Uterine transplantation

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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

Pro UTx

- **pregnancy-risk**, (thromboembolism, hypertension, eclampsia) taken by mother
- **no money** involved
- **natural bonding** during pregnancy/childbirth
- **control of lifestyle factors** (medicine, alcohol, smoking) during pregnancy
- **mother definition** clear
- **not illegal or nonapproved** (ethics, religion)

Con UTx

- **surgical risk**
- **immunosuppression** (fetus, mother, but only restricted time)

Only one human uterus transplantation attempt

- year 2000, in Jeddah, Saudi Arabia
- recipient: 26-year-old, with uterus 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, Febr 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
  - Racho El-Akouri et al Hum Reprod 2006
  - Almén et al Hum Reprod 2007
  - Almén et al Acta Obstet Gynecol Scand 2008
  - Groth et al submitted
- Pig
  - Almén et al J Obstet Gynecol Res 2006
- Sheep
  - Almén et al Fertil Steril 2008
  - Dahm Kähler et al J Obstet Gynecol Res 2008
  - Enskog et al submitted
- Human (in vitro)
  - Almén et al Hum Reprod 2005
- Baboon
  - Enskog et al submitted



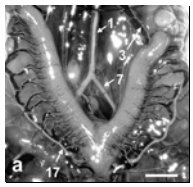


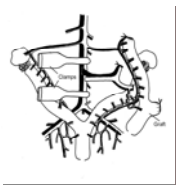
Surgery and vascular anastomosis

- procurement (technique similar to radical hysterectomy)
  - dissection of ureters
  - isolation of arterial supply
  - separate isolation of veins
- backtable preparation
- vascular anastomosis

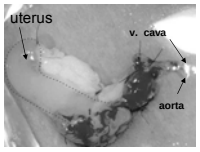
Surgery and vascular anastomosis

Mouse/rat

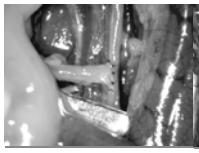




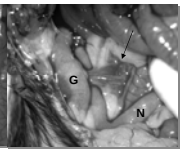
end-to-side
aorta - aorta
v. cava - v. cava



backtable preparation



anastomosis



2 weeks after transplantation

Surgery and vascular anastomosis

Sheep

end-to-side
anterior internal iliac a. – external iliac a.
utero-ovarian v. – external iliac v.

