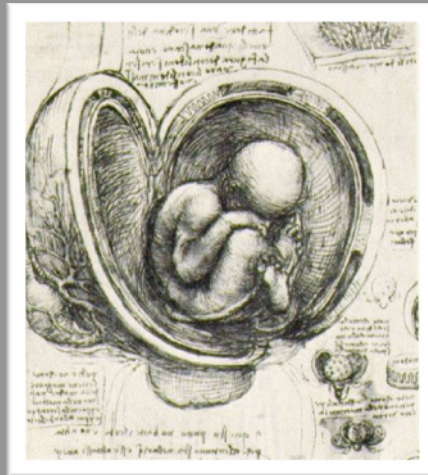
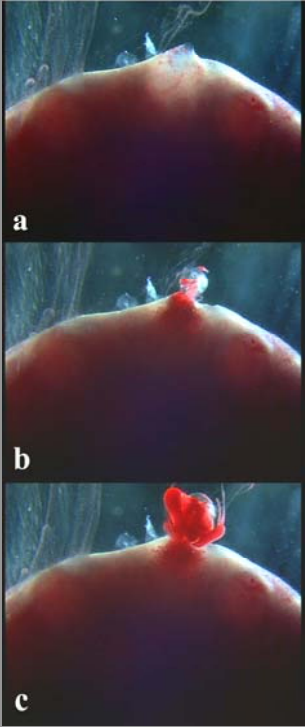


Uterus transplantation - myth or reality?



Mats Brännström MD, PhD
Department of Obstetrics & Gynecology
University of Gothenburg, Sweden



