Uterus transplantation - myth or reality?

Mats Brännström MD, PhD
Department of Obstetrics & Gynecology
University of Gothenburg, Sweden
1998, gyne-oncology fellowship
Royal Adelaide Hospital, Australia
- Angela 27 years
- cervical cancer st 1b
- radical hysterectomy with preservation of ovaries
- UTx????
Absolute Uterine Factor Infertility (AUFI)

- 160,000 in Europe
- 70,000 in North America

14,000 potential uterus transplantation patients in the UK (Sieunarine et al, Int Surg, 2005)
Possibilities at AUFI

- acceptance of infertility
- adoption

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- (gestational surrogacy)
- UTx?
• **Worldwide experience – 11 cases**
  
  - Saudi Arabia (2000)
  - Turkey (2011)
  - Sweden x 9 (2012-2013; ClinicalTrials.gov NCT01844362)
First human UTx attempt (2000)

- 46-years old live donor to 26-years old hysterectomized (EPH)
- no preparatory research studies on UTx
First human UTx (cont.)

- ordinary abdominal hysterectomy
- short ends of the uterine arteries and veins
  - saphenous extensions (7 cm) on uterine arteries and veins

- prolapsed necrotic uterus with vascular thrombosis removed after 99 days
2nd human UTx attempt (2011)

- deceased (heart-beating brain-dead) donor (23-year old)
  to 21-year old Rokitansky patient
- no preparatory research studies on UTx
2nd human UTx (cont.)

- hysterectomy - vasculature including common iliacs
- end-to-side anastomosis to external iliacs
- recipient surgery around 8h

- menstruation after 2-3 months
- ETs spring 2013
- 2 early pregnancies with miscarriages reported
Ethical guidelines- Uterine transplantation

(Int J Gyn Obstet 2009;106:270)

The FIGO Committee for the Ethical Aspects of Human Reproduction and Women’s Health

- 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
Our research-based UTx approach

- **Mouse/rat** from 1999
  - Racho El-Akouri et al J Endocr 2002
  - Racho El-Akouri et al Hum Reprod 2003a,
  - Racho El-Akouri et al Hum Reprod 2003b
  - Racho El-Akouri et al Hum Reprod 2006
  - Wranning et al Hum Reprod 2007
  - Groth et al Hum Reprod 2009
  - Groth et al Hum Reprod 2010
  - Wranning et al Hum Reprod 2011
  - Diaz-Garcia et al Acta Obstet Gynecol 2010
  - Akhi et al Fertil Steril 2012
  - Akhi et al Hum eprod 2013
  - Diaz-garcia et al Acta Obste Gynecol 2013

- **Pig** from 2004
  - Avison et al Transplantation 2009

- **Sheep** from 2005
  - Wranning et al Fertil Steril 2008
  - Wranning et al Human Reprod 2010

- **Human** from 2004
  - Wranning et al Hum Reprod 2005
  - Johanesson et al Obstet Gynecol 2012

- **Baboon** from 2008
  - Enskog et al Hum Reprod 2010
  - Johanesson et al Hum Reprod 2012
  - Johanesson et al Hum Reprod 2012

5 PhDs on UTx
- Randa Racho 2003
- Caiza Wranning 2008
- Klaus Groth 2010
- Liza Johannesson 2012
- Shamima Akhi 2012
Issues to be solved by UTx-research

- surgery and vascular anastomosis
- ischemia - reperfusion injury
- rejection
- immunosuppression
- pregnancy and offspring

- ethics
Mouse

end-to-side
aorta - aorta
v. cava - v. cava
Pregnancy and offspring development

Mouse

Transplanted animals (n=12)

Pregnancy rate (%)

Control animal (n=13)  Native uterus Transplanted uterus
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

24 h

48 h

necrosis

ET (n=6)

pregnant n=5

non pregnant n=1
Rat

Recipient hysterectomy

end-to-side common iliacs
Sheep

end-to-side

anterior internal iliac a. - external iliac a.

utero-ovarian v. - external iliac v.
Baboon

adult, female, olive baboons (*Papio anubis/hamadryas*, 10-14 kg) with regular menstrual cycles

- Mannheimer Foundation, Miami
Backtable preparation

9-0 suture

Diagram of the uterus and fallopian tubes with a 9-0 suture shown.
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 ???
    • Källen et al BJOG 2005
    • "Similar risks in pregnancies before and after organ transplantation” (980 before - 152 after)
Offspring from allogenic UTx

Synchronization (n=10/group)

