Medical Policy Manual Transplant, Policy No. 19

Uterus Transplant

Effective: July 1, 2024

Next Review: May 2025
Last Review: May 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Absolute uterine factor infertility is a condition in which an individual is unable to achieve pregnancy due to an absent or non-functioning uterus. Uterus transplantation is a complex, multi-stage process involving a living or deceased donor, recipient, and genetic partner.

MEDICAL POLICY CRITERIA

Uterus transplantation is considered **investigational** for all indications.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

None

BACKGROUND

ABSOLUTE UTERINE FACTOR INFERTILITY

Absolute uterine factor infertility (AUFI) refers to infertility that is attributable to an absent or

non-functional uterus due to congenital, surgical, anatomical, or acquired factors that prevent embryo implantation and term pregnancy. AUFI is estimated to impact 1 in 500 females of childbearing age.[1, 2]

Uterine agenesis or Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome results in the congenital absence of the uterus or presence of a rudimentary solid bipartite uterus. MRKH syndrome accounts for less than 3% of all müllerian malformations with an estimated prevalence of 1 in 4,500 females.[3, 4] Individuals with MRKH syndrome type I present with two kidneys and are considered ideal candidates for uterine transplantation. Individuals with MRKH syndrome type II presenting with a single kidney have a higher risk of medication-induced nephrotoxicity and associated obstetric complications (e.g., severe preeclampsia).[5]

Hysterectomy is the most common cause of acquired AUFI, with 240,000 procedures taking place in females under age 44 in the United States.[6] In one clinical trial screening study of 239 individuals at the Cleveland Clinic, indications for uterus transplantation included prior hysterectomy (64%) and congenital anomalies (32%). Among individuals with prior hysterectomy, 50% were performed for benign indications, 25% for malignancy, and 25% for obstetric complications.[7]

UTERUS TRANSPLANTATION

Uterus transplantation may provide a unique fertility restoration option for individuals desiring to carry and birth a child.[8] Uterus transplantation is a complex, multi-stage process involving a living or deceased donor, recipient, and genetic partner. Once screening and consent is established for all involved parties, in-vitro fertilization is performed prior to transplantation to ensure fertilization and normal embryo development.[9] The transplantation surgery involves radical hysterectomy in the donor to ensure long vascular pedicles for transplantation;[10] however, several cases of robot-assisted laparoscopic approaches have been reported.[11, 12] An advantage of uterus procurement in a deceased donor involves freedom to transect ureters, but this convenience is balanced by the potential for prolonged uterus ischemic time.[13] The surgical approach in the recipient is dictated by underlying pelvic anatomy which may be impacted by AUFI etiology. For example, in individuals with Asherman syndrome, a traditional total hysterectomy must first be performed in the recipient. Immunosuppression is initiated at the time of transplantation and protocol and for-cause cervical biopsies enable monitoring for organ rejection.[14, 15] After 6 to 12 months of immunosuppression, embryo transfer, pregnancy, and cesarean delivery may follow. When childbearing has been deemed complete, the transplanted uterus is removed to avoid lifelong immunosuppression. Thus, uterus transplantation is the first form of organ transplantation intended to be temporary.[1, 9]

The first human uterus transplant was performed in 2000 in Saudi Arabia with a 46-year-old living donor and 26-year-old recipient that had acquired AUFI due to hysterectomy for prior post-partum hemorrhage. Due to the development of acute vascular thrombosis at three months post-transplant, graft hysterectomy was required.[16] The first successful live birth occurred in 2014 in Sweden in a 35-year-old recipient with MRKH syndrome via a living, 61 year old, two-parous donor. The recipient was admitted with preeclampsia at 31 weeks, and a healthy male child was born five days later via cesarean delivery.[17] The first live birth in the United States occurred in 2017 in a 29 year old recipient with MRKH syndrome via a living, 32-year-old, two-parous donor.[18] According to the Organ Procurement and Transplantation Network (OPTN), 35 uterus transplants have been performed in the United States via 13 deceased and 22 living donors as of March 2022.[19]

Literature has explored the implications of uterus transplantation in transgender women, identifying several theoretical medical issues in genetic males meriting further investigation. These include creation of adequate de novo uterine vascularization, administration of appropriate hormone replacement therapy, and placement of the donor uterus in a nongynecoid uterus.[20, 21]

REGULATORY STATUS

Solid organ transplants are a surgical procedure and, as such, are not subject to regulation by the U.S. Food and Drug Administration (FDA).

The FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation Title 21, parts 1270 and 1271. Solid organs used for transplantation are subject to these regulations.

Restorative or life-enhancing uterine vascularized composite allograft (VCA) procurement and transplantation falls under the oversight of the Organ Procurement and Transplantation Network (OPTN).[22]

EVIDENCE SUMMARY

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome, defined as length of life, quality of life, and ability to function including benefits and harms. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. Randomized controlled trials (RCTs) are preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

There are no RCTs directly comparing uterus transplant with alternatives. Systematic reviews are based on case series. Studies comparing surgical technique, infection prophylaxis, and immunosuppressive regimens are not germane to this evidence review.