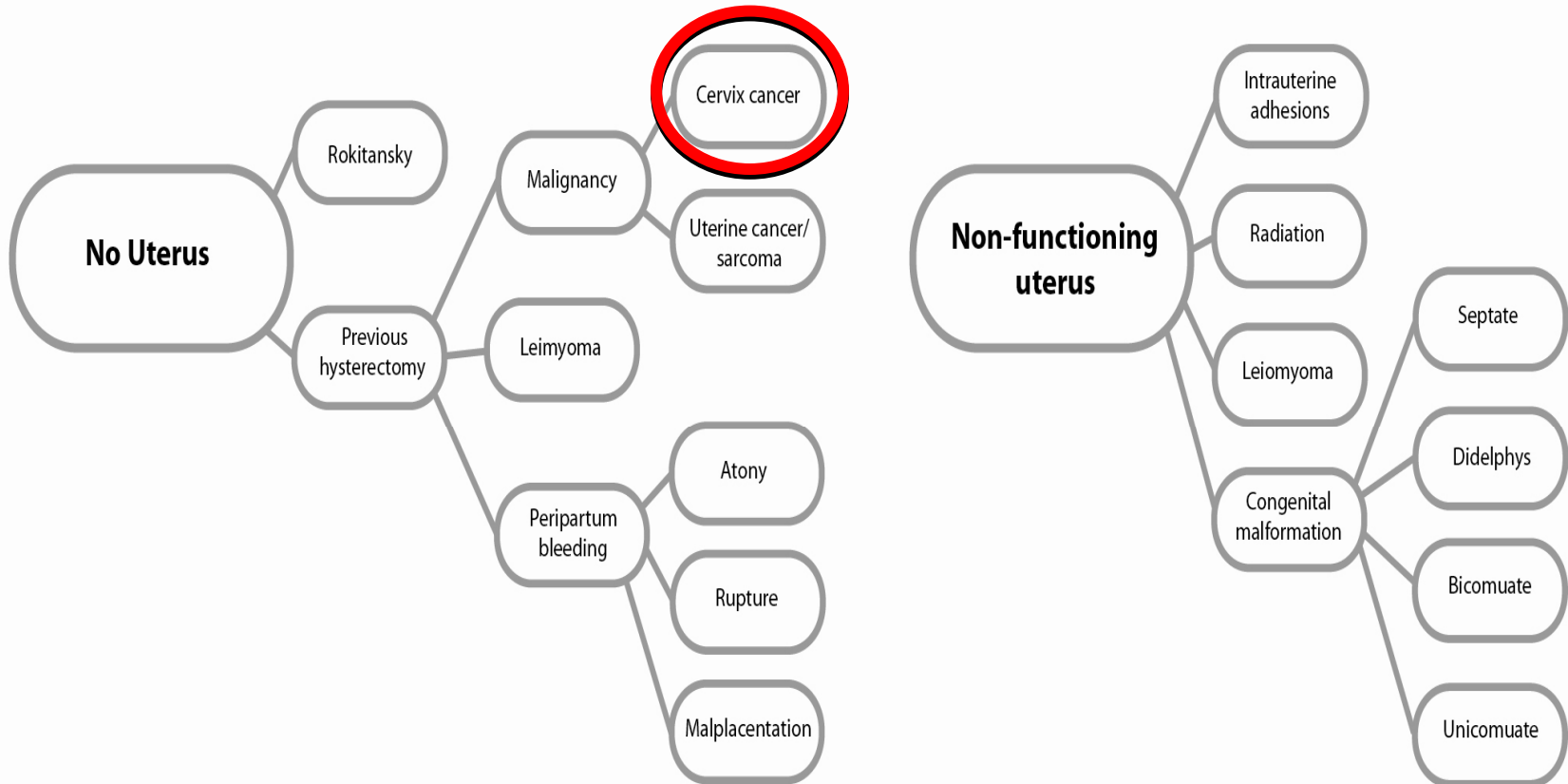


1998, gyne-oncology fellowship
Royal Adelaide Hospital, Australia

- Angela 27 years
- cervical cancer st 1b
- radical hysterectomy with preservation of ovaries
- UTx????



Absolute Uterine Factor Infertility (AUFU)



- 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

- (gestational surrogacy)
- UTx?



- Worldwide experience - 11 cases
 - Saudi Arabia (2000)
 - Turkey (2011)
 - Sweden x 9 (2012-2013; [ClinicalTrials.gov NCT01844362](https://clinicaltrials.gov/ct2/show/study/NCT01844362))



First human UTx attempt (2000)

International Journal of Gynecology & Obstetrics 76 (2002) 245–251

International Journal of
GYNECOLOGY
& OBSTETRICS

www.elsevier.com/locate/ijgo

Case report

Transplantation of the human uterus

W. Fageeh*, H. Raffa, H. Jabbad, A. Marzouki

Multiorgan Transplant Unit, King Fahad Hospital and Research Center, Jeddah, Saudi Arabia

- 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
 - Wranning et al Acta Obstet Gynecol 2008
 - 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
 - Groth et al J Obstet Gynecol Reprod Biol 2012
 - Diaz-Garcia et al Acta Obstet Gynecol 2012
 - Akhi et al Hum eprod 2013
 - Diaz- garcia et al Acta Obste Gynecol 2013
- **Pig** from 2004
 - Wranning et al J Obstet Gynecol Res 2006
 - Avison et al Transplantation 2009
- **Sheep** from 2005
 - Wranning et al Fertil Steril 2008
 - Dahm Kähler et al J Obstet Gynecol Res 2008
 - Wranning et al Human Reprod 2010
- **Human** from 2004
 - Wranning et al Hum Reprod 2005
 - Johannesson et al Obstet Gynecol 2012
- **Baboon** from 2008
 - Enskog et al Hum Reprod 2010
 - Johannesson et al Hum Reprod 2012
 - Johannesson et al Hum Reprod 2012



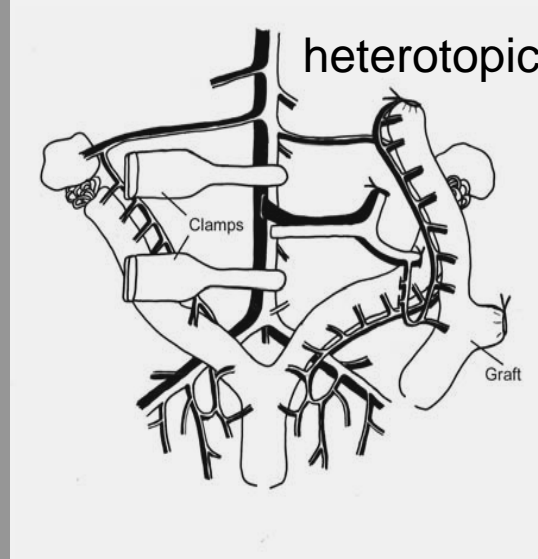
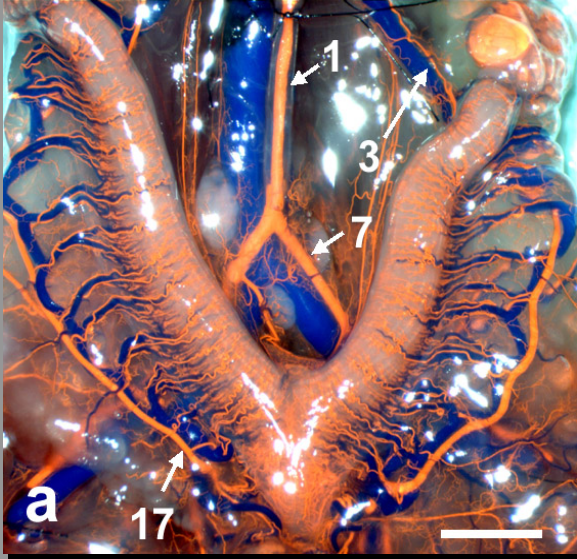
5 PhDs on UTx