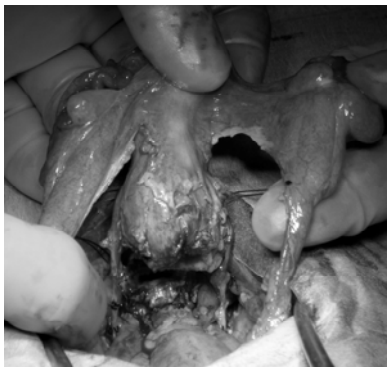
uterus ex vivo

vascular anastomosis

prepartused uterus

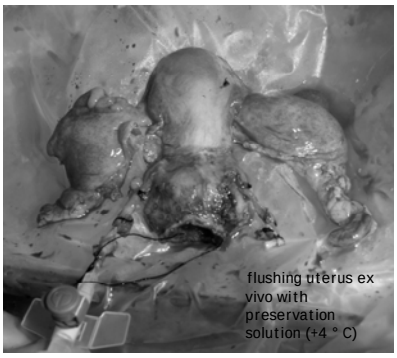
Surgery and vascular anastomosis

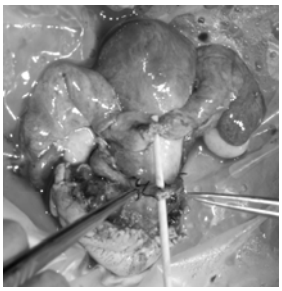
Baboon



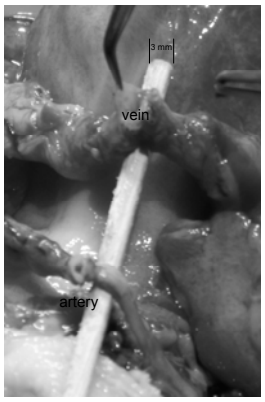
Duration of uterus retrieval

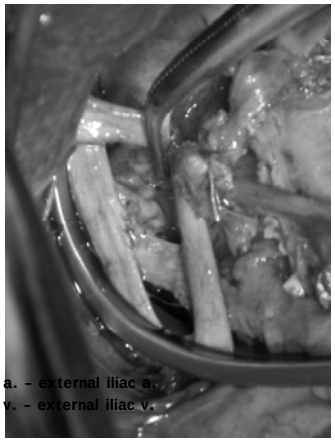
≈ 2 h





2 uterine arteries
2 ovarian veins
⇨
1 artery
1 vein

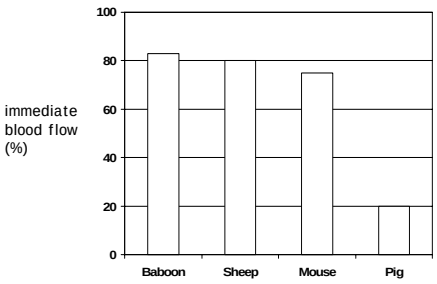




end-to-side

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

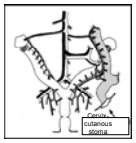
Conclusions

- fixation at multiple sites
- avoid spontaneous labor

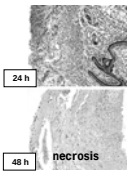
Ischemia (cold/warm) – reperfusion injury

- 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



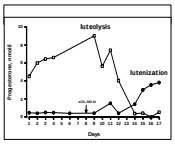
ET (n=6)

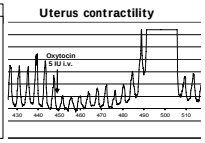
pregnant n=5 | non pregnant n=1

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

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

ovary | uterus | pregnancy

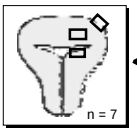




5 animals

3 pregnant | 2 not pregnant

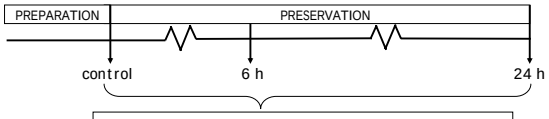
Human (in vitro) cold ischemia (short term effects)



RIN
Ringer Acetate

UW
University of Wisconsin preservation solution (intracellular like, K^+↑)

PER
Perfadex solution (extracellular like, Na^+↑)

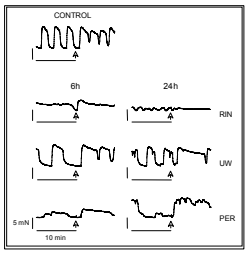


contractility	spontaneous and PGF_2-alpha stimulated
histology	
biochemical factors	glutathione, ATP and protein

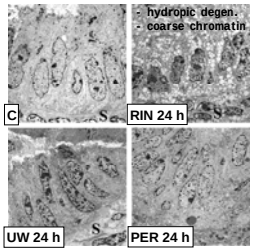
Ischemia – reperfusion injury

Human

myometrial contractions



EM



- spontaneous contractility - UW 24 h ok
- PGF2a-ind. contractility - UW, PER 24h ok

ultramorphology – PER 24h ok

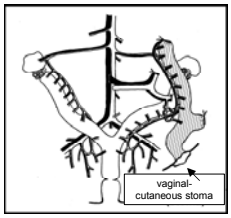
Ischemia – reperfusion injury

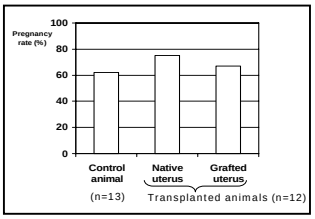
Conclusions

- 24 h preservation at 4º 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

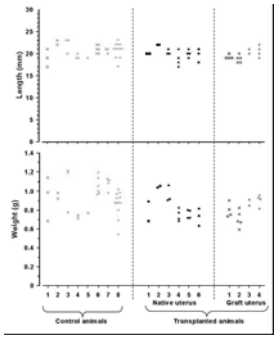
Pregnancy and offspring development

Mouse



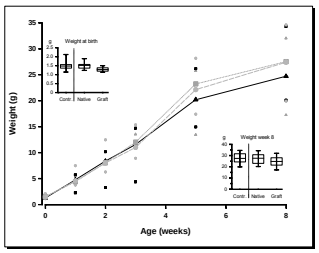


Mouse - offspring



-normal birthweight

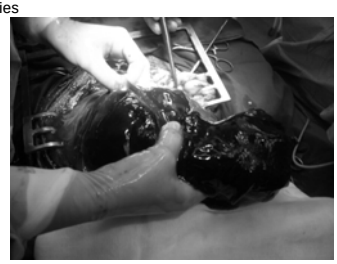
mouse, syngenic



-normal growth trajectory
-fertile offspring

Large animals - pregnancy

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



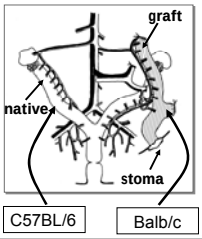
Conclusions

- 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

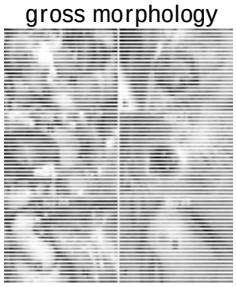


(day 2 – 28)

