, etc. as materials that cannot be donated in the opt-out system, i.e., materials that must be excluded in accordance with the system. According to the notes to HT regulations,[43] since the opt-out system under the deemed consent legislation is intended to expand access to transplantation carried out in general, organ transplantation in accordance with the advancement of new technology cannot be conducted without express consent, and it is explained that the organs that cannot be donated under deemed consent under the HT Regulations have been stipulated.

The Department of Health of the UK believes that any new transplantation procedure using a human-derived substance that is not permitted to be donated under the HT Regulations should be viewed as research and evaluated at the research and service evaluation stage before it can become a routine procedure. Therefore, transplantability, safety and efficacy must be demonstrated with research first. The Research, Innovation and Novel Technologies Advisory Group (hereinafter, RINTAG),[44] an organization within the NHSBT that approves organ donation and transplantation related to research projects, will review all the evidence and send an opinion to the NHS and the NHSBT on the outcome of the review of the corresponding transplant procedure. Based on this, if the NHS is satisfied that the procedure is a service that the NHS can and should provide, it becomes a routine procedure and can be provided as a medical service.[45] Accordingly, as of 2015, the NHS of UK has approved a total of 10 uterus transplantation studies.

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42 Ibid.

43 "EXPLANATORY MEMORANDUM TO THE HUMAN TISSUE (PERMITTED MATERIAL: EXCEPTIONS) (ENGLAND) REGULATIONS 2020," Legislation.gov.uk, 2020, No. 521, p. 3 https://www.legislation.gov.uk/ukdsi/2020/9780111193372/pdfs/ukdsiem_9780111193372_en.pdf (accessed on March 17, 2022.)

44 "Organs and tissues to be excluded from the new system of organ and tissue donation in England (known as "opt-out" or "deemed consent")," Department of Health & Social, 2019. 04. 29. p. 9 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/798467/Organs_and_tissues_to_be_excluded_from_the_new_system_of_organ_and_tissue_donation_in_England_-_consultation_document.pdf (accessed on January 16, 2022.)

45 "Regulation," NHS Blood and Transplant, https://www.odt.nhs.uk/odt-structures-and-standards/regulation/ (accessed on January 16, 2022.)

3) Japan

In Japan, the "Law on Transplantation of Corneas and Kidneys" was the first transplantation-related law established in 1979 in relation to the extraction of organs from cadavers, and the "Law on Organ Transplantation" (hereinafter referred to as the "Japan Organ Transplantation Law") was enacted in 1997, abolishing the previous law.[46] The Japan Organ Transplantation Law and its Enforcement Regulations stipulate post-mortem donation since it adheres to the principle of donation after the determination of brain death in accordance with the consent of the donor prior to death and the consent of the bereaved family. Details of operations not stipulated by the law are managed in accordance with the Guidelines for the Operation of the Law on Organ Transplantation of the Ministry of Health, Labor and Welfare. The Japan Organ Transplant Network, established by the Law, is a public benefit corporation authorized by the Ministry of Health, Labor and Welfare to carry out management tasks necessary for organ donation registration and transplantation, etc. for brain-dead persons.[47] Since the Japanese Organ Transplantation Law does not include regulations for organ transplantation for living people, donation and transplantation from living people are carried out in accordance with the relevant guidelines of the Ministry of Health, Labor and Welfare and the ethical guidelines of the Japan Society of Transplantation, and donation from living people is relatively more active in the case of liver donation because the actual donation by brain-dead people is too strict.[48] The Japan Society of Transplantation provides transplant physicians with the principles of organ transplantation at the level of the Society along with those who can donate as a living person's organ donation, deliberation on the feasibility of transplantation, donor consent and protection of rights, as well as information registration, personal information protection, etc.[49]

Although Article 5 of the Japanese Organ Transplantation Law and Article 1 of the Enforcement Rules of the Law define "organ" as "human heart, lungs, liver, kidneys, intestines (pancreas and small intestine) and eyeballs" as determined by the Ministry of Health, Labor and Welfare," there is no provision for organs that can be donated from a living person like organs that can be extracted and transplanted from a brain-dead person. Therefore, according to the law, although it seems impossible to donate and transplant a uterus from a living person, it could be possible in accordance with the ethical guidelines

46 Kim Gyeong-Seok, "Amendment of Japan's Organ Transplantation Law, (Latest) Foreign Law Information," *Korea Institute of Legal Studies*, 2010, pp. 48-55.

47 日本臓器移植ネットワーク, https://www.jotnw.or.jp/ (accessed on January 16, 2022.)

48 Choi Eun-Gyeong et al., op. cit., p. 42.

49 Choi Eun-Gyeong et al., op. cit., p. 125.

of the Japan Society of Transplantation.