- Randa Racho 2003
- Caiza Wranning 2008
- Klaus Groth 2010
- Liza Johannesson 2012
- Shamima Akhi 2012

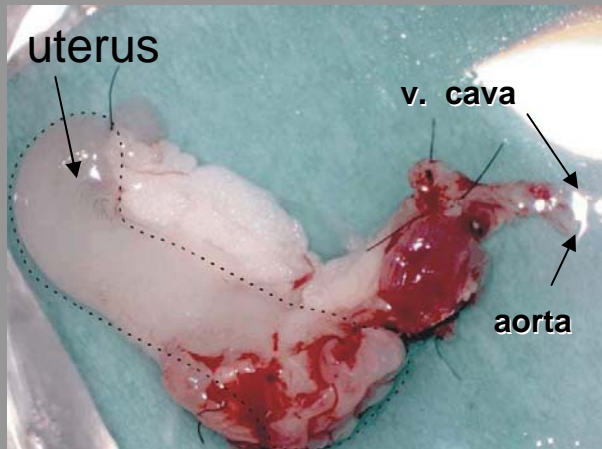
Issues to be solved by UTx-research

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

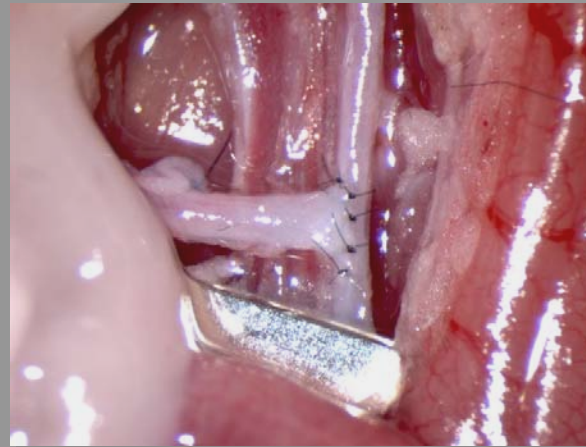
Mouse



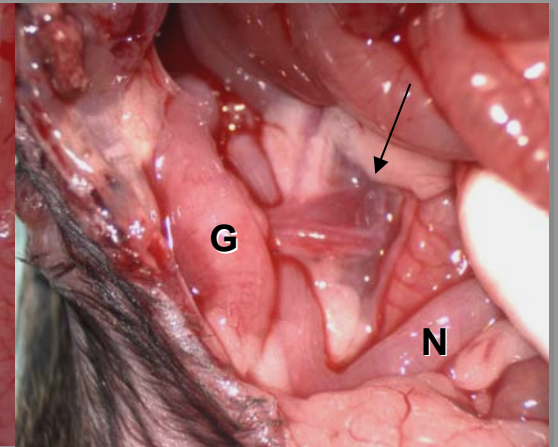
end-to-side
aorta - aorta
v. cava - v. cava



