EDITORIAL

A Life Giver and Life Enhancing Transplant – Uterus Transplant

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Organ transplantation is a medical advancement saving and improving quality of life of individuals. It is a boon for persons with end-organ failure.

The process of organ transplant is complicated and it's a patience testing process for recipient, his or her family members and the medical team involved in it.

It is a remarkable achievement in modern medicine which offers a second chance of life.[1]

For uterus transplantation (Utx) it is said that it is a life giver or a life-enhancing transplant.

Definition of organ transplant is, moving of organ from one body to another body for the purpose of replacing recipients damaged or failing organ with working one from the donor, where the donor can be living or deceased.

As we all well worse with organ transplantation history, enumerate first living donor transplant was a kidney transplant done way long back in 1954 at Boston, Massachusetts USA.

Table 1 shows a list of transplants that took place according to organ and year of its occurrence.

In a female reproductive system, transplants have different importance, as failure of these organs is not end organ failure which will lead to danger to life. Definitely, it is going to fulfill patient's right to achieve gestation parenthood (become mother).

In a female reproductive system, transplants involved are of ovary and uterus. Noticeable and proud event is that first successful ovarian transplant took place in 2002 in Mumbai, Maharashtra and first uterine transplant took place in India at Pune, Galaxy center with followed by successful live birth 1st time in India.

Unlike traditional solid organ transplantation, Utx is not a lifesaving but it is a LIFE GIVING. In utx costs, ethical, and psychological issues are inevitable. Utx is a vascular composite allograft means it can be done in genetically non-identical members of the same species.

Utx represents a significant step forward in addressing infertility in cases of Absolute Uterine Factor Infertility (AUFI). AUFI affects 1:500 women of fertile age. It can be either uterine absence or uterine defect. In AUFI before Utx, the only option for treatment of infertility was surrogacy or adoption. With help of Utx AUFI patients gets chance to have .....a gestation.

HISTORY

All over the world more than 80 Utx procedures have been performed in almost in 20 centers.

More than 40 live births had been achieved by 2022. In the field of Utx animal research is going on from 1999, which was done on mouse, rat, sheep, pig, and non-human primates. In human first live donor (LD) Utx took place in 2000, it took almost 15 years to have a successful first live birth after Utx. At institute of Clinical Science Sahlgrenska Academy at University of Gothenburg, Sweden first live birth after Utx took place. A 35-year-old woman with congenital absence uterus (atypical Rokitansky syndrome) received uterus from LD of 61 years old two parous women in 2013 and who delivered at 31 weeks 5 days gestation a male baby weighing 1,775 g, in 2014.

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Table 1: Organ transplant history

Type of transplant	Year of transplant
Kidney transplant	1954
pancreas transplant	1966
liver transplant	1967
Pancreas and heart transplant	1968
Heart and lung transplant	1981
Single lung transplant	1983
Double lung transplant	1986
Intestinal transplant	1987
Split liver transplant	1988
Living donor liver transplant	1989
Living donor lung transplant	1990
First uterus transplant	2000
First successful ovarian transplant	2002
First uterus transplant with successful live birth	2015

First deceased donor (DD) Utx took place in 2017 and the first live birth from DD Utx took place in 2017.

In May 2017 a successful uterine transplant performed and in October 2018 first live female baby born as the first of Asia's, the first of India, and 12th of world's successful live birth after Utx. This took place in Galaxy center hospital, Pune, Maharashtra and was performed by Dr Shailesh Puntambekar.

As research and technology advances technique of Utx also evolved and the first live birth took place on 25 May 2023 after both donor and recipient surgery took place by Robotic assistance again at Institute of Clinical Science Sahlgrenska Academy at University of Gothenburg, Sweden.[1]

INDICATION

Recipient

1. Mayer-Rokitansky-ku: ster-Hauser syndrome (MRKH): MRKH has incidence of 1 in 5,000 women. Congenital absence of uterus is a manifestation of this syndrome. They have normally functioning ovaries with variable degree of short vagina. Women with atypical MRKH present with additional renal abnormality.
2. Asherman syndrome: Uterus present with dysfunctional endometrium due to adhesions formation affects 1.5% of reproductive age patients. Utx should be considered in severe cases where all other treatment options are exhausted.
3. Hysterectomy: Hysterectomy in reproductive age was included, hysterectomy performed for benign gynecological disorders and for severe postpartum hemorrhage. Hysterectomy due to gynecological cancer requires a special caution before giving consideration for Utx.
4. Other factors: Complex congenital uterine anomalies, radiotherapy damage.

