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MEDICAL POLICY – 4.02.06

Uterus Transplantation for Absolute Uterine Factor Infertility

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Effective Date:	Nov. 1, 2024	RELATED MEDICAL POLICIES:
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Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

Clicking this icon returns you to the hyperlinks menu above.

Introduction

Absolute uterine factor infertility (AUFI) is a condition where a person is not able to get pregnant because there is not a uterus (womb), or the uterus does not function normally. This can happen when the person was born without a uterus, or the uterus did not fully develop. The most common cause of AUFI is the surgical removal of the uterus. For people with AUFI, options for having a child include adoption or someone else carrying and giving birth to the baby. Uterus transplantation has been proposed as a way for people with AUFI to carry and give birth to a child. This is a multi-stage process that involves a donated uterus and transferring a fertilized egg into the uterus before it is transplanted. Uterus transplantation for AUFI is investigational. More studies are needed to see if this type of infertility treatment improves health outcomes.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Service	Investigational
Uterus transplantation for absolute uterine factor infertility	**Uterus transplantation for absolute uterine factor infertility is considered investigational.**

Coding

Code	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

Related Information

Benefit Application

If and when uterus transplant might be considered for coverage, more than one benefit or contractual consideration may be applicable: traditional organ transplant benefits and/or assisted reproductive technology services.

Evidence Review

Description

Absolute uterine factor infertility (AUFI) is a condition in which an individual is unable to achieve pregnancy due to an absent or non-functioning uterus. Uterus transplantation may present a childbearing option that is an alternative to existing family planning pathways, including adoption, foster parenting, and gestational carrier pregnancy. Uterus transplantation is a complex, multi-stage process involving a living or deceased donor, recipient, and genetic partner.

Background

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 4500 females.[3,4] Individuals with MRKH syndrome type I present with 2 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 with acquired AUFI due to hysterectomy for prior post-partum hemorrhage. Due to the development of acute vascular thrombosis at 3 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 5 days later via cesarean delivery.[17] The first live birth in the US 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, 35 uterus transplants have been performed in the US via 17 deceased and 24 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 pelvis.[20,21]

Summary of Evidence

For individuals with AUFI who receive uterus transplantation, the evidence includes a systematic review and five case series. Relevant outcomes are health status measures, perinatal outcomes, quality of life, treatment-related morbidity, and treatment-related mortality. Two systematic reviews found similar surgical success rates of 64% for deceased donor procedures and 78% for living donor procedures. These reviews reported 24 to 29 live births, and it was estimated that the overall live birth success rate exceeded 80% among surgically successful transplants. Complications have been reported in 19% of recipients and 18% of living donors. High rates of preterm birth (80%) and episodes of acute respiratory distress syndrome in the newborns have been reported. Data for individuals with acquired AUFI are lacking. Further study is necessary to increase success rates, decrease complications and preterm births, and assess long-term outcomes in recipients and their children. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in **Table 1**.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02573415	Uterine Transplantation for the Treatment of Uterine Factor Infertility	10	Oct 2025
NCT03252795	Uterus Transplantation From a Multi-organ Donor: A Prospective Trial	20	Dec 2027
NCT04244409	INvestigational Study Into Transplantation of the Uterus (INSITU)	10	Feb 2024

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03689842	Feasibility Study of Uterine Transplantation From Living Donors in Terms of Efficacy and Safety in Patients With Mayer-Rokitansky-Küster-Hauser Syndrome (MRKH)	20	Jun 2025
NCT04026893	Deceased Uterine Transplant in Absolute Uterine Infertility	250	Oct 2025
NCT03277430	Uterus Transplantation From Live Donors and From Deceased Donors - Clinical Study (UTxLD/DBD)	20	Dec 2025
NCT03581019	Uterus Transplantation From Deceased Donor - Gothenburg III	8	Dec 2025
NCT04314869	Feasibility Study of Uterus Transplantation Procedure From a Live Donor Obtaining the Graft by Laparoscopy	10	Dec 2025
NCT02656550	Uterine Transplantation and Pregnancy Induction in Women Affected by Absolute Uterine Infertility	20	Jan 2026
NCT03307356	The University of Pennsylvania Uterus Transplant for Uterine Factor Infertility Trial (UNTIL)	5	Jul 2029
NCT05263076	Uterine Transplantation and Pregnancy Induction in Women Affected by Absolute Uterine Factor Infertility	10	Dec 2030
NCT05646992	Uterus Transplantation to Treat Infertility (OPRTUNTI)	40	Feb 2033
NCT05726305	Transplantation of Uterus for Uterine infertiLIty From Living Donor or Deceased Donor (TULIPE)	16	Dec 2037
Unpublished			
NCT02741102	Uterine Transplant in Absolute Uterine Infertility (AUIF)	10	Jan 2023 (unknown status)

NCT: national clinical trial

Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Obstetricians and Gynecologists

In 2018 (reaffirmed 2024), the American College of Obstetricians and Gynecologists Committee on Adolescent Health Care issued a Committee Opinion (Number 728) on the diagnosis, management, and treatment of müllerian agenesis.[33] 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 issued a position statement recognizing uterus transplantation as the first successful medical treatment for absolute uterine factor infertility, emphasizing its experimental nature.[34] 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.

Medicare National Coverage

There is no national coverage determination.

Regulatory Status

Solid organ transplants are a surgical procedure and, as such, are not subject to regulation by the US 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 procurement and transplantation falls under the oversight of the Organ Procurement and Transplantation Network.[22]

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History

Date	Comments
07/01/22	New policy, approved June 14, 2022. Policy created with literature review through March 14, 2022. Uterus transplantation for absolute uterine factor infertility is considered investigational.
11/01/23	Annual Review, approved October 9, 2023. Policy updated with literature review through June 16, 2023; reference added. Policy statements unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
11/01/24	Annual Review, approved October 7, 2024. Policy updated with literature review through June 21, 2024; reference added. Policy statements unchanged.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.