The ethical guidelines of the Japan Society of Transplantation (21.9.18) stipulate that a clinical study for the purpose of developing new medical technologies or systems for the advancement of transplantation medicine must be conducted in compliance with the [Clinical study Act], the [Act on Securing the Safety of Regenerative Medicine, etc.], the [Ethical Guidelines for Research in the Life Sciences and Medical Sciences Involving Human Subjects] jointly issued by the Ministries of Health, Labor and Welfare, the Ministry of Education, Culture and Science, and the Ministry of Economy, Trade and Industry, as well as other relevant laws and regulations, and national guidelines. Therefore, in the event of planning a clinical study on organ transplantation, a request for an opinion from the Japan Society for Transplantation can be made after a review by the ethics committee of the affiliated institution and approval by the head of that institution. However, it is specified that the final decision and responsibility for implementation rests with the corresponding institution.[50]

Therefore, in 2018, a research team from KEIO University[51] submitted a clinical study plan to transplant a uterus donated by a relative such as a mother or sister to a patient with Rokitansky syndrome to the Japanese Society of Obstetrics and Gynecology and the Japanese Society of Transplantation,[52] and in November 2018, the Japanese Society of Obstetrics and Gynecology and the Japanese Society of Transplantation requested a review by the Japanese Medical Society. In response, the Japan Medical Society operated an ethical review committee related to uterus transplantation (hereinafter, review committee) consisting of 14 experts to review uterus transplantation to an infertile patient from medical, ethical, legal and social (ELSI) perspectives from April 2019, and published the results as the [Report by the Review Committee on the Ethics of Uterus transplantation of the Japanese Society of Physicians (hereinafter, Japan Medical Society Report)] in July 2021.[53] This report presents the necessity and basic principles of research review on uterus transplantation, the current status of uterus transplantation overseas and research in Japan, uterus transplantation from living donors, uterus transplantation from brain-dead patients, adoption and surrogacy as options other than uterus transplantation, soliciting opinions from women with congenital absence of the uterus, performing

50 "日本移植学会倫理指針, The Japan Society for Transplantation, 2021, P. 6([5]臨床研究), http://www.asas.or.jp/jst/about/doc/info_20210918_1.pdf (accessed on May 22, 2022.)

51 https://keio-utx.org/index.html (accessed on May 22, 2022.)

52 Kim, Byeong-Gyu, "Japan pushes to allow 'surrogate birth by transplanting uterus' ... medical community to discuss," *Yonhap News Agency*, 2018.11.08. http://www.yonhapnews.co.kr/international/2018/11/08/0619000000AKR20181108064900073.HTML (accessed on May 22, 2022.)

53 The Japanese Association of Medical Sciences, op. cit., Chapter 1, https://jams.med.or.jp/news/059_2.pdf (accessed on May 22, 2022.)

uterus transplantation, basic conditions for conducting clinical studies, etc. The Review Committee was of the opinion that although uterus transplantation is an incomplete medical technology with numerous anticipated significant risks including unknown risks at this stage, there is a strong desire of women with uterine infertility to undergo uterus transplantation. Therefore, it is possible to acknowledge the execution of a clinical study on them if they wish to do so after all the parties, including donors and recipients, have fully understood the risks and specific procedures accompanying uterus transplantation. They further noted that while striving to minimize the risks of conducting a clinical study on uterus transplantation, the clinical study should be carefully validated by repeatedly assessing the short- and long-term risks, including unknown risks, as well as reviewing whether to proceed further or stop with such validation.

Although the corresponding review committee expects that uterus donation from brain-dead patients will be permitted, this change will require constant efforts to seek public understanding in the long term, and it is emphasized that uterus transplantation is not the only treatment for patients afflicted with congenital absence of the uterus. In order to conduct an appropriate clinical uterus transplantation study, a dual review process in which (1) the ethics committee of the research institution reviews the study according to the basic conditions outlined in this report, and (2) the results are reviewed again by the "Joint Implementation Review Committee of the Japan Society of Transplantation and the Japanese Society of Obstetrics and Gynecology" (provisional name) is proposed. It was put forward that the review committee should be regularly briefed on the progress of the study, including the review of individual cases, that it is important to have the authority to advise on the study and examine whether the study should be continued, and that the clinical study organization should establish a follow-up system to provide counseling, etc. to the donor, recipient and the child to be born. In addition, the report suggested that it is necessary to establish basic conditions for conducting clinical studies on uterus transplantation using living donors by dividing donors and recipients on the basis of confirming their free will with consideration for the special nature of the uterus, along with existing laws and guidelines on organ transplantation.[54] First, with regard to the donor, (1) they have the physical strength to undergo a hysterectomy, (2) receive an assessment that there is high possibility of pregnancy with the uterus being donated, and (3) confirm that they do not intend to become pregnant and give birth in the future. The recipient must be (1) a congenitally or acquired uterine infertile patient,[55] (2) medically capable of conceiving and carrying her own child through uterus transplantation by obtaining a fertile embryo with

54 The Japanese Association of Medical Sciences, op. cit., Chapter 9.

55 The specific scope of patients with uterine infertility is not explicitly limited since it should be reviewed in the context of a comprehensive review of clinical studies.

in vitro fertilization and embryo transfer (generally under the age of 40 years), (3) physically and mentally capable of tolerating uterus transplantation, pregnancy, childbirth and child rearing, and (4) have the ongoing understanding and cooperation of her partner.[56] Accordingly, donors, recipients, and their partners should be fully informed of the information required for uterus transplantation and asked to make a decision after understanding them, and it is recommended that they confirm their intentions as individually as possible so that pressure from others can be excluded from the decision-making process. A coordinator who can verify each individual's free will from a third-party perspective is required, and should be a person who is not affiliated with the uterus transplantation organization. The implementing institution must organize a long-term consultation system for the donor and recipient. When uterus transplantation is conducted as a clinical study, research subjects should be able to refuse to participate in the research, and if they do, they should be able to withdraw their consent at any time with the guarantee that it will not affect their usual treatment.