At present Utx can be performed in a person who is genetically XX. In Androgen insensitivity syndrome person and in a person who have undergone gender reassignment role of Utx is uncertain till date due to ethical considerations.[2]

Other factors needed to be evaluated with main indication for Utx.

a. Recipient age should be in between 18 and 45 years of age
b. Healthy organs of other systems
c. No presence of major trauma or surgery for negative effect on outcome of Utx
d. Psychological stability
e. Healthy person with no limitation to prescribe immunosuppression agents with informed consent about adverse effect of these drugs
f. Recipient should be aware about long-term post-operative rehabilitation.

Potential Donor

About 80% of Utx have been performed from multiparous living donors.

LD

Planning of elective surgery is easier than in DD where on-call and transport arrangements needed to be done.

LD needs to undergo many investigations to prevent microbiological transmission of infections.

Investigations include Human immunodeficiency virus, Hepatitis B and C, cytomegalovirus, Epstein Barr virus, syphilis, toxoplasma, and human T cell lymphotropic virus. Added advantage of living donor is that time availability to do cervical smear and human palloma virus (HPV) testing to rule out precancerous and cancerous lesions of cervix. Chlamydia, gonorrhea and trichomonas infection ruled out by vaginal secretion culture.

Transvaginal sonography (TVS) needed to be done to rule out structural abnormalities. Magnetic resonance imaging or computed tomography angiography is done to provide information of vessel morphology and caliber and patency of vessels.

Most of the living donors were related to the recipients. Use of 1sto relatives provides immunological benefits. Age of donor at donation have impact on success of transplant as age increases chances of atherosclerotic changes in pelvic vessels increases and may lead to an organ of insufficiency quality for embryo implantation. Increasing age might cause

arterial inflammation which can cause post-transplant graft vasculopathy.[2]

DD

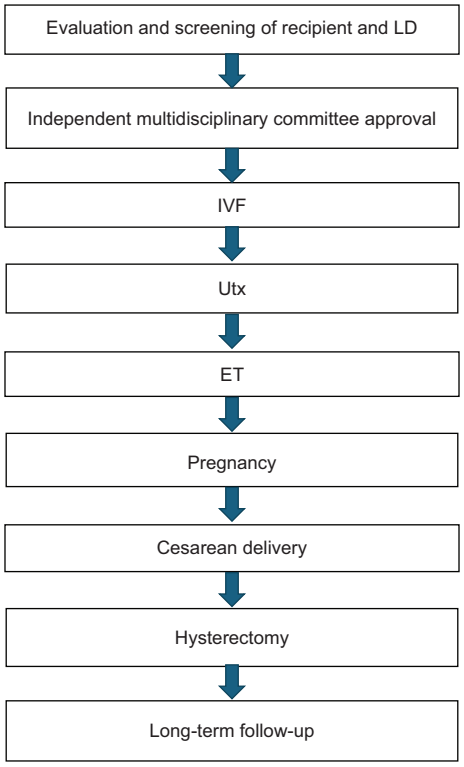
Use of DD allows more radical dissection, enabling larger caliber vessels to reduce the risk of graft thrombosis. It is advocated to retrieval of uterus before retrieval of other lifesaving organs for donation. DD also needs to screen for sexual transmitted disease screen and cervical cytology and HPV testing. TVS is mandatory to rule out presence of uterine structural anomalies. Risk of inflammation increases, which may influence organ quality due to brain dead state in DD.

Even though uterine graft tolerance for cold ischemia is up to 24 h still increase in transplant time is potential for ischemia – reperfusion injury, which may increase risk of acute and chronic rejection of graft.

In decease donors there is an increase risk of fungal infection.[2]

CLINICAL FLOW OF HUMAN UTERUS TRANSPLANT

Utx transplant is different from other transplants as in Utx, there is a involvement of Recipient, Donor, partner of recipient, and possible future child.



Flowchart of uterus transplantation in human. LD: Live donor, DD: Deceased donor, ET: Embryo transfer, UTx: Uterus transplantation, IVF: *In vitro* fertilization

SURGERY TECHNIQUE FOR LD HYSTERECTOMY

Surgery in donor can be performed by laparotomy or laparoscopy, laparoscopic-assisted robotic surgery.

