Uterus transplantation with live donors: outcome of the first clinical trial

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Bridging reproductive medicine and gyneco-oncology surgery

Patient-initiated research

1998, Royal Adelaide Hospital, Australia
- Angela 27 years
- cervical cancer st 1b
- radical hysterectomy with preservation of ovaries
- UTx? - mother donor???
Absolute Uterine Factor Infertility (AUFI)

≈200,000 AUFI patients in Europe
(Sieunarine et al, Int Surg, 2005)

Motherhood options: adoption, gestational surrogacy

First two human UTx attempts

- Jeddah, Saudi Arabia, 2000
  - 46-years live donor to 26-years hysterectomized (EPH)
  - questionable whether properly perfused
  - necrotic uterus removed after 3 months
- failure
- no preparatory research studies on UTx

- Antalya, Turkey, 2011
  - deceased (heart-beating brain-dead) donor (23-year old) to 21-year old Rokitansky patient
FIGO; Ethical guidelines - Uterine transplantation

- Uterine transplantation, which may reach clinical experimental stage, should only occur after significant and adequate research in appropriate large animal models, including primates.

- The lengths to which some women will go to experience uterine transplantation, even with the availability of such options as adoption and surrogacy in some cultures, can lead to a conflict of interest and pressure on researchers to move prematurely to human application.

- It is unethical to remove a uterus for transplantation from a young woman who did not complete having the desired number of children.

- Given the lack of data on safety and the known hazards to live donors, the procedure is considered ethically inappropriate.

(Int J Gyn Obstet 2009;106:270)

Translational research

- Animal research (1999-2012)
  - Mouse
  - Rat
  - Pig
  - Sheep
  - Baboon
- Clinical trial (2013-)
- First livebirths (2014)

“15 years”
IVF - 1963-1978
UTx - 1999-2014
Mouse

backtable preparation  anastomosis  2 weeks after transplantation

end-to-side
aorta - aorta
v. cava - v. cava

Pregnancy and offspring development

Mouse

Pregnancy rate (%)

<table>
<thead>
<tr>
<th></th>
<th>Control animal (n=13)</th>
<th>Native uterus</th>
<th>Grafted uterus, Transplanted animals (n=12)</th>
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<tbody>
<tr>
<td>Pregnancy rate</td>
<td>60</td>
<td>80</td>
<td>60</td>
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uterus  heterotopic  v. cava

uteros  heterotopic  v. cava

vaginal cutaneous stoma
Mouse (syngenic) - ischemia and reperfusion injury (long term effects)

- procurement
- cold ischemia (UW) 24, 48, 72 h
- transplantation (warm ischemia, reperfusion)
- histology or ET 2 weeks post transplantation

Sheep (autotransplantation) - ischemia (4 h) and reperfusion injury (long-term effects)

- cold ischemia 1 h
- warm ischemia 3 h (uterus + ovary transplantation)
- evaluation 2 months post op.
Non-human primate model - why?

- Safety issue - closest to human
  - reproductive/vascular anatomy
  - reproductive physiology
  - immunology

Adult, female, olive baboons (*Papio Anubis*, 10-14 kg) with regular menstrual cycles
Immunosuppression

- effects on fetus (>15000 births; 2006)
  - NTPR-US, European Dialysis and Transplant Association Registry, UK Transplant Pregnancy Registry
  - no increased risk of congenital malformation (McKay, Josephson NEJM 2008)

- prematurity, SGA, preeclampsia 
  - All births in Sweden between 1973-2002
  - Before transplantation: 980, After transplantation: 152
  - "Similar risks in pregnancies before and after organ transplantation" (980 before - 152 after)

- No increase in malformation reported

Rat - orthotopic placement

Recipient hysterectomy
**Offspring from allogenic UTx**

Synchronization (n=10/group)

- UTx+TAC
- SHAM+TAC
- SHAM

MATING

- BC
- BC+TAC

PUPS

- NO PREGNANCY
- d48
- d22
- CS

**PHENOTYPING** - normal

- Birth weight
- Metabolism
  - Weight gain (weekly)
  - Body composition (DEXA)
  - Glucose overload
  - Basal metabolism (Somedic)
- Cardiovascular
  - BP
  - Functional echocardio
- Behavior
  - Anxiety
  - Memory
- Urinary
  - Kidney function
- Fertility
- Aging
Preclinical report on allogeneic uterus transplantation in non-human primates

- live donor concept used (100% survival)
- durations: retrieval 3 h, transplantation 3.5 h
- single immunosuppress. (IS) with tac - reject. in 3 months
- triple IS (tacrolimus, MMF, corticosteroids) needed for 3 months survival
- cervical biopsies ok for rejection diagnosis

Allogeneic uterus transplantation in baboons: surgical technique and challenges to long-term graft survival

- deceased donor concept (donor 0.5 h, recipient 2.5h)
- IS with ATG followed by tac and corticosteroids
- rejection episodes treated with ATG
- survival for up to 14 months with reversed (ATG) rejection episodes
- grading system for rejection (cervical and endometrial biopsies)
  - borderline
  - mild
  - moderate
  - severe
Gothenburg - live donor UTx

Based on >10 years of animal UTx-research

May 2012 - ethics approval
- case series (n=9)
- paid 100% by private research foundation
- surgery on weekends