The conclusion of the report was that it is necessary to conduct clinical studies based on the current level of medical ethics and to review the results, and if it is deemed necessary to review the basic conditions proposed by the review committee and apply to the Japan Medical Society, a review organization will be established to handle applications on a permanent basis.[57]

2. Review of characteristics between legislation

Organ transplantation has historically started as a form of "research" limited to patients with no other treatment options, and has been expanded by reducing the risks of the procedure and ensuring its safety and effectiveness by sharing the experience internationally. In addition to the medical risks of transplantation itself, transplantation requires organs derived from humans.

Due to the various legal and ethical issues that arise between donors and recipients in organ donation and transplantation, most countries have strictly regulated organ transplantation with laws and guidelines at the national level. Although organ donation and transplantation are influenced by sociocultural factors, the fundamental nature of organ donation is curative medical treatment, which varies according to the healthcare environment and has a very decisive impact on the system of each country. Therefore, it is

56 The relationship with the recipient's partner means a legally married couple in a stable common-law relationship, given that uterine transplantation is a long-term medical procedure.

57 The Japanese Association of Medical Sciences, op. cit., Chapter 10.

important to review the system of organ transplantation in each country in conjunction with the healthcare system of the corresponding country.

The United States operates a dual system of healthcare with Medicare for the disabled and low-income provided by the government, and most people rely on private health insurance, including workplace insurance with the exclusion of Medicare for the elderly over the age of 65. Therefore, the management of organ transplantation is also governed by law, and although the law lists the organs that can be transplanted, it fundamentally stipulates the broad principles, standards and procedures, and the details are implemented and managed according to the standards and procedures within the scope delegated to supplementary decrees. The actual administrative center is a private nonprofit organization (UNOS) that has a federal contract with the Department of Health and Welfare, and the Organ Procurement and Transplantation Network (OPTN) is operated by that organization. Uterus transplantation is also governed by OPTN policy, which established and provides relatively detailed evaluation guidelines.

On the other hand, since the United Kingdom has a public healthcare system in which medical care is managed by the state under the National Health Service (NHS), organ donation and transplantation based on the NHS are also managed by the state with its own implementation basis, management organization, etc. However, the donation of organs for transplantation, etc. is managed by the HTA based on the Human Tissue Act, while transplantation is managed by the NHSBT, which is in charge of blood and tissue transplantation within the National Health Service, since it is a medical procedure. Recent legislation has introduced an opt-out system to verify and manage the legality of consent in relation to the donation process, and the range of transplantable organs and surgeries are managed on medical grounds. Although there are categories of human derivatives that are not allowed to be donated with opt-out consent, transplantation for research purposes is possible with NHS and NHSBT approval. After safety and efficacy have been demonstrated, it can be evaluated as a service that can be provided. Recruitment of study subjects is currently underway at the research stage rather than as a surgical procedure.

Although Japan defines the range of organs and procedures that can be transplanted in the Organ Transplantation Act, it does not include regulations for organ transplantation from living individuals. Therefore, donations from living individuals and transplantation are carried out in accordance with the relevant guidelines of the Ministry of Health, Labor and Welfare and the ethical guidelines of the Japan Society of Transplantation. In Japanese society, which operates the system in such a way that when new issues arise, compliance with the ethical codes and guidelines of the relevant professional organizations is more important than the provisions of the relevant laws and regulations, the Japanese Society of Physicians, together with the Society of Obstetrics and Gynecology and the

Transplantation Society, conduct a review and issue an opinion on the relevant issues of uterus transplantation studies, and there is a history of giving permissive opinions to studies conducted by Keio University research team.

In cases of the law intervening in a highly specialized medical practice such as organ transplantation, it is appropriate that not only the approach but also the scope and method should be reviewed based on the basic characteristics and environment of the corresponding healthcare system. That is, although the state is responsible for managing expertise by securing safety and effectiveness related to medical practice, it is the responsibility of medical practitioners to verify and confirm their expertise and provide actual medical care. Therefore, it is important to secure and manage appropriate expertise and independence between the state and medical practitioners.

