BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Uterus Transplantation for Absolute Uterine Factor Infertility

Policy #: 747
Latest Review Date: May 2022
Category: Surgery

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **uterus transplantation for absolute uterine factor infertility** as a **non-covered benefit** and as **investigational**.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

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 effect 1 in 500 females of childbearing age.

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 one in 4500 females. 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).

Hysterectomy is the most common cause of acquired AUFI, with 240,000 procedures taking place in females under age 44 in the United States. 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.

Uterus Transplantation

Uterus transplantation may provide a unique fertility restoration option for individuals desiring to carry and birth a child. 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. The transplantation surgery involves radical hysterectomy in the donor to ensure long vascular pedicles for transplantation; however, several cases of robot-assisted laparoscopic approaches have been reported. 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. 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. 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.

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. 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. 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. 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.

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 non-gynecoid uterus.

KEY POINTS:

The most recent literature update was performed through March 14, 2022.

Summary of Evidence:

For individuals with AUFI who receive uterus transplantation, the evidence includes a systematic review and case series. Relevant outcomes are health status measures, perinatal outcomes, quality of life, treatment-related morbidity, and treatment-related mortality. One systematic review of 62 uterus transplants has reported 24 published live birth accounts, with an estimated overall live birth success rate exceeding 80% among surgically successful transplants. Surgical success rates have ranged from 64% to 78% for deceased and living donor procedures, respectively. 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 newborn 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.

Practice Guidelines and Position Statements
American College of Obstetricians and Gynecologists
In 2018 (reaffirmed in 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. 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 identifying uterus transplantation as the first successful medical treatment for absolute uterine factor infertility, emphasizing its experimental nature. 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.

U.S. Preventive Services Task Force Recommendations
Not applicable

KEY WORDS:
Absolute Uterine Factor Infertility, (AUFI), uterus transplantation, Mayer-Rokitansky-Küster-Hauser syndrome; (MRKH); infertility; pregnancy; transplantation; uterus; Asherman syndrome; müllerian agenesis; UTx, womb transplant

APPROVED BY GOVERNING BODIES:
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).

BENEFIT APPLICATION:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:

CPT codes:

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

REFERENCES:

1. Brannstrom M, Belfort MA, Ayoubi JM. Uterus transplantation worldwide: clinical activities and outcomes. Curr Opin Organ Transplant. Dec 01 2021; 26(6): 616-626. PMID 34636769
2. Hellstrom M, El-Akouri RR, Sihlbom C, et al. Towards the development of a bioengineered uterus: comparison of different protocols for rat uterus decellularization. Acta Biomater. Dec 2014; 10(12): 5034-5042. PMID 25169258
3. Grimbizis GF, Camus M, Tarlatzis BC, et al. Clinical implications of uterine malformations and hysteroscopic treatment results. Hum Reprod Update. Mar-Apr 2001; 7(2): 161-74. PMID 11284660
4. Folch M, Pigem I, Konje JC. Mullerian agenesis: etiology, diagnosis, and management. Obstet Gynecol Surv. Oct 2000; 55(10): 644-9. PMID 11023205
5. Garg AX, Nevis IF, McArthur E, et al. Gestational hypertension and preeclampsia in living kidney donors. N Engl J Med. Jan 08 2015; 372(2): 124-33. PMID 25397608
6. Brett KM, Higgins JA. Hysterectomy prevalence by Hispanic ethnicity: evidence from a national survey. Am J Public Health. Feb 2003; 93(2): 307-12. PMID 12554591
7. Arian SE, Flyckt RL, Farrell RM, et al. Characterizing women with interest in uterine transplant clinical trials in the United States: who seeks information on this experimental treatment?. Am J Obstet Gynecol. Feb 2017; 216(2): 190-191. PMID 27865979

