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Uterine Transplantation as a Treatment for Absolute Uterine Factor Infertility

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Uterine Transplantation as a Treatment for Absolute Uterine Factor Infertility

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Overview

1. **Background and History**
    a. Significance of uterine transplantation
    b. Absolute uterine factor infertility
    c. Research timeline
2. **Successful Uterine Transplants**
    a. Then: The first uterine transplant study
    b. Now: Uterine transplant in the US
3. **Procedure and Outcomes**
    a. Operative procedure
    b. Immunosuppression and rejection monitoring
    c. Fertility and pregnancy implications
4. **Summary and Closing Thoughts**
    a. ASRM Committee Opinion
    b. Patient perspective
    c. Ethical considerations

Why is this important?

- The first temporary organ transplant
- Promising research shows the efficacy and feasibility of the procedure
- 1 in 500 reproductive-aged women, or 1.5 million women globally, are affected by AUFI due to absence or dysfunction of the uterus [1, 2]
- Until recently, there was no treatment available for those with absolute uterine factor infertility (AUFI) who wished to carry their own child [1,4]
    - Historically, other methods of family building have been relied upon
    - Social, religious, legal, financial, ethical barriers [1]
    - Studies have shown preference for UTx over surrogacy due to privacy, control, choice, desire for gestation [5]
- There have been >90 uterine transplants from both living and deceased donors globally [6]

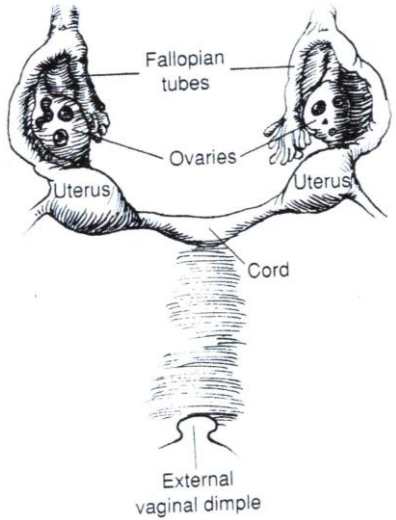
Absolute uterine factor infertility

Congenital absence: [2]

- Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome
  - 46,XX karyotype
  - Type 1/typical: utero-vaginal agenesis
  - Type 2/atypical: Associated renal, skeletal, cardiac, or other defects [7]
  - Affects ~1/4,500 women
  - Likely heterogeneous etiology [7,8]
  - Unknown heritability [7]

Acquired anatomic or functional absence: [2]

- Oncologic surgery
- Emergency obstetric procedures
- Leiomyomatosis
- Asherman syndrome



Anatomic illustration of MRKH [9]

LD = Live donor
DD = Deceased donor

1966 — Research begins

- Uterine-oviduct transplant on dogs; poor results likely due to poor efficacy of immunosuppressives [2]
- Since then: animal studies in mice, rats, rabbits, pigs, and non-human primates [4]
- Assessment of growth in utero, immunosuppression effect, rejection analysis, etc

2000 — First uterine transplant attempt [10]

Jeddah, Saudi Arabia

- Salpingo-uterus transplant
- Patient with history of emergency hysterectomy
- Living donor
- Graft failure secondary to poor pelvic fixation

2011 — Second uterine transplant attempt [2]

Antalya, Turkey

- Uterus transplant
- Patient with MRKH received a uterus from a deceased nulliparous donor
- Embryo transfers began after 18 months
- Two early miscarriages

-

2014 — First live birth from LD uterine transplant [11]

Gothenburg, Sweden

- 35-year old with MRKH received a transplant from a living, P2 61-year old donor.
- Maintained on tacrolimus, azathioprine, corticosteroids
- Single embryo transfer after 12 months
- Delivered via C-section at 31+5 for pre-eclampsia

2016 — First live birth from DD uterine transplant [3]

São Paulo, Brazil

- 32 year old with MRKH received a transplant from a deceased, 45-year old P3 multiorgan donor
- Cold ischemic time 7hr 50min
- First cycle cancelled; second cycle with single FET 7 months post-op

Brännström, *et al.* (2014)

- First clinical observational trial of human uterine transplant
- Key background tenants
  - ~15,000 babies born to mothers with other types of organ transplants while on immunosuppression with no increased risk of fetal malformation
  - Preceded by years of internal animal research
- Prospective observational study
  - 9 uterine transplant recipients (age 31.5 +/- 3.9) from known donors (age 53.0 +/- 7.0)
  - 8 recipients with MRKH; 1 with history of cervical cancer
- Complications
  - 1 donor with ureterovaginal fistula
  - 1 recipient with retroperitoneal hematoma and blood transfusion
  - *1 recipient with recurrent E. faecalis uterine infection
  - *1 recipient with acute thrombosis of the uterine vessels on POD #3
  - Mild rejection in 3/7 patients
- Plan for FET after 12-18 months and hysterectomy after 1-2 live births