First, transection of round ligament and opening of vesicovaginal spaces is done. Dissection of uterine tunnel and the distal aspect of ureter is a crucial step (Area from tunnel outlet to bladder). In uterine tunnel, there will be overriding of uterine artery and under-riding or overriding of deep uterine vein [Figures 1 and 2]. Tunnel is covered by connective tissue by several small arteries and veins. These need to be dissected. Ureter is fully freed. Large vessels are fully attached to ureter and cervix. One or two deep uterine veins are used in graft. Both sides vascular pedicle, uterine artery, and deep uterine vein are dissected with – ligation and transection of branches. In cases with thin uterine vein with insufficient venous outflow utero ovarian vein is dissected. Before going further, the oviduct, the utero ovarian ligament, and Sacro – uterine ligament are divided. The vagina is transected 2 cm below cervix. Vascular pedicles are clamped and transected with back-table flushing and cooling.

SURGICAL TECHNIQUE FOR TRANSPLANT IN RECIPIENT

Surgery time is less, compared to in donor. It is 2–6 h in 73% of cases. First clearance of vaginal vault from the bladder and external iliac vessels is done. In women with MRKH, the rudimentary uterus in midline is cleaved to vault level. The graft is lifted into pelvis to perform end-to-end anastomosis of uterine vessels to external iliac vessels with 8–0 polypropylene. The vault is opened and vaginal-vaginal anastomosis is done. [Figure 2] Fixative sutures connect round and uterosacral ligament.

The presence of good pulses distal to arterial anastomosis site and the uterine tissue turns pale to reddish which is a sign of peripheral tissues perfusion.

IMMUNOSUPPRESSIVE PROTOCOL

For all solid organs transplant, it is essential and mandatory the burden of immunosuppressive medication. Aim is to keep it in small doses and avoidance of steroids wherever possible. In uterine transplantation, tacrolimus is a preferred agent. Initially only mycophenolate mofetil is preferred to use. mycophenolate mofetil can be used along with prednisolone. Mycophenolate mofetil is later withdrawn in anticipation of embryo transfer (ET) as it is teratogenic in nature. It is usually replaced with azathioprine. Alternative regimen used for maintenance is a combination of tacrolimus and azathioprine

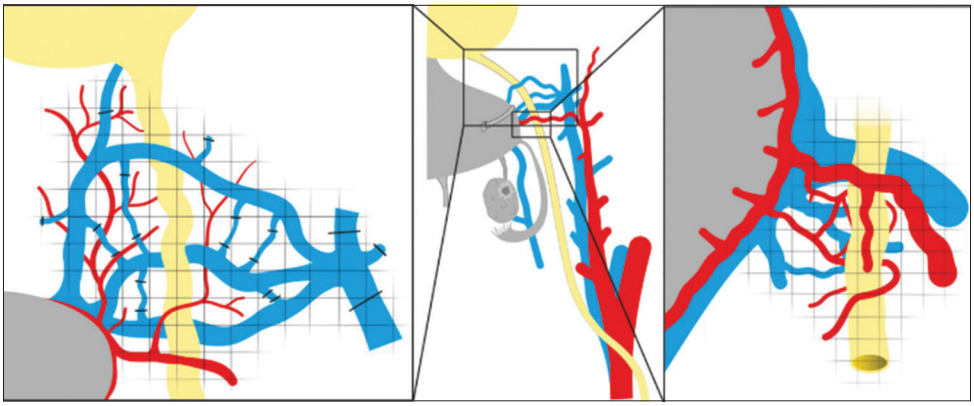


Figure 1: Anatomy of donor right pelvic side middle large square shown on the left side shows overriding and under riding of uterine veins on ureter and small square shown on the right side shows overriding of uterine artery over ureter. (Ureteric tunnel). Uterine vein blue in color, uterine artery red in color, Bladder and ureter yellow in color, Uterus in grey color

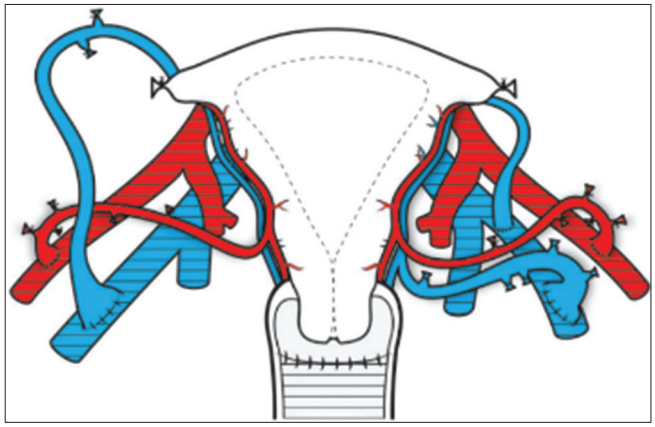


Figure 2: Vascular and vaginal anastomoses recipient tissues of recipient are lined the anterior portion of internal iliac arteries are anastomosed end to side to the external iliac arteries both sides. Left side deep uterine vein anastomosed end to side to the external iliac vein on right side utero-ovarian vein anastomosed end to side to external iliac vein