3. Review of domestic laws related to uterus transplantation in the future

Although Korea operates a national health insurance system for the provision of healthcare services, not all organ transplants are covered by it. In addition, the Korea Organ Donation Institute is in charge of organ donation and distribution under the Organ Transplantation Act, but it lacks policy expertise and capability in establishing management measures like the OPTN. Therefore, it is largely dependent on laws and national policies. Also, if research is to be conducted with organs as a new transplant material that is not specified in the Organ Transplantation Act, it is stipulated that the corresponding organ transplantation technique needs to be designated as a new medical technology with a new medical technology evaluation before implementing it. This is comparable to the evaluation system under the NHSBT in the UK NHS. Thus, it can be said that the legal system for organ transplantation in Korea has the characteristics of both the American and British healthcare systems.

Institutionally, the Organ Transplantation Act of Korea takes the approach of directly defining transplantable organs, as do the laws of Japan. The revised Organ Transplantation Act specifies “hand and arm, or foot or leg as a composite tissue consisting of bone, skin, muscle, nerve and blood vessels” as a transplantable category, and provides a foundation for expanding it in order for the Minister of Health and Welfare to decide and announce them after deliberation by the Organ and Transplantation Ethics Committee. However, there is no publicly established standard or procedure for the ethics committee’s deliberations. For example, there is no criterion for applying for deliberation such as that a uterus transplantation study must be approved as a clinical study by an institutional committee in the corresponding institution or that the safety and effectiveness of the

study must be evaluated by the New Medical Technology Evaluation Committee, etc. As a result, it is difficult to predict what factors should be considered in determining whether the uterus is a transplantable organ under the Organ Transplantation Act. Moreover, since the uterus is not an explicit transplantable organ under the Act in our current legal system, it is inevitable that studies will be conducted as "research" in the future. However, there is no principle or standard in place for each institution to deliberate on the ethical and scientific validity of a clinical study for each individual case. Although the autonomy of research is recognized, it is necessary to provide minimum standards for autonomy in terms of the environment of the research team or research institution for safe research that cannot be solved by the will and capacity of the researcher, the selection of recipients who can be referred to as research subjects, the selection of donors, etc.

The Act on the Safety and Support for Advanced Regenerative Medicine and Advanced Regenerative Biopharmaceuticals (hereinafter, Advanced Regenerative Medicine Act), which is currently being implemented, defines biopharmaceuticals such as advanced regenerative medicine or treatment medicine, and regulates the environment and conditions, etc. for conducting advanced regenerative medicine as a research endeavor. However, there still is no review in accordance with the research situation for transplantation surgery. The uterus or uterus transplantation does not meet the definition of "human cells, etc."[58] or "advanced regenerative medicine" in the Act.[59] Although it does not fit the definition of medical and therapeutic products limited to cells or tissues, it seems necessary to at least review its novelty and risks, and in particular, to review and propose requirements for multidisciplinary research teams, for example, including facilities and personnel to enable research attempts. Furthermore, there is a need to consider methods such as conducting and managing limited research in cases where the feasibility of conducting this research is clear based on sufficient scientific and clinical evidence, and to ensure that the safety and efficacy of uterus transplantation can be verified and evaluated based on carefully accumulated clinical study cases.

In the future, legal policies related to uterus transplantation need to establish principles at the guideline level, rather than revising the system on a case-by-case basis according to realistic needs, as was the case with the revision of legislation on partial-body transplantation. Within the limits of relevant laws such as the Organ Transplantation Act, the Act on Bioethics and Safety (hereinafter, Bioethics Act), the Medical Service Act, and the Advanced Regenerative Medicine Act, it will be necessary to explicitly present relevant

58 Refers to cells, tissues and organs stipulated under Presidential Decree including human-derived stem cells, hematopoietic stem cells, somatic cells, immune cells, xenocytes, etc.

59 Cell therapy, gene therapy and tissue engineering therapy that are performed using human cells to regenerate, restore, or form human body structures or functions, or to treat or prevent diseases, as stipulated under the Presidential Decree.

principles such as the matters and procedures to be reviewed within the institution at the research level, the requirements that can be determined and announced by the Minister of Health and Welfare after deliberation by the Organ Transplantation Ethics Committee regarding acceptance in the Organ Transplantation Act and the matters to be submitted and confirmed for this purpose, the relationship between internal and external approvals, and the monitoring and management of this research.

IV. Controversial Ethical Issues of Uterus Transplantation

In 2008, the Ethical Committee of International Federation of Gynecology and Obstetrics (FIGO) classified and announced uterus transplantation as unethical due to the lack of data on safety and efficacy.60 As can be seen from the aforementioned current status of uterus transplantation, it is performed as an investigational procedure in most countries. Therefore, the requirements for donors and recipients, the provision of sufficient explanations and information, and voluntary consent from the recipient are emphasized. In addition, due to its characteristics that are distinguished from those of other solid organ transplants, controversial issues related to the ethical conduct of a clinical study must be examined first. However, unlike general research, ethical review is required for each donor and recipient. Furthermore, if the success of uterus transplantation research is defined as a healthy birth, it is necessary to consider the birth of a healthy person.

When the stability and validity of a clinical study is secured and its demand as universal medical care, etc. needs to be reviewed, we will also examine the issues that need to be considered in the institutionalization process such as the selection criteria for donors (including living donor) and recipients. Lastly, when uterus transplantation is opted for the purpose of healthy pregnancy and childbirth, unlike other organ transplants, considerations will be made on to what extent the state should institutionalize and support uterus transplantation.

