Uterine transplantation

Patients

Uterus factor infertility

- acquired
  - previous hysterectomy
  - cervical/uterine malignancy
  - postpartum bleeding
  - uterine rupture
  - leiomyoma
  - intrauterine adhesions
  - large/inoperable leiomyoma
  - radiation-damaged uterus
- congenital (müllerian anomaly)
  - uterine-vaginal agenesis (Rokitansky syndrome)
  - about 20% of patients with partial müllerian anomalies
    - septate, bicornuate, didelphys, unicornuate

Patients

- about 3% of all infertile couples have uterus factor infertility

- 12000-15000 potential uterus transplantation patients in United Kingdom (Sieunaire et al, Int Surg, 2005;90:249)

- 2000-3000 potential uterus transplantation patients in the Nordic countries
Uterus transplantation vs. gestational surrogacy

Pros (UTx)
- pregnancy-risk (thromboembolism, hypertension, eclampsia) taken by mother
- no money involved
- natural bonding during pregnancy
- control of lifestyle factors (medicine, alcohol, smoking) during pregnancy
- mother definition clear
- not illegal or nonapproved (ethics, religion)
- surgical risk
- immunosuppression (fetal, mother, but only restricted time)

Cons (UTx)
- surgical risk
- immunosuppression (fetal, mother, but only restricted time)
- immunosuppression (fetus, mother, but only restricted time)

Only one human uterus transplantation attempt

- year 2000, in Jeddah, Saudi Arabia
- recipient: 26-year-old, with uterine lost due to post partum hemorrhage
- donor: 46-year-old with benign ovarian cysts
- cyclosporine A, azathioprine and prednisolone
- hysterectomy at day 99 because of signs of uterine infarction
- massive necrosis of uterine body but not oviducts
- "Not based on enough research in animal models"
- "Next attempt can not be a failure"

A hot topic

Nature, Feb 2007
New Scientist, Nov 2006
Issues to be addressed before a new human trial

- surgery and vascular anastomosis
- fixation of transplanted uterus
- ischemia – reperfusion injury
- pregnancy and offspring development
- rejection
- immunosuppression
- ethics
- health economics

Our experimental models

- Mouse/rat
  - Racho El-Akouri et al J Endocr 2002
  - Racho El-Akouri et al Hum Reprod 2003a
  - Racho El-Akouri et al Hum Reprod 2003b
  - Groth et al submitted
  - Almén et al Hum Reprod 2007
- Pig
- Sheep
  - Almén et al Fertil Steril 2008
  - Enskog et al submitted
- Human (in vitro)
  - Almén et al Hum Reprod 2005
- Baboon
  - Enskog et al submitted

Surgery and vascular anastomosis

- procurement (technique similar to radical hysterectomy)
  - dissection of ureters
  - isolation of arterial supply
  - separate isolation of veins
- backtable preparation
- vascular anastomosis
Mouse/rat
Surgery and vascular anastomosis
end-to-side
aorta - aorta
v. cava - v. cava

Sheep
Surgery and vascular anastomosis
end-to-side
anterior internal iliac a. - external iliac a.
utero-ovarian v. - external iliac v.

Baboon
Surgery and vascular anastomosis
uterus
Duration of uterus retrieval ≈ 2 h

flushing uterus ex vivo with preservation solution (+4 °C)

2 uterine arteries 1 artery
2 ovarian veins 1 vein
end-to-side
joined uterine a. – external iliac a.
joined ovarian v. – external iliac v.

- uterus retrieval 2-3 h
- vascular anastomosis 1 h

Conclusions
- surgical techniques for uterus retrieval and vascular anastomosis mastered in several animal models
- optimal site for vascular anastomosis in the human?
Fixation of transplanted uterus

Our experience in animal models

Sheep/baboon
- vaginal - vaginal rim anastomosis
- round ligaments
- vascular anastomosis sites on external ilacs

Mouse/rat
- cutaneous - vaginal rim anastomosis
- vascular anastomosis sites on aorta/cava

Problems encountered
Sheep
- one case of uterine torsion at spontaneous labor

Human (Fogh et al 2002)
- torsion and prolaps of organ -> vascular thrombosis

Conclusions

- fixation at multiple sites
- avoid spontaneous labor

Ischemia (cold/warm) - reperfusion injury

- cold ischemia (+4°C) at preservation of graft ex vivo
  - energy depletion
  - membrane polarity change
- warm ischemia and reperfusion
  - major damage
  - organelle destruction (ROS)
  - inflammation
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

ET (n=6)
- pregnant n=5
- non pregnant n=1

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

- cold ischemia 1 h
- warm ischemia 3 h (uterus + ovary transplantation)
- reperfusion 10 months