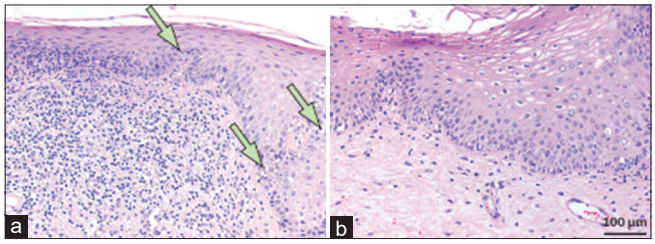


Figure 3: (a) Biopsy showing mild rejection. A dense infiltrate of leukocytes, mainly lymphocytes, exists in stroma and infiltrates into basal layers of epithelium, with occasional apoptotic cells (arrows) (b) 1 week after anti-rejection treatment, leucocyte infiltration completely reversed

with no difference in rejections. Tacrolimus (0.2 mg/kg/day) with maintenance blood level of 15–20 µg/mL in 1st month and 12–15 µg/mL in 2nd month. Mycophenolate mofetil is given at 2 g/day dose and prednisolone and azathioprine are given at 10mg/day and 2 mg/kg/day dose respectively.

Utx does not involve transplantation of fallopian tubes. *In vitro* fertilization (IVF) is required as a part of Utx process.

IVF

Ovarian reserve is generally good in MRKH patients. IVF before Utx is essential and is more beneficiary. In some cases, post-Utx IVF is required due to exhaustion of pre Utx embryo, or couple separated, the patient may want to attempt pregnancy with a new partner Post Utx. In such cases, IVF cycles have been tried post-Utx and been without complication resulting in live pregnancy.

Usually, a long protocol with gonadotropin-releasing hormone (GnRH) agonist and human chorionic gonadotropin trigger and a short protocol with GnRh antagonist and GnRH agonist trigger is used. Oocyte retrieval can be performed transvaginally or transabdominally.

ET

Frozen embryos are used commonly than frozen ocyte. 5–10 embryos required to be banked before Utx. Live birth rate per ET with cleavage stage verses blastocyte embryos is 12.5% and 4%, respectively.

Debatable issue is regarding whether to perform preimplantation genetic testing for aneuploidy (PGT-A). Argument in support of using PGT-A is that it reduces time to pregnancy, reduces cost, and reduces the risk of miscarriage and emotional burden.

Argument against using PGT-A is that its efficacy is questionable due to false negative and false positive, requiring additional oocyte retrieval. It is associated with adverse

obstetrics outcomes, leading to cause low birth weight, and maternal hypertension.

ET is done in routine manner. Transfer of a single embryo is compulsory in Utx. Increased risk of multiple pregnancy which can cause obstetric, neonatal, and postnatal complications in Utx.

Original protocol by Swedish group recommendation 1 year gap between Utx and ET. However short interval of 4–6 months been reported with uneventful recovery. Shorter interval between Utx and ET has psychological and physiological advantages with successful live birth.

Both spontaneous and exogenous hormone-induced programmed endometrial preparation are acceptable for ET.

Vaginal bacterial colonization especially in patients in whom neovagina is created can be associated with implantation failure and repeated miscarriage.

LIVE BIRTH AND OBSTETRICS OUTCOMES

In utx delivery by caesarean section is mandatory. Till date, total live birth rate/ET was 27.8% and 35.6%. The median gestational age at birth is 36 weeks 6 days. Almost 47% required 1-day neonatal intensive care unit stay.

HYSTERECTOMY

As explained in the flowchart, hysterectomy is a fate of Utx. Once a desirable number live children born, a hysterectomy is mandatory. It reduces burden of immunosuppressive agents and complications related to it recipients and her partner also needed to explain the right and need of exit causes in Utx. These causes may be graft-related, recipient-related, pregnancy-related, or psychology-related. Detail of causes has been enumerated in Table 2.