* Required hysterectomy

Current US Programs

- United States Uterus Transplant Consortium (2019)
  - Cleveland Clinic (2015)
  - Baylor University Medical Center (2016)
  - University of Pennsylvania (2017)
- Outside of clinical research trials:
  - University of Alabama (2020)
  - *Johns Hopkins*

“The First Five Years…” (2022)

A Report from the United Status Uterus Transplant Consortium

- Cohort study of 33 uterus transplant recipients from 2016-2021
  - ½ of uterus transplants and live births at time of publishing
- 74% graft survival after 1 year
- 83% of recipients with viable graft at 1 year post-op had at least 1 live birth
- Demonstrated technical feasibility and efficacy
- Increased pregnancy complication rates
  - Particularly for pre-term delivery

“The First Five Years…” (2022)

A Report from the United Status Uterus Transplant Consortium

Recipients:

- 31/33 with MRKH; prior hysterectomy in 2/33
- Mean age 31 +/- 4.7 years
- Immunosuppression induced with thymoglobulin and corticosteroids; transitioned to tacrolimus, azathioprine, +/- corticosteroids

Donors:

- 21/33 living donors, 12/33 deceased donors
- Primarily non-directed
- Age at donation: 37.7 +/- 6.5 (LD), 31.5 +/- 7.6 (DD)

Reproductive Outcome:

- Mean time to first menses: 30 days (10-59)
- Median time to first delivery: 14-15 months after transplant
- Graft hysterectomy after LB of 1-2 live births.

Complications:

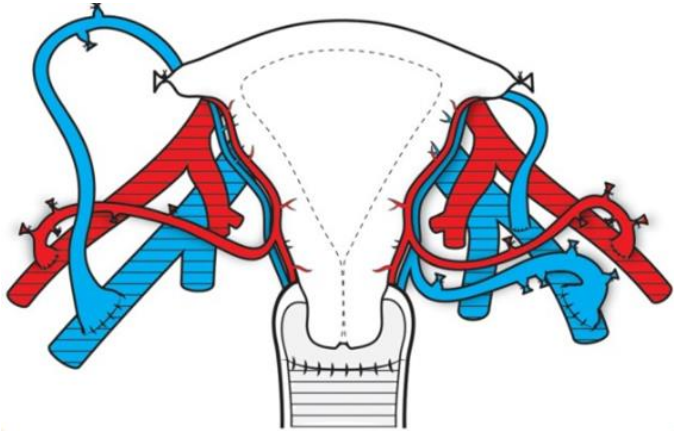
- Graft loss in 8 recipients
  - Leading cause: thrombosis of the graft vessels immediately post-op
- Infection in 10 recipients; leading causes UTI and CMV
- Vaginal stricture (72%)
- Rejection (43%)
- **Preterm delivery (63%)**
  - Maternal/obstetric indications
- Gestational hypertension (24%)
- Gestational diabetes (12%)
- Pre-eclampsia (12%)

Infants:

- Median gestational age 36+6 (30+1 - 38+0)
- Median birth weight 58th percentile (6th-98th%)
- 100% liveborn via C-section, 0% congenital malformations

Procedure

- Organ procurement [14]
  - Similar to a radical hysterectomy
  - LD: ~10 hour surgery, challenging ureteric tunnel dissection
  - DD: Able to transect ureters and ligate other branches off of the vascular pedicles
- Recipient surgery [14]
  - Laparotomy: 2-6 hours duration
  - Anastomosis
    - Arteries: Uterine arteries + anterior internal iliac arteries side-to-end with external iliac arteries
    - Veins: Superior and/or inferior uterine veins side-to-end with external iliac vein
    - Vaginal-vaginal
  - Fixation
    - Fixation sutures between the round and sacrouterine ligaments [6]



Schematic drawing of the vascular and vaginal anastomoses in the recipient [14]

TABLE 3. LIVING- VERSUS DECEASED-DONOR MODELS.