backtable preparation



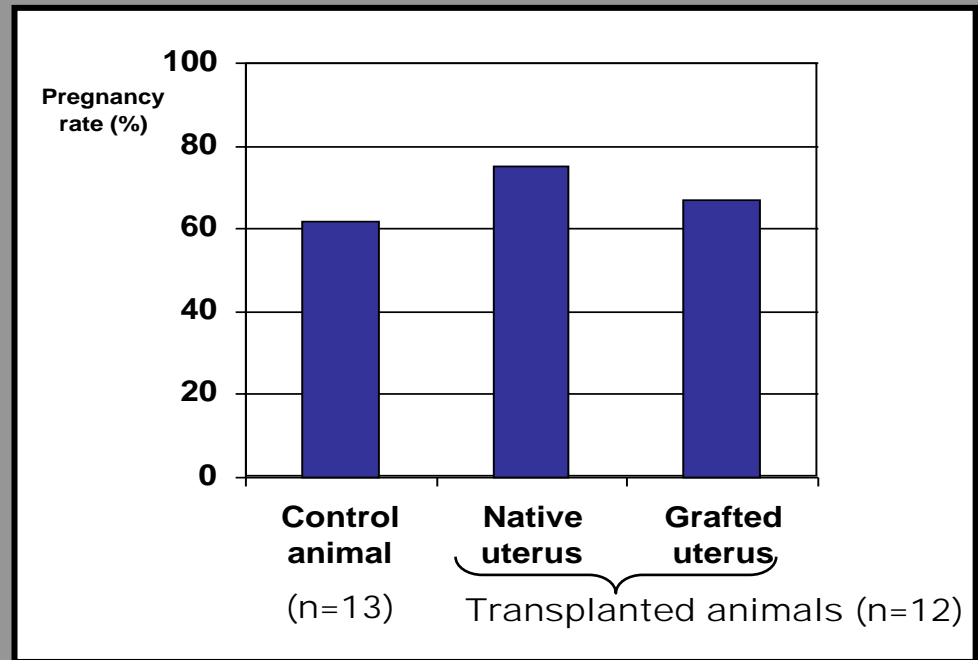
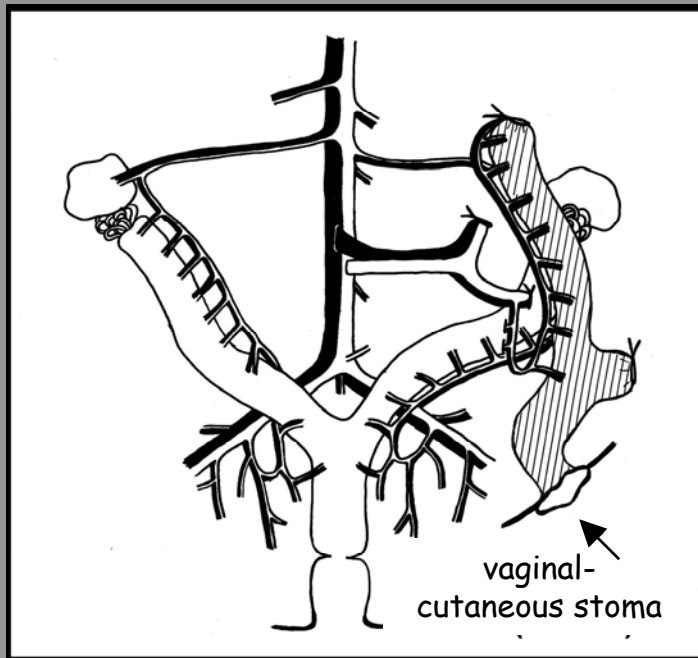
anastomosis



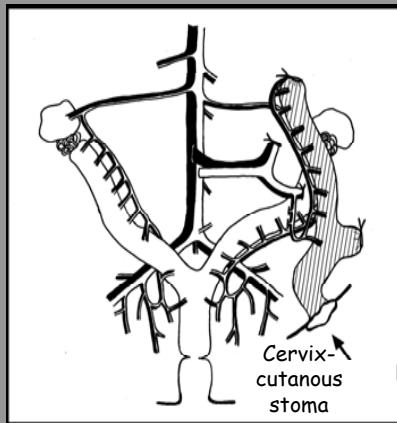
2 weeks after transplantation

Pregnancy and offspring development

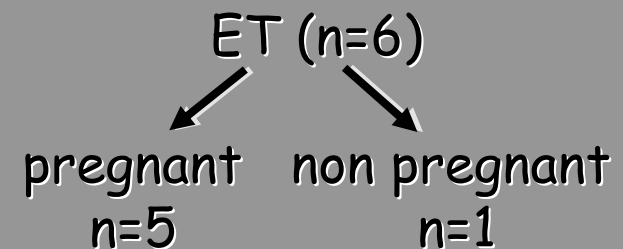
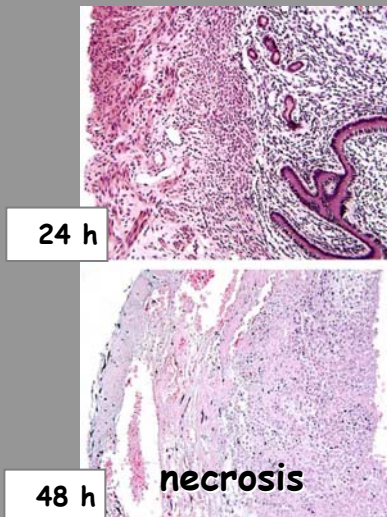
Mouse