1. Conducting ethical clinical studies

The ethical conduct of a clinical study generally requires a valid research design based on scientific evidence. Measures to protect the safety and rights of research subjects are required at the stage of conducting research. For this purpose, it is also necessary to check the researcher's basic skills, research qualifications, etc. at the deliberation stage. Therefore,

60 Zaami S et al., op. cit, p. 5291.

it is necessary to review at the unit of the research protocol as the basis, but in some cases, it is also necessary to review the institution where the research is conducted.

In addition, under the assumption that the research protocol is scientifically and ethically valid, sufficiently informed and voluntary consent must be obtained from the research subjects (recipients and donors). During the performance of the research, the safety of the corresponding research subjects must be given the utmost priority.

However, a clinical study involving the transplantation of new organs may have little scientific basis and may only be a theoretical proposal. The ability to actually perform a transplant often depends on the competence of the researcher or research team and the environment in which the transplant will be performed. Therefore, when deliberating on a clinical study on uterus transplantation, it is of utmost importance to verify from the submitted study protocol whether the researchers are competent to conduct the research and whether the environment in which the research will be conducted is appropriate.

2. Donor selection and protection

The issue of donor selection for organ transplantation is always ethically problematic since it requires exposure to risk without any potential benefit. However, the donation of a life-saving organ is ethically justified on the basis of the principles of rescue ethics. Nonetheless, it is difficult to define the uterus as a life-saving organ. It is a quality-of-life donation, and the beneficence to the recipient is usually the justification for uterus transplantation.[61] Therefore, it is important to clarify the donor's autonomous choice of donation and the selection criteria.

In particular, in the case of living donors, it will be important to assess the donor's risk after donation and take measures to ensure their quality of life. Given the current level of uncertainty about clinical efficacy following donation, it is inevitable to further emphasize the importance of consent based on sufficient information.

However, the reality is that the donor is responsible for any adverse events that may occur after said consent. According to an investigation by Mats B. et al., uterus transplantation from a living donor requires additional testing in accordance with the uterus characteristics such as cervical smear/human papillomavirus testing, testing to exclude sexually transmitted diseases, candidiasis and bacterial vaginosis, and transvaginal ultrasound scanning to exclude structural abnormalities, in addition to the infectious disease testing required for other solid organ transplants. It is further explained that magnetic resonance angiography or computed tomography angiography are needed for information

61 Bruno B et al., op. cit., p. 6.

on vessel morphology, caliber and patency.

In the case of uterus transplantation in particular, approximately 80% of donations are from living donors, and it has been reported that 11.4% of donors experienced complications requiring additional surgery after donation.[62] Iori K. et al. reported that complications after open hysterectomy that accompanied the donors included bleeding (1%), blood transfusion (2-12%), infection (high fever of unknown cause (10-20%), surgical site (6.6-24. 7%), wound (4-8%), pelvic (3.2-10%), and urinary tract (1.1-5%)), pneumonia (0.4-2.6%), bladder injury (1-2%), intestinal injury (0.1-1%), ureteral injury (01.-0.5%) and bladder fistula (01.-0.2%). Although the risk can be minimized with laparoscopic or robotic surgery and it is not the case that these complications always occur, the uterine arteries may be too short for angioscopy, thereby requiring the removal of visceral vessels to obtain sufficient length,[63] and there could be complications of ligation of the visceral arteries including hip rupture, bladder and rectal ischemia and pain. Furthermore, the ovarian vein is preferred to be used for anastomosis during uterus transplantation because it is longer and thicker than the uterine vein, which in itself may require removal of the ovary with the possibility of ovarian dysfunction if the donor is a premenopausal woman. Additionally, when the uterus is transplanted from a premenopausal living donor, it may be accompanied by uterine dysfunction, which may induce ovarian deficiency syndrome that requires hormone replacement therapy. Other burdens borne by living donors in uterus transplantation include surgical complications such as complications of hysterectomy, sequelae from the removal of vascular pedicles, ovarian dysfunction, decreased quality of life and psychiatric problems.[64]

In fact, as a result of a 1-year observation study on nine living donors who donated uterus after uterus donation in 2013, there were reports of one major surgical complication, occurrence of a post-hysterectomy ureteral-vaginal fistula that required surgical repair, and two cases of enuresis and paresthesia.[65]

According to the Japan Medical Society Report, while long-term follow-up and observation were not included for 63 cases of biological donors, post-extract urinary tract infection (seven cases), urinary tract injury (four cases), bladder vaginal leakage (two cases), hair loss (two cases), dysuria (two cases), gluteal pain (two cases), and chest

62 Brännström M, Kähler PD, Greite R, "Uterus Transplantation: A Rapidly Expanding Field," *Transplantation* 102(4), 2018, pp. 569–577.

63 In uterine transplantation, the uterine arteries and veins and the ovarian veins are used for anastomosis with the external uterine vessels, which can be removed from the donor uterus.