8. Jarvholm S, Enskog A, Hammarling C, et al. Uterus transplantation: joys and frustrations of becoming a 'complete' woman-a qualitative study regarding self-image in the 5-year period after transplantation. Hum Reprod. Aug 01 2020; 35(8): 1855-1863. PMID 32619006
9. Malasevskaia I, Al-Awadhi AA. A New Approach for Treatment of Woman With Absolute Uterine Factor Infertility: A Traditional Review of Safety and Efficacy Outcomes in the First 65 Recipients of Uterus Transplantation. Cureus. Jan 18 2021; 13(1): e12772. PMID 33614361
10. Johannesson L, Diaz-Garcia C, Leonhardt H, et al. Vascular pedicle lengths after hysterectomy: toward future human uterus transplantation. Obstet Gynecol. Jun 2012; 119(6): 1219-25. PMID 22617587
11. Wei L, Xue T, Tao KS, et al. Modified human uterus transplantation using ovarian veins for venous drainage: the first report of surgically successful robotic-assisted uterus procurement and follow-up for 12 months. Fertil Steril. Aug 2017; 108(2): 346-356.e1. PMID 28778283
12. Ayoubi JM, Carbonnel M, Pirtea P, et al. Laparotomy or minimal invasive surgery in uterus transplantation: a comparison. Fertil Steril. Jul 2019; 112(1): 11-18. PMID 31277761
13. Gauthier T, Piver P, Pichon N, et al. Uterus retrieval process from brain dead donors. Fertil Steril. Aug 2014; 102(2): 476-82. PMID 24837613
14. Molne J, Broecker V, Ekberg J, et al. Monitoring of Human Uterus Transplantation With Cervical Biopsies: A Provisional Scoring System for Rejection. Am J Transplant. Jun 2017; 17(6): 1628-1636. PMID 27868389
15. Balko J, Novackova M, Skapa P, et al. Histopathological examination of the ectocervical biopsy in non-transplanted uteri: A study contributing to the provisional scoring system of subclinical graft rejection after uterus transplantation. Acta Obstet Gynecol Scand. Jan 2022; 101(1): 37-45. PMID 34693986
16. Fageeh W, Raffa H, Jabbad H, et al. Transplantation of the human uterus. Int J Gynaecol Obstet. Mar 2002; 76(3): 245-51. PMID 11880127
17. Brannstrom M, Johannesson L, Bokstrom H, et al. Livebirth after uterus transplantation. Lancet. Feb 14 2015; 385(9968): 607-616. PMID 25301505
18. Testa G, McKenna GJ, Gunby RT, et al. First live birth after uterus transplantation in the United States. Am J Transplant. May 2018; 18(5): 1270-1274. PMID 29575738
19. Organ Procurement and Transplantation Network (OPTN). National data: Transplants by Donor Type [GU: Uterus]. March 2022; https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#. Accessed March 14, 2022.
20. 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 Uterine Transplantation. Fertil Steril. Oct 2013; 100(4): 924-6. PMID 23768985
21. Jones BP, Rajamanoharan A, Vali S, et al. Perceptions and Motivations for Uterus Transplant in Transgender Women. JAMA Netw Open. Jan 04 2021; 4(1): e2034561. PMID 33471119
22. Organ Procurement and Transplantation Network (OPTN). Vascular composite allograft. n.d.; https://optn.transplant.hrsa.gov/professionals/by-organ/vascular-composite-allograft. Accessed March 14, 2022.

23. Johannesson L, Testa G, Flyckt R, et al. Guidelines for standardized nomenclature and reporting in uterus transplantation: An opinion from the United States Uterus Transplant Consortium. Am J Transplant. Dec 2020; 20(12): 3319-3325. PMID 32379930
24. Johannesson L, Testa G, Putman JM, et al. Twelve Live Births After Uterus Transplantation in the Dallas Uterus Transplant Study. Obstet Gynecol. Feb 01 2021; 137(2): 241-249. PMID 33416285
25. Putman JM, Zhang L, Gregg AR, et al. Clinical pregnancy rates and experience with in vitro fertilization after uterus transplantation: Dallas Uterus Transplant Study. Am J Obstet Gynecol. Aug 2021; 225(2): 155.e1-155.e11. PMID 33716072
26. Fronek J, Kristek J, Chlupac J, et al. Human Uterus Transplantation from Living and Deceased Donors: The Interim Results of the First 10 Cases of the Czech Trial. J Clin Med. Feb 04 2021; 10(4). PMID 33557282
27. Amies Oelschlager AE. ACOG Committee Opinion No. 728: Mullerian Agenesis: Diagnosis, Management, And Treatment. Obstet Gynecol. Jan 2018; 131(1): e35-e42. PMID 29266078
28. Allyse M, Amer H, Coutifaris C, et al. American Society for Reproductive Medicine position statement on uterus transplantation: a committee opinion. Fertil Steril. Sep 2018; 110(4): 605-610. PMID 30196945

POLICY HISTORY:

Medical Policy Group, May 2022

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.