SYSTEMATIC REVIEWS

Escandon (2022) published a systematic review of uterine transplant data from 1995 to November 2020.[23] 64 uterus transplants were included in the review across 40 publications including 16 case reports, five case reports which were part of an observational study, two commentaries, 13 prospective observational studies, and four reviews. 16 studies were graded as either low-quality RCTs or individual cohort studies. Four studies were graded as poor-quality cohort, case series, or case-control studies. No overall assessment of the quality of evidence was provided. 75% (48 of 64) grafts survived or fulfilled the purpose of transplantation. 85% (41 of 48) grafts were from a living donor source. Reasons for transplant failure included: mechanical occlusion of the uterine vessels (n=1), arterial obstructive disease (n=1), arterial and/or venous thrombosis (n=11), or fungal, viral, or bacterial infections (n=3). 25 (47.2%) live births occurred in patients with a living donor and four with deceased donors

(36.4%). Complications for recipients included urinary tract infections (n=5), pleural effusion (n=2), retroperitoneal hematoma (n=1), emotional distress (n=1), significant intraoperative blood loss (n=3), bladder injury (n=1), viral respiratory infection (n=2), vaginosis (n=1), vagina anastomosis (n=7), ovarian hyperstimulation syndrome (n=2), persistent post-operative anemia (n=1) and genital tract infections. Mild or borderline rejection episodes were reported in 9 patients, and 1 patient had acute rejection. However, all episodes were successfully controlled with intravenous and oral corticosteroids.

Brannstrom (2021) published a systematic review of all published clinical uterus transplantation data and major interim results from 2000 through 2019.[1] Of 62 uterus transplants identified for the review, the overall technical success rate defined as subsequent regular menstruation, was 76%. Technical success rates for living and deceased donor procedures were 78% and 64%, respectively. Rates of serious postsurgical complications were 18% for living donors and 19% for recipients. Most uterus transplantation procedures to date have involved living donors (51/62, 82%). Complications in living donors have included ureteric laceration, urinary bladder hypotonia, unplanned bilateral oophorectomy, vaginal dehiscence, fecal impaction, and unilateral pyelonephritis and hydronephrosis. Postoperative complications in recipients have included vaginal anastomotic stenosis and treatable episodes of minor to severe graft rejection.

The cumulative live birth rate per transplant attempt, and per surgically successful uterus transplant is estimated to be >60% and >80%, respectively, as based on 24 published live birth accounts from interim data. High rates of preterm birth (19/24, 80%) and respiratory distress syndrome in the newborn (9/24, 38%) have been observed across cases. Obstetric complications have included preeclampsia, gestational hypertension, and several cases of placenta previa and gestational diabetes. Newborns had an Apgar score of 8 or higher at five minutes. One minor malformation in a female newborn involving an anteriorly caudally displaced urethra was reported, which was surgically corrected at 11 months. The reviewers concluded that "the modest success rate and the fairly high complication rate among [living donors], indicate that further research and development under strict governance are needed before this option should be widely offered."

Case Series

Characteristics and interim results from select case series are summarized in Tables 1 and 2.

Table 1. Summary of Key Case Series Characteristics

Study	Country (Years)	LD Criteria	Recipient Criteria	Participants
Wilson (2023)[24]	United States (2016-2019)	NR	Female 20 to 35 years of age, diagnosis of AUFI with intact native ovaries, BMI≤ 30, systemic or active infection, history of cancer in previous 5 years, history of solid organ or bone marrow transplant, history of or prior vaccination for HPV, no history of smoking or drug abuse in previous year, meets physiological criteria	Mean recipient age, 31 years (range 20 to 35); 13 (93%) MRKH; 1 (7%) prior hysterectomy
Brannstrom (2023)[25]	International Registry (Sweden,	Female with at least one normal	Female of fertile age (generally <39 years of age), BMI <28 and absent overt systemic or psychiatric illness.	Mean recipient age, 29 years (range 22 to 38);