RT1l → RT1c

UTx+TAC → SHAM+TAC → SHAM

BC → BC+TAC

MATING → PUPS

NO PREGNANCY → CS

PUPS

- Mating rate

- Pregnancy rate

- Morphology
  - macro
  - micro

- Phenotyping
RESULTS - WEIGHT GAIN
PHENOTYPING - normal

✓ Birth weight
✓ Metabolism
  • Weight gain (weekly)
  • Body composition (DEXA)
  • Glucose overload
  • Basal metabolism (Somedic)
✓ Cardiovascular
  • BP
  • Functional echocardiography
✓ Behavior
  • Anxiety
  • Memory
✓ Urinary
  • Kidney function
✓ Fertility
✓ Aging
Fertility

- Rodents
  - Syngeneic 2002
  - Allogeneic 2010

- Sheep
  - Autologous 2006
  - Allogeneic

- NH-primates
  - Autologous 2012

- Humans
• Research on UTx was 2012 more extensive than prior to introduction of major procedures in transplantation surgery and ART

- heart transplantation
- liver transplantation
- hand transplantation
- face transplantation
- IVF
- ICSI
Gothenburg - live donor UTx

Based on > 10 years of animal UTx-research

January 2012 - ethics application for case series (n=9-10)
May 2012 - ethics approval
(safety committee)

-paid entirely by private research foundations

autumn 2012 - spring 2013: case 1-9
Recipients

- age 27-38 years
- healthy
- non-smokers
- BMI 21-25
IVF treatment before transplantation

- ascertain fertility within couple
- cryopreserve embryos for single embryo transfer 12-18 months after UTx
Donors

- 38-61 years
- BMI < 28
- no systemic diseases
- normal pregnancy
- no major intraabdominal surgery
- no malignancy

- mother (5)
- older sister (1)
- mother’s sister (1)
- mother-in-law (1)
- family friend (1)
• **extensive investigation of patients, partners and donors for >12 months**
  - psychologist (multiple visits)
  - transplant counsellor
  - physician
  - anesthesiologist (x2)
  - gynecologist (x3)
  - transplant surgeon

• **blood tests, MRI, TVU, virology**

**10 surgeons** (2 patients in partially parallell surgery)
  - 4 gyne-oncology surgeons
  - 3 transplant surgeon
  - 3 gynecologists
Donor surgery
Donor surgery

- **duration 10-12h**
  - (hysterectomy 45 min)
  - (radical hysterectomy 3 h)

- **time consumption**
  - ureteric dissection
  - isolation of uterine veins

- no blood transfusions
- no ICU
- 4-5 days hospital stay
Flushing ex vivo

- CUSTODIOL PRESERVATION SOLUTION
- ICE SLUSH
- BACKTABLE PREPARATION OF VESSELS
Recipient surgery

- Duration 5-6 h
- No blood transfusion
- No ICU
- Hospital stay 6 days
Follow up

Months
1     (2 weekly)
2-4   (1 weekly)
5 -   (1 every 3d week)

• TVU
• Doppler
  - uterine artery
  - tissue perfusion cx
• Biopsies
• Blood testing
patient #8; normal cx

mild rejection, - corticosteroids 7 days

3 weeks later
Conclusions

• Ongoing first clinical trial of human UTx (Sweden) - ETs just started

• Graft failure in Saudi Arabia (2000)
• Graft survival in Turkey (2011)

• Preparations for UTx in the USA, UK, France, Belgium, Spain, China, Japan and Australia

• “Successful UTx” - live birth of healthy baby (results expected 2014)
UTx - Team effort !!!!!

DRs
Mats Brännström  Gyne-onc. surgeon
Liza Johannesson  Gynecologist
Pernilla Dahn-Kähler  Gyne-onc. surgeon
Michael Olausson  Transpl. surgeon
Andreas Tzakis  Transpl. surgeon (Cleveland Clinic)
Cesar Diaz  Gynecologist (Univ. of Valencia)
Janusz Marcickiewicz  Gyne-onc. surgeon
Niclas Kvarnström  Transpl. Surgeon
Marcus Gäbel  Transpl. surgeon
Saskia Eklind  Gyne-onc. surgeon
Ash Hanafy  Gynecologist (Griffith Univ.)
Klaus Groth  Gynecologist
Johan Möhne  Pathologist
Lars Nilsson  IVF specialist
Kenny Rodriguez  IVF specialist
Anders Enskog  Anesthesiologist
Lars Sahlman  Anesthesiologist
Lena Sand  Anesthesiologist
Christina Svensson  Anesthesiologist

OR nurses
Anest nurses
Ward nurses
Nurse assistants