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

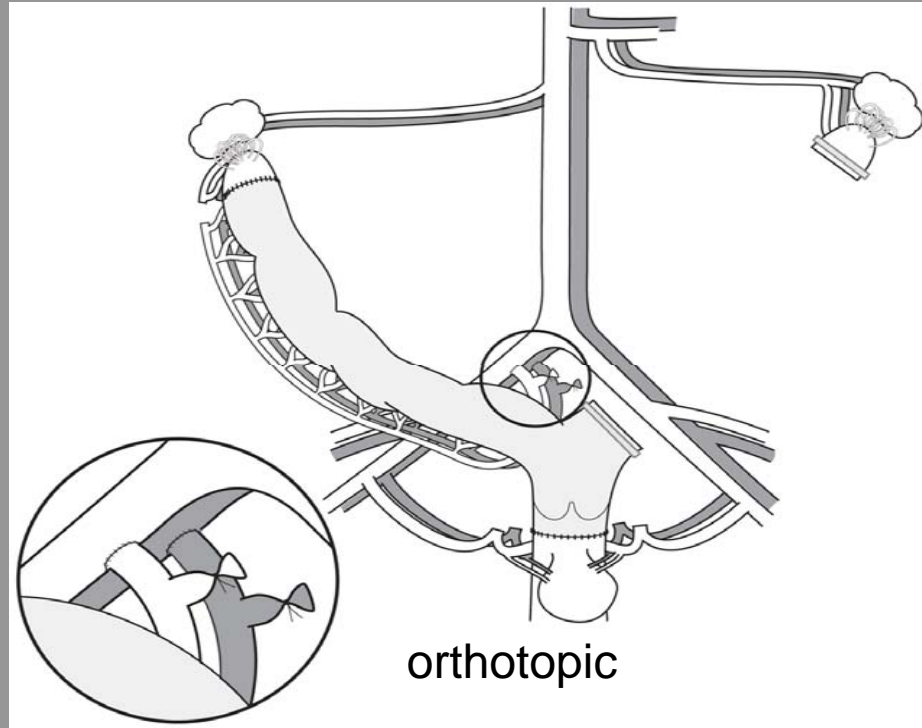
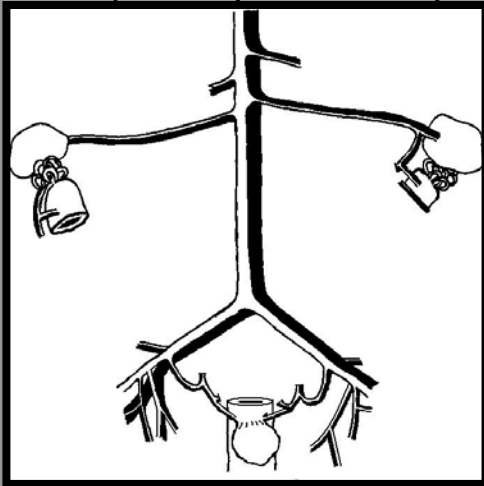


- procurement
- cold ischemia (UW) 24, 48, 72 h
- transplantation (warm ischemia, reperfusion)
- histology or ET 2 weeks post transplantation



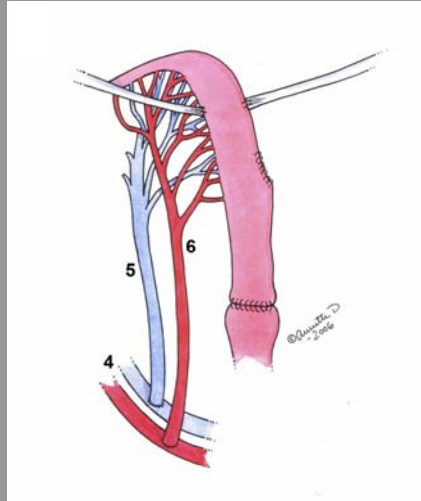
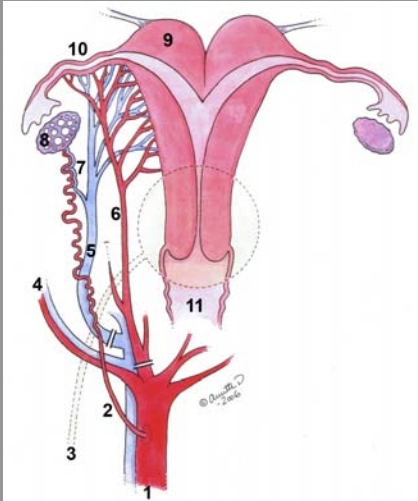
Rat

Recipient hysterectomy



end-to-side common iliacs

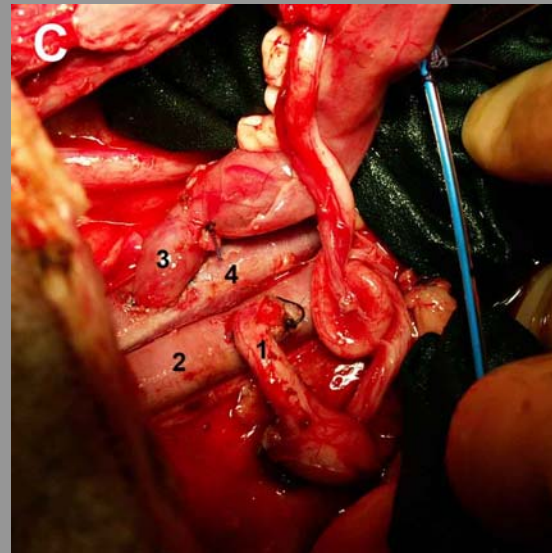
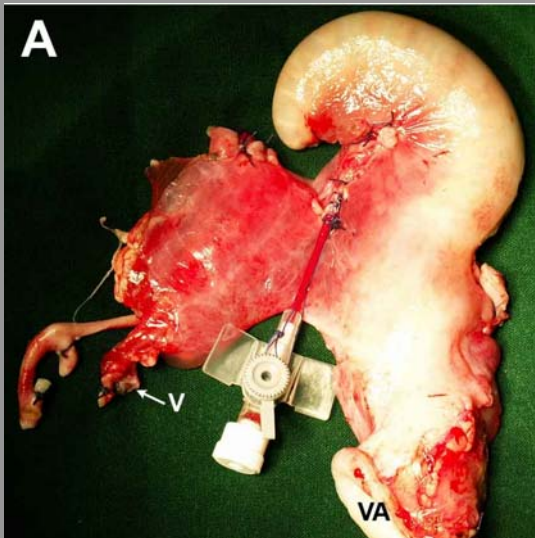
Sheep