LONG-TERM HEALTH OUTCOME

Transplantectomy should take place after all pregnancy attempts have been made and if transplant graft fails. Qualitative research data based on repeated interview have been collected. Prospective data on the psychological and medical health of LD, recipient, and recipient partner were also collected.

LD: No major negative effects on health secondary to uterus donation. Donor psychological well-being may decrease if her donation does not lead to live pregnancy.

Table 2: Exit causes

Cause	Pathophysiology
Graft related	Ischemia-related graft dysfunction Untreatable intrauterine infection Endometrial atrophy Irreversible rejection
Recipient related	Severe nephrotoxicity Post-transplantation lymphoproliferative disease Malignancy Serious systemic infection needing omission of immunosuppression
Pregnancy-related	Malignant gestational trophoblastic disease Massively repeated implantation failure/miscarriages without childbirth Life-threatening obstetric bleeding, untreatable by conventional techniques
Psychology	Serious psychiatric disorder Recipient wish

Complications in LD

Due to uterus retrieval, minor to major complications have been seen in LD. Minor complications or morbidity includes Urinary tract infection, fecal impaction, wound infection, bladder hypotonia, leg pain, anemia, respiration failure during anesthesia, and depression.

Major morbidity is due to ureteric injuries. Preservation of uterine vein and complicated procedure of Utx causes various serious injuries to Ureter. Complications vary from intraoperative ureter transection, ureteric laceration, post-operative ureterovaginal fistula formation.

In future cases, there may have reduce chances of ureteric injuries, as use of ovarian or utero-ovarian veins instead of uterine vein will be done and has been tried in recent cases.

Recipient Health Outcome

Followed not only during graft retention but several years thereafter. Utx experience common worry about implantation failure at ET. Specific worries of graft rejection, when become mother, they feel like other mothers with the associated stresses and rewards. They had feelings of joy and frustrations of becoming complete women, changed self-perception, and a changed body and sexuality.

Recipient Partner

Relatively stable with no negative effects of graft failure. At 3 years, follow-up had negative deviation in HRQOL when birth had not yet been achieved. They had continued high satisfaction with marital relationship.

Child Health Outcome

Overall normal growth of both weight and height.

TRANSPLANT REJECTION

Symptoms of rejection include abdominal pain and fever or vaginal bleeding. Symptoms become apparent once rejection has been firmly established.

Grading system for uterine allograft rejection in which cervical biopsies were constant achievable means of detection of rejection on graft [Figure 3]. One of the signs of rejection in renal transplantation is lymphocyte subpopulation. Mild to moderate rejection can be managed by 3-day intravenous methylprednisolone. Severe rejection requires anti thymocyte globulin.

In uterine transplantation, the need of immunosuppression is temporary so less chance of cancer, diabetes mellitus, and nephrectomy.

ETHICS OF UTERINE TRANSPLANT

Ethical issues-related to Utx are different from other organ transplant as:

1. Uterus is life-giving or life-enhancing. When other organ transplant is to prevent recipient mortality
2. Uterine transplant has both elements of transplant medicine and ART
3. Prospect of uterine transplant underscores the potential moral and social not only for genetic parenthood but also gestational parenthood.

Montreal criteria for ethical feasibility of uterine transplant constitute comprehensive ethical guideline for uterine transplant. In this, there is a widespread agreement that the physical, psychological, and broader societal rules of uterine transplant ought to be identified and assessed.

Ethical calculus of balancing benefits requires consideration of four pillars of uterine transplant that is recipient, donor, recipient partner, and child to be born.

Ethical acceptability of uterine transplant likely depends on religion, moral, and legal particularities of different countries.

Ethical issues concern whether prevention of gestational parenthood should be promoted.

Individuals with MRKH in USA strongly desire for uterine transplant to become affordable and available. Cross-sectional study in USA suggests it is ethical and supports allowing women with AUFI for uterine transplant. Japanese population 32% women responders ready to become donor and 37% of male responders considered asking their partners to become donors.

Informed consent from potential donor and families whether it is a LD or dead donor is another major theme in ethical discussions. Through discussions of risk, benefit, and alternates are prerequisites including that LDs revoke all parental rights to any resulting children gestated from donated uterus and future relation with child is by no means guaranteed.

For individuals registered as dead donors, explicit consent from families or other representative is legally required.

Another ethical debate is in future if comparable level of clinical follow-up with both LD and dead donor achieved, then uterine transplant may no longer be ethically justifiable.