64 Kisu I, Mihara M, Banno K, "Risk for Donors in Uterus Transplantation," *Reproductive Sciences* 20(12), 2013, p. 2.

65 Kvarnström N, Järvholm S, Johannesson L, "Live Donors of the Initial Observational Study of Uterus Transplantation—Psychological and Medical Follow-Up Until 1 Year After Surgery in the 9 Cases," *Transplantation* 101(3), 2017, pp. 664-670.

tightness (one case) were reported. Moreover, it was reported that vaginal cuff dehiscence occurred in approximately 30% of cases, and complications requiring postoperative pharmacologic therapy including urinary tract infection, fecal incarceration, wound infection, decreased bladder tone, leg/buttock pain, anemia, respiratory failure during anesthesia, and depression also occurred.66

In spite of these risks, living donation is more commonly attempted than brain-dead donation because donation from brain-dead donors requires a cold ischemia time that is more than two times longer than that of living donors, which is a shortcoming that can increase the likelihood of ischemic injury and subsequent risk of chronic graft dysfunction including acute or chronic rejection, increased risk of infection, etc. In addition to the generally required pre-testing of donors for infectious diseases and so on, since various functional and structural tests required for the smooth functioning of the uterus after transplantation, and rapid confirmation of sexually transmitted diseases are required, living donation has been shown to be more efficient than brain-dead donation.

In the case of actual living donors, it is important to note that more than half of living donors are family members of the recipient (sisters, mothers, aunts, etc.), in addition to the physical and psychological risks to the donor. Obviously, there is an immunologic advantage in transplantation in the case of immediate family members. On the contrary, in the case of older donors, sufficient time should be given to consider donation due to the possibility of an increase in other risks such as increased rates of acute allograft rejection, etc. Furthermore, they may be less able to make an autonomous choice and may be more vulnerable because they are family members, thereby needing more time to ponder over the decision, and protective measures for this should be put in place. Considering that it must be possible to minimize the risks to the donor in organ transplantation and that the uterus is not a vital organ directly related to life and death, it is also possible to consider the principle of post-mortem donation rather than living donation for uterus transplantation.

3. Criteria for selecting recipients

In general, it is accepted as a principle of medical ethics that in a clinical study, voluntary consent is given by research subjects after sufficient explanation, including uncertainties such as the risks and benefits of participating in the research. However, it is not easy to explain the potential benefits or risks of a uterus transplantation clinical study with sufficient information because the outcome is difficult to predict. Uterus transplantation is

66 The Japanese Association of Medical Sciences, op. cit., Chapter 4, p. 4.

not yet a medically proven procedure, particularly because successful pregnancy after implantation requires additional surgeries on the cervix, vaginal cuff, surrounding uterine and connective tissues, major blood vessels that supply and drain the uterus, etc. When the purpose of the uterus is fulfilled with pregnancy and childbirth, the uterus is usually extracted. However, there is the problem of the recipient needing to take immunosuppressive drugs, steroids, etc. to prevent immune rejection until pregnancy and childbirth are over, as is the case with all organ transplant recipients. Furthermore, simply informing the recipient of these risks does not guarantee the autonomy of the recipient. Rather, it is necessary to collect information based on long-term follow-up and monitoring along with provision of the collected information and allowing sufficient deliberation on such information by the recipient.

In addition, since uterus transplantation is only the beginning of a process aimed at pregnancy and childbirth, and the success of transplantation cannot be defined by the engraftment of the transplanted organ and the survival of the recipient after transplantation, the prediction of the fertility treatment process for the actual goal after the clinical study needs to be fully explained in advance. It is already a well-known fact that most women who undergo fertility treatment complain of psychological and mental distress. Therefore, it is necessary to explicitly and repeatedly confirm their intention to participate in the study or to undergo uterus transplantation, because women whose uterus is the underlying infertility factor may have to undergo fertility treatment to become pregnant and give birth, thereby multiplying the pain they have to endure.

It cannot be denied that pregnancy, childbirth and motherhood have a special meaning for women in some way. However, as with many criticisms of assisted reproductive technologies, procedures and medical technologies that focus on motherhood can be criticized for making motherhood a central part of a woman's identity, and for reinforcing traditional biological and genetic family ideologies.[67] Since the purpose of uterus transplantation is for pregnancy and childbirth, social reflection is necessary before institutionalizing uterus transplantation.

The recipient selection criteria will become even more important as uterus transplantation becomes more clinically safe, effective and accessible as a medical procedure. In the current study, recipients were genetic women of childbearing age who were diagnosed with absolute uterine factor infertility (UFI), either congenital or acquired, according to the Montreal Criteria for the ethical practice of uterus transplantation, and who have not received a medical opinion that uterus transplantation is not possible.[68] However, if uterus

67 O'Donovan L et al., op. cit., pp. 21.

68 Lefkowitz A, Edwards M, Balayla J, "Ethical considerations in the era of the uterine transplant: an update of the Montreal Criteria for the Ethical Feasibility of Uterus Transplantation," *Fertil Steril* 100(4), 2013, pp.

transplantation is to move beyond medical practice as a therapeutic prescription, it will be necessary to further discuss whether women with other uterine dysfunctions and those who have undergone sex change surgery as women and others can receive uterus transplantation for the purpose of pregnancy and childbirth.