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

Mouse

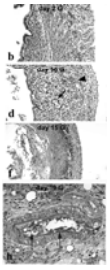
gross morphology



uterus stoma

(rejection signs day 15)

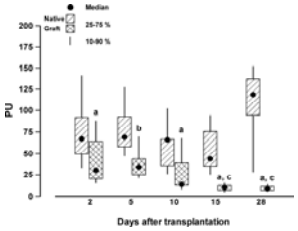
light microscopy



(rejection signs day 10)

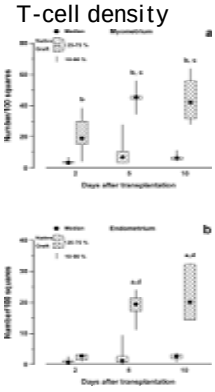
Mouse

blood flow



(decrease from day 2)

T-cell density



(increase from day 2)

Conclusion

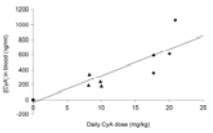
Allogenic uterus graft (mouse) shows early signs of rejection from day 2 and severe rejection from day 10-15

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 pregancies before organ transplantation" (980 before – 152 after)

Mouse

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

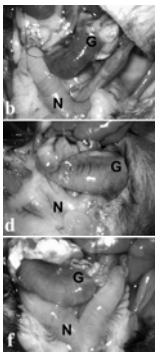


- evaluation 10 days post transplantation

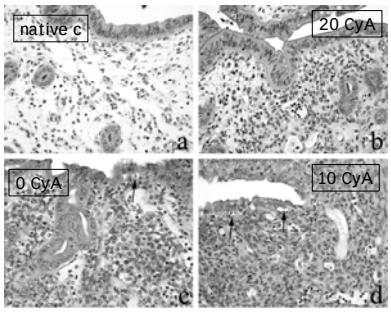
00
0

10

20



Mouse



Sheep

Allogeneic Transplantation

- N = 9 (14 transplanted, 5 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.

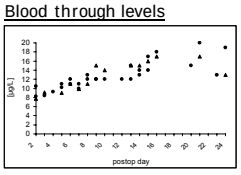
Parameters

- Immunosuppressant through levels
- Gross appearance of transplant
- Histology

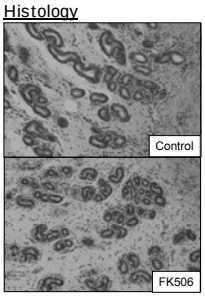
Results allo-transplants FK506

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

Blood through levels



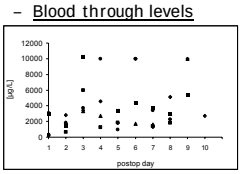
Histology



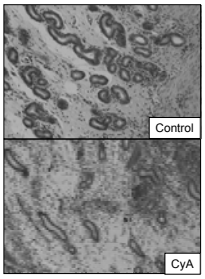
Results allo-transplants CyA

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

- Blood through levels



Histology



Conclusion

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

Attempted pregancies 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

Mats Brännström	Gyne-oncologist
Michael Olausson	Transplantation surgeon
Randa Racho El-Akouri	Post Doc
Caiza Almén Wranning	Post Doc
Klaus Groth	PhD student
Liza Johanneson	PhD student
Ann Wallin	Biomed. scientist
Cecilia Lundmark	Op. nurse
Maria Lidemyr	Op. nurse
Göran Kurlberg	Colo-rectal surgeon
Johan Mölne	Pathologist
Anders Enskog	Anesthesiologist
Janusz Marcickiewicz	Gyne-oncologist
Pernilla Dahm-Kähler	Gyne-oncologist

International collaborators

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Univ of British Columbia, Canada
Institute of Primate Research, Kenya
Cleveland Clinics,USA
Griffith Univ, Australia
La Salle Univ. Colombia