Informed consent: Recipient poses a greater risk than routine ART. Clear statement of risk of rejection, clear instructions about exit plan after desire pregnancies, and live birth achievement to prevent further risk associated with immunosuppression drugs. Or due to rejection of graft that cannot be managed. Association of complex emotional, ethical, and medical issues regarding termination of a desired pregnancy. Counseling regarding when the patient decides to retain the organ against medical advice regarding the safety of the mother and fetus.

Consent should include that recipient will not be able to feel same experience of pregnancy as normal pregnancy. She will not feel fetal movements and experience contractions.

Reproductive Autonomy

Individuals possess the capacity to self-determine their reproductive decisions. There can be negative rights and positive rights to gestation.

Other options available for AUFI, are gestation surrogacy and adoption. This options morally outweigh desire to have genetically and gestationally related Offspring.

Ethical disagreements exist around inclusion criteria for donor and recipient related to age, length of waiting time, relation status, and prior children.

Capacity after good parenting would likely be included in ethical issues.

Another issue is raised whether there is a right to a donor to decide which recipient her uterus to be transplanted to.

Ethics in XY Individuals

Uterus is preferred and allowed in genetically XX female. Utx May extend to genetically XY persons, including transgender male to female. As in individuals who had undergone gender transition process Utx could meaningfully contribute to the success of gender transformation after achieving gestation parenting.

Revise Montreal criteria suggest equal consideration in both assigned female at birth and male-to-female transgender. Often Ethical issues arise negatively on the appropriate designation of parenthood.

DEVELOPMENT AND FUTURE

Uterine transplantation is now a clinical treatment. It has been accepted in the national health system in Germany. An international quality registry of uterine transplant was launched by international Utx society in 2020. Advances in robotic and noninvasive rejection diagnosis focus on safety and efficacy, increase donor pool, and uterus bioengineering.

Robotic

Advantages are that it has magnified three-dimensional vision, articulated wrist instruments, tremor reduction, florescent images, and excellent surgery ergonomics.

First, robotic-assisted laparoscopic surgery is done. In 2021, fully robotic surgery was performed. Uterine transplant is done by robotic surgery in the recipient in 2021 with vascular and vaginal anastomosis. In this surgery, recovery was uneventful with fruitful birth of a healthy boy in May 2023. As skill advances, more and more robotic surgeries will have greater future in uterine transplant.

Non-invasive Rejection Diagnosis

As now, cervical biopsy is performed to identify rejection, which leads to an invasion procedure. In renal transplantation, new identification of biomarkers and lymphocyte markers, cytokines, and chemokines are developed to diagnose rejection. Studies are ongoing with multi – omics analysis of vaginal/cervical fluids to find noninvasive uterine biomarkers.

Increase of Donor Pool

- Following steps can be in cooperate to increase donor pool
- To motivate family-completed women at perimenopausal age for uterus donation
- Female to male transgender hysterectomized uterus to use for donation
- To increase the age for donation.

Bioengineered Uterus

Bioengineered uterus can be one of option for shortage of donor uterus. It is in an experimental basis in animals and uterine segments have been experiments, not whole uterus. It will take at least one decade to utilize a human bioengineered uterus to be prepare.

CONCLUSION

Uterine transplantation is a life-given on life enhancer. Before the first birth, after uterine transplant in year 2019, AUFI was regarded as unattainable. As experience increased safety and efficacy for the LD, recipient and child will continue and cost will likely to decrease. Improved ethical issues in uterine transplantation will go on an increase as advancement in indication in recipient and criteria for donor will change. Cost issue accepted under coverage health insurance will be a positive step in Utx.

Ray of hope is shouldered on bioengineered uterus in terms of uterine transplantation and then definitely uterine transplantation will be a widely accepted treatment option for infertility in AUFI.

REFERENCES

1. Brannstrom M, Racowsky C, Carbonnel M, Wu J, Gargiulo A, Adashi EY, *et al*. Uterus transplantation: From research, through human trials and into the future. Hum Reprod Update 2023;29:521-44.
2. Jones BP, Saso S, Yazbek J, Thum MY, Quiroga I, Ghaem-Maghami S, *et al*. Uterine transplantation: Scientific impact paper no. 65 April 2021. BJOG 2021;128:e51-66.
3. Brännström M, Johannesson L, Bokström H, Kvarnström N, Mölne J, Dahm-Kähler P, *et al.* Livebirth after uterus transplantation. Lancet 2015;385:607-16.

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