Recipients

- age 27-38 years
- healthy
- non-smokers
- BMI 21-25

MRKH (n=8) - kidney
- 3 single normal kidney
- 1 single pelvic kidney
- Cervical cancer (squamous) stage Ib1
- Radical hysterectomy (ovaries preserved) 2005
- No adjuvant therapy

- IVF before
  - ascertain fertility within couple
  - cryopreserve embryos for single ET 12-18 months after UTx
- BMI < 28
- no systemic diseases
- normal pregnancy (one Cs Ok)
- no malignancy
- relatives and friends
  - mother (n=5)
  - mother’s sister (n=1)
  - sister (n=1)
  - mother-in-law (n=1)
  - family friend (n=1)

**Donors**

**Recipient-donor pair**

**Donor surgery**
- Dissection of uterine vein(s) to inlet into internal iliac vein

- Clamping of internal iliac artery (distal to gluteal artery)
- Clamping to obtain patch of internal iliac vein
- SEVERANCE OF INTERNAL ILIAC ARTERY
- INTERNAL ILIAC VEIN PATCH(SEGMENT DURATION

Durations - anesthesia and surgery
Donor surgery

- duration 10-12h
  - (radical hysterectomy 2.5 h)

- time consumption
  - ureteric dissection
  - isolation of uterine veins

- no ICU
- 6 days hospital stay

One grade 3 (Clavien-Dindo system) complication (donor 2):
- ureteric-vaginal fistula 2 weeks after surgery;
- ureteric implantation 3 months later; then in good health

Recipient surgery

- SEPARATION OF BLADDER AND RECTUM FROM UTERINE RUDIMENT
- Cleavage of uterine rudiment tissue
- Fixation sutures (2-0 prolene) in sacrouterine ligaments

Fixation sutures in cleaved uterine rudiment and round ligaments
VENOUS END-TO-SIDE ANASTOMOSIS (8-0 PROLENE)

END-TO-SIDE ANASTOMOSIS (7-0 PROLENE)
Vaginal anastomosis

Fixations
- sacrouterine ligaments
- uterine rudiments to lateral cervix
- round ligaments
- extensive bladder peritoneum overlay

- overlaying bladder peritoneum over bladder
Recipient surgery

- No blood transfusion
- No ICU
- Hospital stay 3-9 days

- Regular menses from 1-2 months in 7 patients
- Single embryo transfers (sET) in 7 patients
- Delivery by c-section
- Hysterectomy after maximum two births
Immunosuppression

The first clinical uterus transplantation trial; a six-month report. Brännström et al Fertil Steril 2014; 101:1228-36

Livebirth no. 1

- **Recipient**
  - 35 years
  - MRKH (single kidney)
  - BMI 21
- **Donor**
  - 61 years, non-related friend
  - 2-parous (vaginal, term deliveries)
  - BMI 20
- **Surgery**
  - Donor 10 h 7 min (blood loss 0.6L)
  - Recipient 4 h 55 min (blood loss 0.75L)
  - Total (cold+warm) ischemia 2h 19min
- **12 months**
  - 3 reversible mild rejection episodes
- pregnant after her first single embryo transfer
- triple immunosuppression (tac, azath, predn.) because of frequent rejection episodes

- normal fetal growth curves
- uterine artery PI - normal to low
- umbilical artery PI - normal

- mild rejection w. 18
PE in 31+5
BP 180/120
headache
proteinuria
lowered platelets

C-section 31+6 (1775 g (-11%) Apgar 9, 9, 10)

Today: 13,5 months - 12kg

Possible PE causes
- Immunosuppression
- Aged uterus (63 at childbirth)
- IVF
- Single kidney

“Vincent”

Livebirth no. 2 - “Albin”

- Mother-to daughter
  - Donor
    - Para 3
    - Age 30
    - Premenopausal
  - Recipient
    - MRKH
    - Double kidneys
    - Age 28
- Surgery
  - 11h 35min
  - 4h 4
- Pregnant at first blastocyst transfer
- Cesarean section (34+4) due to cholestasis
- Apgar score 9-10-10. birth weight 2335g (-7%)
- NO PREECLAMPSIA
Livebirth no. 3 - “Henry”

- Mother-to daughter
  - Donor
    - Para 2
    - Age 53, premenopausal
  - Recipient
    - Age 32
    - Cervical cancer (scc, stage 1b, radical hyst. 2005)
- Surgery
  - 10h 54 min
  - 4h 10 min
- Pregnant at 4th sET (day 2-3 embryos)
- Single immunosuppression (tac.)
- C-section in week 35+1 (nov 2014)
- Healthy, 2700g (+4%)
- Today - almost 1 year, 11,5kg

Livebirth no. 4 - “Cash Douglas”

- Sister to sister pregnant at 6th sET
- Single kidney
- Cholestasis week 33+5
- PROM and PE 34+1
- C-section (June 27, 2015)
- 3075 g (+19%)
- Today 4 mths, 7 kg
Summary

• 86% clinical pregnancy rate
  - 4 delivered (all boys)
  - 1 ongoing (week 24)
  - 1 miscarriage (w. 14)
  - 1 no pregnancy yet
• 57% (exp. ≥ 71%) take-home-baby rate
• Better pregnancy results than IVF
Conclusion

• UTx is an effective surgical method to treat uterine factor infertility
• AUFI does not longer exists
• UTx needs to be developed further

UTx - Team effort !!!!