Uterus contractility

5 animals
- 3 pregnant
- 2 not pregnant

Human (in vitro) cold ischemia (short term effects)

RIN
- Ringer Acetate
- UW University of Wisconsin preservation solution (intracellular like, K+)
- PER Perfadex solution (extracellular like, Na+)

PREGNANCY

PREPARATION
- control
- 6 h
- 24 h

PRESERVATION

- spontaneous and PGF2-alpha stimulated
- histology
- biochemical factors glutathione, ATP and protein
Conclusions

- 24 h preservation at 4° C in UW/PER is OK in mouse and human
- metabolic stabilization at reperfusion within 1 h after 3h ischemia (1 h cold, 2h warm) in sheep
- long term functionality (ovary + uterus) in terms of pregnancy after 4h ischemia in sheep

Pregnancy and offspring development

Mouse
**Mouse - offspring**

- normal birthweight

- normal growth trajectory
- fertile offspring

**Large animals - pregnancy**

- sheep - autotransplantation
  - pregnancy rate = 60% (3/5)
    - our ongoing studies

**Conclusions**

- pregnancy rate and offspring trajectory normal in small animal (mouse) uterus-transplantation (syngenic) model
- pregnancy rate normal in large animal (sheep) uterus transplantation (auto) model
Rejection

- hyperacute rejection (min to h)
- acute rejection (days to months)
- chronic rejection (from day 1, slow process)

**Mouse**

(day 2 - 28)

- morphology (gross/light microscopy)
- blood flow
- T-cell density

---

**Rejection**

- gross morphology
- light microscopy

- rejection signs day 2
- rejection signs day 15

---

**Mouse**

- blood flow

(decrease from day 2)

---

**Mouse**

- T-cell density

(increase from day 2)
Conclusion

Allogenic uterus graft (mouse) shows early signs of rejection from day 2 and severe rejection from day 10-15

Immunosuppression

- effects on fetus (>15000 births)
  - 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 ???
    - Källén et al BJOG 2005
    - “Similar risks in pregnancies before organ transplantation” (900 before - 152 after)

Mouse

- donor F1 hybrid of (CBA/ca x C57BL/6)
- recipient C57BL/6
- CyA (0, 10, 20 mg/kg/day)
- evaluation 10 days post transplantation
Mouse

Immunosuppression

20 CyA
10 CyA
0 CyA

native c

Sheep

Allogeneic Transplantation
- N = 9 (6 transplanted, 3 losses)
- Parallel donor/recipient surgeries
- CyA (n=6) at 2-5 mg/kg
- FK506 (n=3) at 0.3 – 0.4 mg/kg
- Sacrifice at 3 w

Parameters
- Immunosuppressant through levels
- Gross appearance of transplant
- Histology

Results allo-transplants FK506
- N = 3 (of 6 transplanted)
- 2 transplants normal gross appearance, spontaneous contractions
- 1 transplant atrophied

Blood through levels

Histology
Results allo-transplants CyA

- N = 6 (of 8 transplanted)
- 2 transplants normal gross appearance, spontaneous contractions
- 4 transplants non-vital
- Blood through levels

Conclusion

Further studies carried out by us in rat, sheep and baboon models

Attempted pregnancies in allotransplanted mouse and sheep but not successful so far

Before a new human uterus transplantation attempt

- additional research in animal models before a new human attempt?
  - rodent models: healthy offspring from allogenic transplanted uterus under immunosuppression
  - primate and large animal models: surgery mastered and preserved fertility after autotransplantation
Human uterus transplantation

• donor?
  - living (mother, older sister), brain-dead
• recipient criteria
  - age limit, ovarian reserve, general health
• IVF before
• surgery and post op period
  - retrieval (2-3h)
  - transplant (2-3h)
  - ICU not needed
  - rejection monitored by cervical/endometrial biopsy
• delivery
  - CS
• duration of transplant
  - removal of uterus after birth(s)

Ethics

• Surgical innovations (Moore, Arch Surg, 2000)
  - laboratory background
  - field strength
  - institutional stability

• Risk - benefit analysis
  - donor and family
  - recipient
  - partner and prospective father
  - future child

Requirements for team undertaking human uterine transplantation

- extensive experience of uterine transplantation in several animal models
- institution with experienced units in
  - gynecologic-oncology surgery
  - solid organ transplantation
  - intensive care
  - reproductive medicine
  - high risk obstetrics
  - counseling/psychology
General conclusion

- If research progresses well, uterus transplantation will reach a clinical stage as an experimental procedure in the human within 3 years

Uterus Transplantation Group in Gothenburg, Sweden