Study	Country (Years)	LD Criteria	Recipient Criteria	Participants
	China [2 centers]), Czech Republic, Brazil, Germany, Serbia, France, Belgium, Lebanon, Mexico, Spain, and Italy) (2012-2020)	pregnancy, BMI <28, no serious systemic psychiatric illness, and completion of childbearing		44 (98%) MKRH type I or II; 1 (2%) prior hysterectomy; Mean donor age, NR; 33 LD Utx (all related); 10 DD UTx
Brannstrom (2022)[26]	Sweden (2016-2021)	NR	Females with AUFI <38 years of age, BMI< 30, without systemic or psychiatric illness	Mean recipient age, 31.5±3.9; 8 (89%) MRKH type I or II; Mean donor age, 53±7; 9 LD UTx (all related)
Johannesson (2022);[27] Johannesson (2021);[28] Putman (2021)[29]	United States (2016-2021)	NR	Women with AUFI and intact native ovaries and of childbearing age 20 to 35, negative history of or prior vaccination for HPV, and meets physiological criteria	Median age, 31 years (range, 20 to 35); 31 (94%) MRKH type I or II 2 prior hysterectomy for leiomyoma(s) Mean donor age, 35±7.3 21 LD UTx; 12 DD UTx
Fronek (2021)[30]	Czech Republic (2016-2018)	Female 18 to 60 years of age, ≤4 childbirths, ≤1 cesarean section, good general health	Female 18 to 40 years of age, AUFI based on congenital or acquired uterus absence, desire for a child, having a male partner, and good general health	Mean recipient age, 28±3 years; 9 MRKH type I; 1 MRKH type II; Mean donor age, 46±14 years; 5 LD UTx (all related); 5 DD UTx; 5 postmenopausal; 2 nulliparous

AUFI: absolute uterine factor infertility; DD: deceased donor; HPV: human papillomavirus; LD: living donor; MRKH: Mayer-Rokitansky-Küster-Hauser syndrome; NR: not reported; UTx: uterus transplant.

Table 2. Summary of Key Case Series Results

Study	Survival	Embryo Transfers, total (range)	Clinical Pregnancy, total (n)	Live Births, total (n)	Live Birth Success Rate	Complications
Johannesson (2022);[27] Johannesson (2021);[28] Putman (2021)[29]	Graft: 23/31 (74% at 1 years)	59 (1 to 4+)	NR	13 (12); 11 LD and 1 DD; 10 MRKH type I; 1 MRKH type II; 1 prior hysterectomy	Overall: 60%; With surgical success: 86%	acute rejection, gestational hypertension, preeclampsia, gestational diabetes mellitus, placenta previa, preterm delivery
Fronek (2021)[30]	Graft: 7/10 (70% at 1 year); Recipient: 10/10 (100% at 2 years)	40 (4 to 11)	7 (5)	3 (3); 2 LD and 1 nulliparous DD	Overall: 30%; With surgical success: 43%	vaginal stenosis, leukopenia, UTI, acute rejection, CMV replication, graft HSV infection, *C. difficile* infection; HLA mismatch, CKD

CKD: chronic kidney disease; CMV: cytomegalovirus; DD: deceased donor; HLA: human leukocyte antigen; HSV: herpes simplex virus; LD: living donor; MRKH: Mayer-Rokitansky-Küster-Hauser syndrome; UTI: urinary tract infection.

Section Summary

Case series of uterus transplantation for AUFI have predominantly enrolled individuals with MRKH syndrome type I. A systematic review of interim trial data has reported live birth success estimates exceeding 60% overall and 80% among transplant attempts with surgical success. Slightly higher technical success rates have been reported for living donor compared to deceased donor procedures (78% vs. 64%, respectively). Rates of serious complications are high among both recipients (19%) and living donors (18%). High rates of preterm birth (80%) and episodes of acute respiratory distress syndrome in the newborn have been reported. Long-term health outcomes in children born via uterus transplantation and recipients following graft hysterectomy continue to accumulate in ongoing trials.

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

In 2018 (reaffirmed 2020), the American College of Obstetricians and Gynecologists (ACOG) Committee on Adolescent Health Care issued a Committee Opinion (Number 728) on the diagnosis, management, and treatment of müllerian agenesis.[31] Regarding future fertility options, the opinion states that while live births have resulted from uterine transplantation,

"given limited data, this procedure currently is considered experimental and is not widely available."

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

In 2018, the American Society for Reproductive Medicine (ASRM) issued a position statement recognizing uterus transplantation as the first successful medical treatment for absolute uterine factor infertility, emphasizing its experimental nature.[32] The statement recommends that the procedure should be performed within an Institutional Review Board-approved research protocol, with recommendations for the composition of "well-coordinated and multidisciplinary" uterus transplantation teams and suggested recipient inclusion and exclusion criteria.

SUMMARY

There is not enough evidence to show that uterus transplantation can improve health outcomes for patients. Further study is necessary to increase success rates, decrease complications and preterm births, and assess long-term outcomes in recipients and their children. In addition, there are no evidence-based clinical practice guidelines that recommend this procedure. Therefore, uterus transplant is considered investigational for all indications.

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CODES

Codes	Number	Description
CPT	0664T	Donor hysterectomy (including cold preservation); open, from cadaver donor
	0665T	Donor hysterectomy (including cold preservation); open, from living donor
	0666T	Donor hysterectomy (including cold preservation); laparoscopic or robotic, from living donor
	0667T	Recipient uterus allograft transplantation from cadaver or living donor
	0668T	Backbench standard preparation of cadaver or living donor uterine allograft prior to transplantation, including dissection and removal of surrounding soft tissues and preparation of uterine vein(s) and uterine artery(ies), as necessary
	0669T	Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; venous anastomosis, each
	0670T	Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; arterial anastomosis, each
HCPCS	None	

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