Donor Type	Advantage	Disadvantage
Living	• Opportunity to obtain detailed medical/surgical history • Donor and recipient in close geographic proximity • Convenient scheduling and assessment	• Procedural risks associated with pelvic surgery • Undue pressure to donate • Possible "donor guilt" if unsuccessful • Potential risks with older uteri/vascular grafts • Use of ovarian vessels may require oophorectomy
Deceased	• No donor risks • Grafts from younger-aged donors • Greater variety of vascular pedicles available, including ovarian vessels	• Limited preoperative assessment • Scarcity of suitable organs and inconvenient scheduling/geography • Possible difficulties in obtaining consent from next of kin

ASRM Committee Opinion on Uterus Transplants (2018)

Immunosuppression & Monitoring Rejection

- Established based on research and knowledge of other solid organ transplant, particularly renal [6]
- Induction with thymoglobulin and corticosteroids
- Adoption of the renal maintenance protocol [6, 13]
  - Calcineurin inhibitor (often tacrolimus)
  - Azathioprine
  - +/- Corticosteroids
  - Avoidance of sirolimus or mycophenolate mofetil prior to conception
- Risks: infection susceptibility, renal toxicity, post-transplant lymphoproliferative disease
- Long-term effects unknown at this juncture
- Monitoring for rejection [6]
  - Scheduled histologically-examined cervical biopsies
  - Treated with corticosteroid bolus

IVF Success Rates

Pooled multicenter IVF outcomes from 31 uterus transplant recipients: [15]

- Mean number of oocyte retrievals: 2
  - Post-transplant egg retrieval in 19% of participants
- Banked, on average, 8 untested (3-24) or 6 euploid (2-10) embryos
- PGT-A used by 74% of participants
- 72 single embryo transfers in 23 patients
  - 70 frozen, 2 fresh
- Endometrial prep with programmed protocols (n=61) and natural cycle (n=9)
  - No significant difference between rates of pre-eclampsia, live birth, neonatal birth, placental weight between the cycle types
- No difference in live birth rates between LD and DD

Statistics

- Live birth rate per embryo transfer: 35%
- ~2.2 transfers per 1 live birth
- Live birth rate after first embryo transfer: 57%
- Rose to 74% after second embryo transfer

Summary and Current Recommendations

ASRM 2018 Committee Opinion [1]

- Recognizes uterine transplant as an effective, experimental treatment for absolute uterine factor infertility
- Emphasizes multi-disciplinary approach
- Deceased or living donors are both acceptable each with associated risks and benefits
- Inclusion of appropriate subjects
- Immunosuppression as guided by current research and data; rejection monitoring through cervical punch biopsies

TABLE 2. SUGGESTED INCLUSION AND EXCLUSION CRITERIA FOR RECIPIENTS OF A UTERUS TRANSPLANT.

Inclusion	Exclusion
• Meets criteria for an absent or a nonfunctional uterus • Reproductive-aged female (18–45 y) with sufficient number of goodprognosis embryos • Willing and able to undergo criteria of the study including psychiatric and social-work evaluation • Willing and able to undergo general anesthesia, in vitro fertilization, major gynecologic surgery, pregnancy with potential high-risk complications, cesarean delivery, and eventual hysterectomy to remove the graft • Willing and able to receive immunosuppressive medications • Willing to receive standard vaccinations • Social support and ability to sign informed consent • Nonsmoker • Approval of multidisciplinary treatment team • Willing and able to follow infection prophylaxis protocols associated with solid-organ immunosuppression practice, including but not limited to cytomegalovirus and pneumocystis pneumonia prophylaxis	• Age >45 y or poor reproductive status of embryos • History of hypertension, diabetes, or significant systemic illness, including serious abnormalities of the heart, liver, kidney, hematologic, or central nervous system • Any medical diagnosis placing the subject at high risk of surgical complications based on the transplantation team's review of medical history • Smoker within 3 mo of study enrollment • History of prior malignancy (excluding early-stage cervical cancer or other cancers at low risk for recurrence) • History of human immunodeficiency virus or any history of mycobacterial infection (treated or untreated) • Presence of active documented systemic infection or recent systemic infection within the past 3 mo • Active chemical and/or alcohol dependency or abuse • Anatomical abnormality which would make the pelvic transplantation surgery unlikely to be successful • Body mass index >30 kg/m2 • Relative or absolute contraindication to immunosuppression • Untreated hepatitis C or active hepatitis B viremia or carrier state

ASRM Committee Opinion on Uterus Transplant (2018)

One woman’s story

[Images redacted for online publication]

Discussion: Ethics + Future Directions

- Justifying the high risk and cost of a non-life-saving transplant
  - Benefit: allowing those with AUFI to carry a pregnancy
  - Many risks: donor surgery, recipient surgery, immunosuppression, C-section x1-2, hysterectomy
- Wise resource allocation: how should we decide who gets a uterus?
- Reasons for seeking out uterine transplant versus other options
  - Ex. lack of iliac nerve connection: may not feel fetal movement
  - The idea of “normal” pregnancy may detract from other options despite risk and lack of guarantee of success
- The ethics of living donors: pressure to donate and risk management
  - How does asking a healthy donor to go through this risk psychologically affect the recipient?
- Thinking forward, might uterine transplant, one day, be a usable treatment for transgender women?

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