Moreover, considering that implantation of embryos is conducted within a year after uterus transplantation, it may be necessary to determine the upper and lower limits of the transplantation age, taking into account the physical age appropriate for pregnancy and childbirth and the ability to raise children. It may be possible to select recipients by placing an upper limit from the age above that of a minor to the physical age of pregnancy and childbirth with the additional measure of giving priority to or a longer waiting period for older recipients within the range for transplantation.[69]

In addition to uterus transplantation, adoption and (gestational) surrogacy are other ways for women with uterine infertility to become mothers. However, personal beliefs, religious reasons, inability to fulfill legal requirements for adoption or prohibitions on surrogacy in the country, or a voluntary and healthy decision to become a mother should be considered as very important factors.

4. Consideration of the child born with the transplanted uterus

Uterus transplantation is different from other organ transplant treatments in that the goal is not the success of the transplant itself, but the birth of a healthy child. In general, although the fallopian tubes are retrieved as part of the graft during transplantation, they are removed after the actual transplantation to reduce the risk of ectopic pregnancy.[70] Accordingly, it is inevitable for the recipient to use assisted reproduction to become pregnant, including in vitro fertilization after uterus transplantation. In addition, after uterus transplantation, considerations may be required to ensure the availability of embryos such as anatomical distortion due to the transplanted uterus or procedure, or increased risk of infection due to the use of immunosuppressive drugs after transplantation. Furthermore, issues related to the use of assisted reproductive technologies such as multiple gestation with the risk of complications including premature labor, miscarriage, pre-eclampsia and gestational diabetes should be considered. In particular, it would be

924-926.

69 Bayefsky MJ, Berkman BE, "The Ethics of Allocating Uterus Transplants," *Cambridge Quarterly of Healthcare Ethics* 25(3), 2016, pp. 355-359.

70 Roy TK, Bradley CK, Bowman MC, "Single-embryo transfer of vitrified-warmed blastocysts yields equivalent live-birth rates and improved neonatal outcomes compared with fresh transfers," *Fertil Steril* 101(5), 2014, pp. 1294–301.

necessary to secure the minimum time needed for stabilization of the immune system by immunosuppressive drugs or surgical healing after transfer surgery with regard to the timing of embryo transfer, and consideration should be given to the effects on fetal health after pregnancy. Among the 23 cases of births after uterus transplantation (mostly from living donors and including three brain-dead donors) currently reported, three cases of preeclampsia, two cases of obstetric cholestasis and one case of rupture of membranes in premature labor were reported as prenatal complications. The women who developed preeclampsia were of appropriate gestational age, but all gave birth prematurely at 31-35 weeks.[71]

No direct risks have been monitored and reported for individuals born with a transplanted uterus until now. However, it has been less than 10 years since reports of children born via uterus transplantation have been made. In consideration of the need to take immunosuppressive medications during pregnancy, ongoing safety monitoring will be necessary in the future. Even though uterus transplantation is carried out as a clinical study rather than as a medical procedure, it cannot be taken lightly if pregnancy and child-birth result from it. In the case of uterus transplantation research, the research outcome is the beginning of a human life, and it is necessary to consider the health and welfare of the human being first and foremost. In this context, Bayefsky and Berkman proposed that the ability to raise a child should be part of the recipient's qualifications. This means that, at the minimum, the recipient should not have any criminal record of child abuse or neglect, and should have the financial means to provide a safe environment for the child to be born.[72]

V. Conclusion

Uterus transplantation is still in the early stages of implementation in the format of research attempts by only a small number of specialized medical staffs and at limited facilities performing the procedure. However, there is a need to thoroughly review the timing, method and criteria for its introduction in the future in advance. In particular, although uterus transplantation is an expensive medical technology that requires a high level of expertise, it is a procedure accompanied by unknown risks because there is no data on the risks to the donor, recipient or the child to be born through it. Therefore, it is essential to secure medical evidence that the procedure must and can be performed and the feasibility of the procedural method, along with the needs of the recipient, and the

71 Brännström M et al., op. cit.

72 Bayefsky MJ et al., op. cit., pp. 359-360.

autonomy of the donor and recipient. Even if clinical studies are currently at the stage of confirming clinical efficacy and safety, the same attention should be paid to the procedure and research since the ultimate goal of transplantation is to start a new life with a healthy pregnancy and childbirth. Therefore, it is necessary to secure the scientific and ethical validity of research plans and methods, and appropriate measures for safety and risks for the process and results to ensure that research is conducted ethically. In particular, special care and management of donors is required since donors who are required to bear very high physical risks are needed, unlike recipients who are research subjects that receive potential benefits in spite of the very high risks accompanying unproven research attempts. In addition, although the uncertain risks associated with the process of the development and application of various technologies in medicine are not unique to uterus transplantation research, it is important to approach the additional ethical issues raised by uterus transplantation with caution, given that the uterus, as a graft, is not an organ directly associated with the life of the recipient. Obviously, although it will be necessary to consider the direction of universal institutionalization as a corresponding medical procedure if medical safety and efficacy are secured with a clinical study, this must be predicated on systematic data management and monitoring of the clinical study.