end-to-side

anterior internal iliac a. - external iliac a.

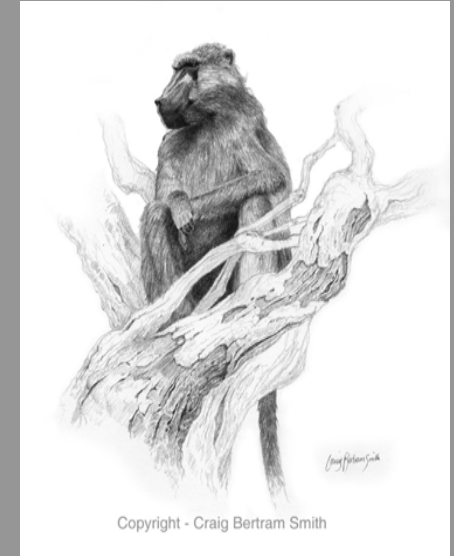
utero-ovarian v. - external iliac v.



Baboon

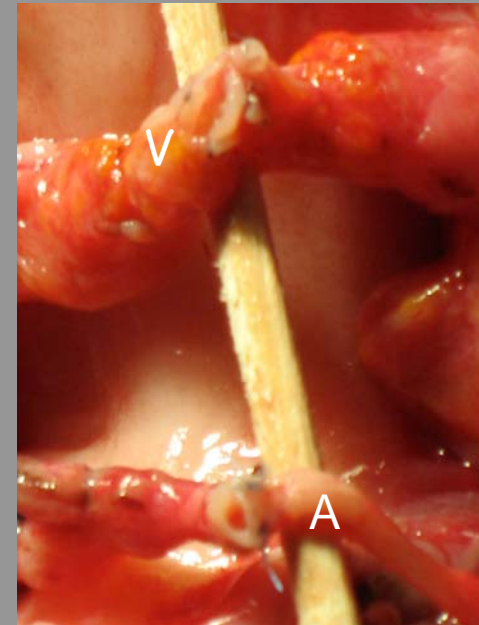
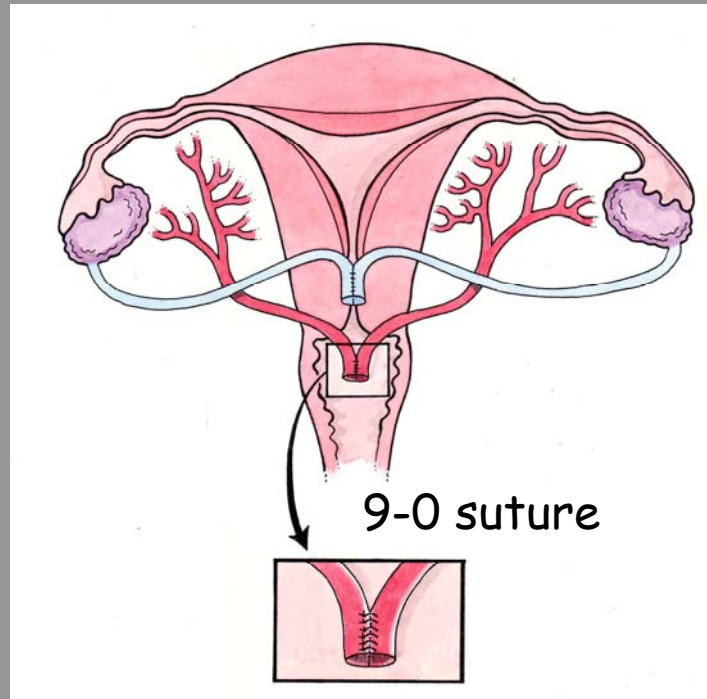
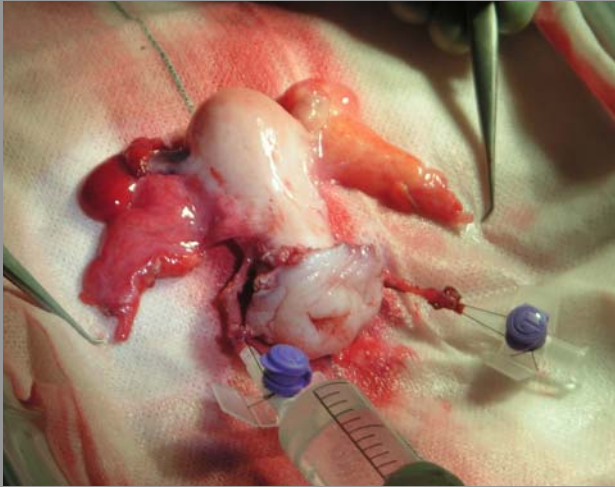