In consideration of the reality in which the medical technology related to transplantation is constantly progressing and the categories of transplantable organs are constantly expanding, the way we currently manage the specific transplantable organs under the currently applicable organ transplantation laws does not reflect the characteristics of the objects covered by these laws and needs to be improved. In fact, it is worth noting that most countries recognize the possibility of adding or expanding transplantable organs regardless of whether they are explicitly listed in their laws, and have established and are managing criteria and procedures for making policy decisions on how to manage transplantation. Furthermore, the expertise of the facility and manpower at the medical institution planning to conduct uterus transplantation is very important since uterus transplantation is a task that requires medical staff in various fields such as transplantation, anatomy, obstetrics and gynecology to jointly support the entire process from donation to transplantation, pregnancy and childbirth, and to provide mental and psychological counseling support and continuous monitoring to donors, recipients and all those involved in transplantation. Therefore, systematic monitoring and management of performance is required at the government level. There also is the need for an organization such as the OPTN in charge of requesting data submission and receiving information based on the federal law in the United States. In addition, efforts should be made by professional organizations such as the Uterus Transplantation Association to establish a registry for data disclosure and analysis. At the 2011 Uterus Transplantation Conference, expert groups

and stakeholders gathered to discuss recent technological assessments and concerns in the art of human uterus transplantation (UTn), and deduced the Indianapolis Consensus[73] on procedures for clinical application, etc. The Indianapolis Consensus states that uterus transplantation will be performed in accordance with the standards proposed by Francis D. Moore (MD Harvard Surgery) in 2010[74] and the four principles of bioethics by Beauchamp and Childress. Moreover, the need for (i) additional pregnancy attempts in a variety of large animal/primate models, (ii) ongoing evaluation of women diagnosed with AUFI in the context of uterus transplantation, (iii) ongoing evaluation using psychological tools at transplant centers, adoption agencies and assisted reproductive medical institutions with potential recipients, and (iv) ongoing prudent ethical reflection, evaluation and approval were emphasized even if uterus transplantation becomes more universalized.

On the other hand, given that this very expensive and highly risky procedure that requires a very high level of specialization is ultimately just one of the options available to women for reproduction, our society must first fundamentally examine whether it is appropriate to guarantee access to this medical technology as a right, and if so, at what level. In terms of setting criteria for women as recipients in the research phase, it is appropriate in light of international standards to define recipients as women of childbearing age for whom transplantation has not been medically declared impossible but are determined to be infertile due to congenital or acquired uterine causes and for whom all currently available standard care and conservative therapies have failed. However, a decision needs to be made on whether to include consideration of uterus transplantation if it is the only option in the event that adoption and surrogacy is not possible due to personal or legal restrictions for women who wish to have a child, and moreover, consideration of their ability to undergo expert psychological evaluation and diagnostic testing and to assume responsibilities for motherhood and follow-up, including taking immunosuppressive medications in the process of decision making on undergoing uterus transplantation. Although whether this should be restricted to patients with uterine infertility should be considered based on the safety of the procedure, it should be accompanied by a medical determination of the presence of healthy eggs and ovarian function outside the uterus, and

73 Priore G Del, Saso S, Meslin EM, "Uterine transplantation—a real possibility? The Indianapolis consensus," *Human Reproduction* 28(2), 2013, pp. 288– 291.

74 Francis D. Moore (MD Harvard Surgery) proposed three criteria for assessing whether a surgical innovation is ethical, namely, 1) laboratory background (soundness of the research base), 2) field strength (appropriate integration of expertise in all relevant fields), and 3) institutional stability (overall level of expertise of the performing institution: clinical services, how well it operates in an interdisciplinary format and the quality of support services available to patients), and "institutional stability" among these was proposed.
Moore F.D., "Ethical problems special to surgery: surgical teaching, surgical innovation, and the surgeon in managed care," *Arch Surg* 135(1), 2000, p. 15.

testing to determine whether pregnancy with IVF and embryo transfer is possible, at the very least.

Lastly, although it is appropriate to promote post-mortem rather than living donation in consideration of the risks to the donor, donations are currently received from living donors because the time required for organ extraction and transplantation is longer in the case of post-mortem donation and there are difficulties in terms of the supply of transplant materials. Under the laws of Korea, although a separate legal regulation is required to allow donation from a living person, it is necessary to consider whether to apply it in related research attempts or to review the need to improve the relevant legal system after allowed it in research, it is expected to cause fertility and related risks after transplantation. Therefore, it is necessary to address the relevant ethical issues by systematically and independently reviewing whether women of childbearing age with no intention or plan for further pregnancy and childbirth have the intention for repeated altruistic donation.

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