adult, female, olive baboons (*Papio anubis/hamadryas*, 10-14 kg)
with regular menstrual cycles



- Mannheimer Foundation, Miami

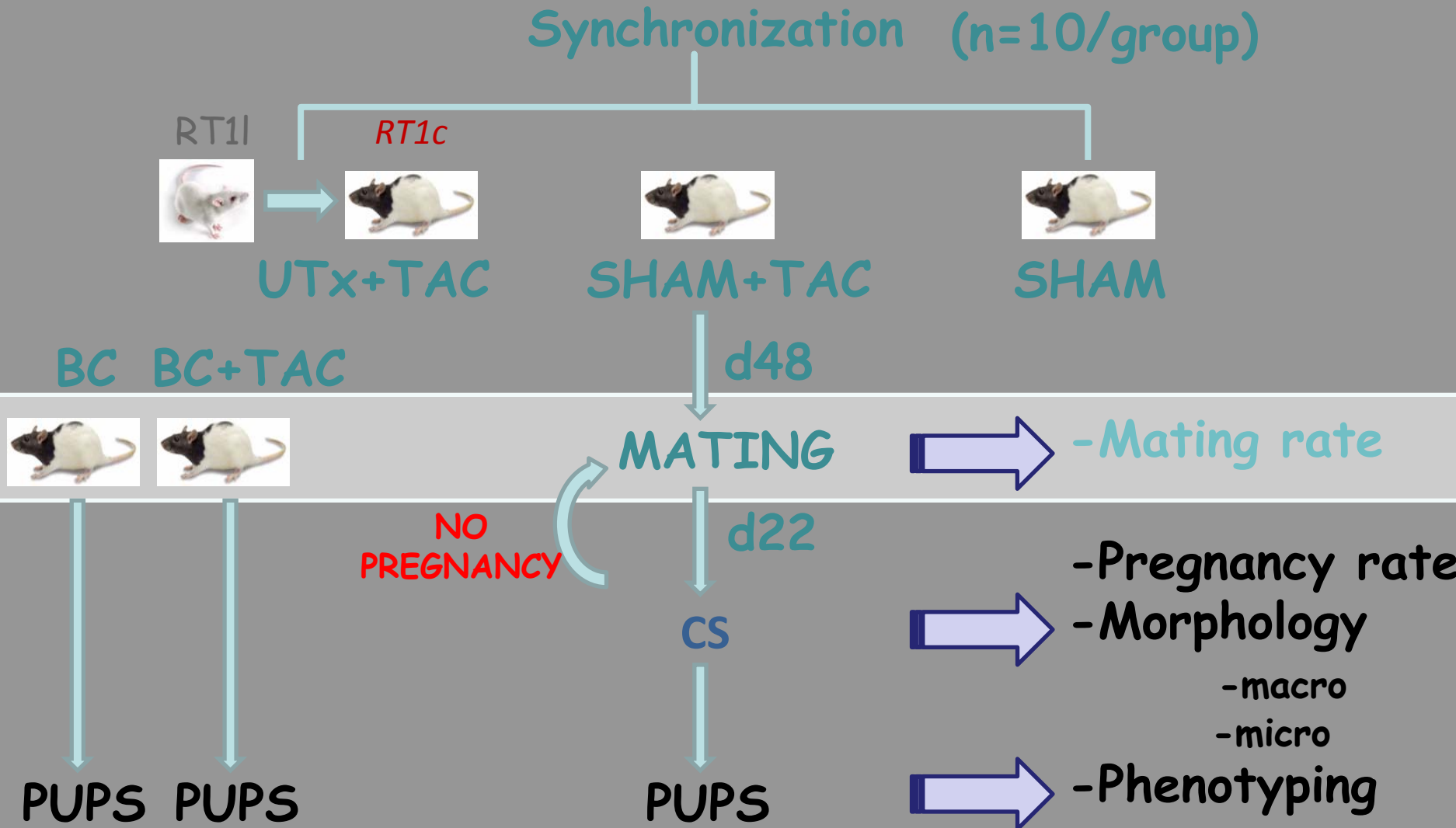
Backtable preparation



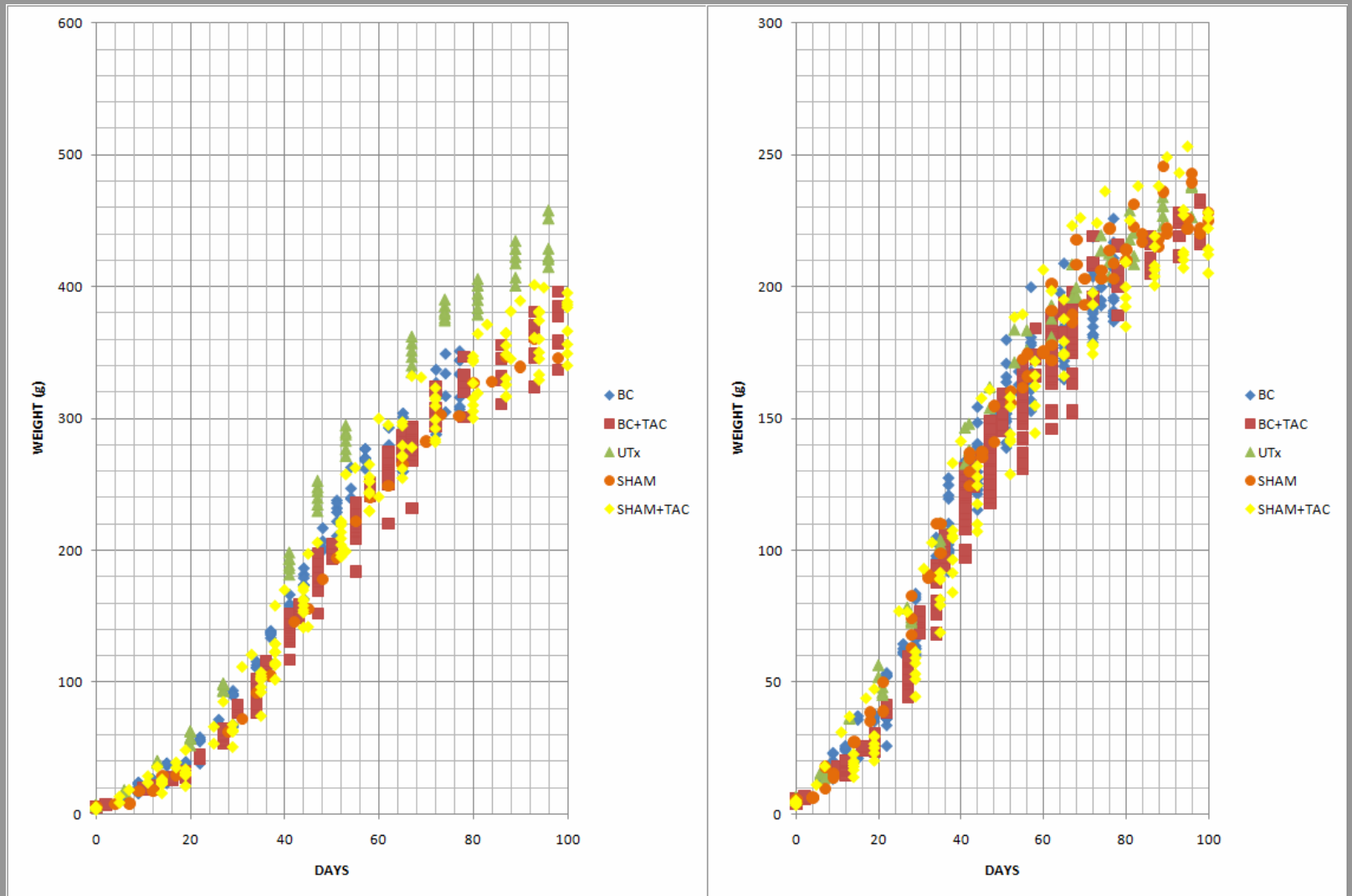
Immunosuppression

- 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 allogeneic UTx



RESULTS-WEIGHT GAIN



PHENOTYPING - normal

✓ Birth weight

✓ Metabolism

- Weight gain (weekly)
- Body composition (DEXA)
- Glucose overload
- Basal metabolism (Somedic)

✓ Cardiovascular

- BP
- Functional echocardiogram

✓ Behavior

- Anxiety
- Memory

✓ Urinary

- Kidney function

✓ Fertility

✓ Aging

Fertility

Rodents

- Syngeneic
2002
- Allogeneic
2010



NH-
primates

Autologous
2012



Sheep

- Autologous
2006
- Allogeneic



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**)

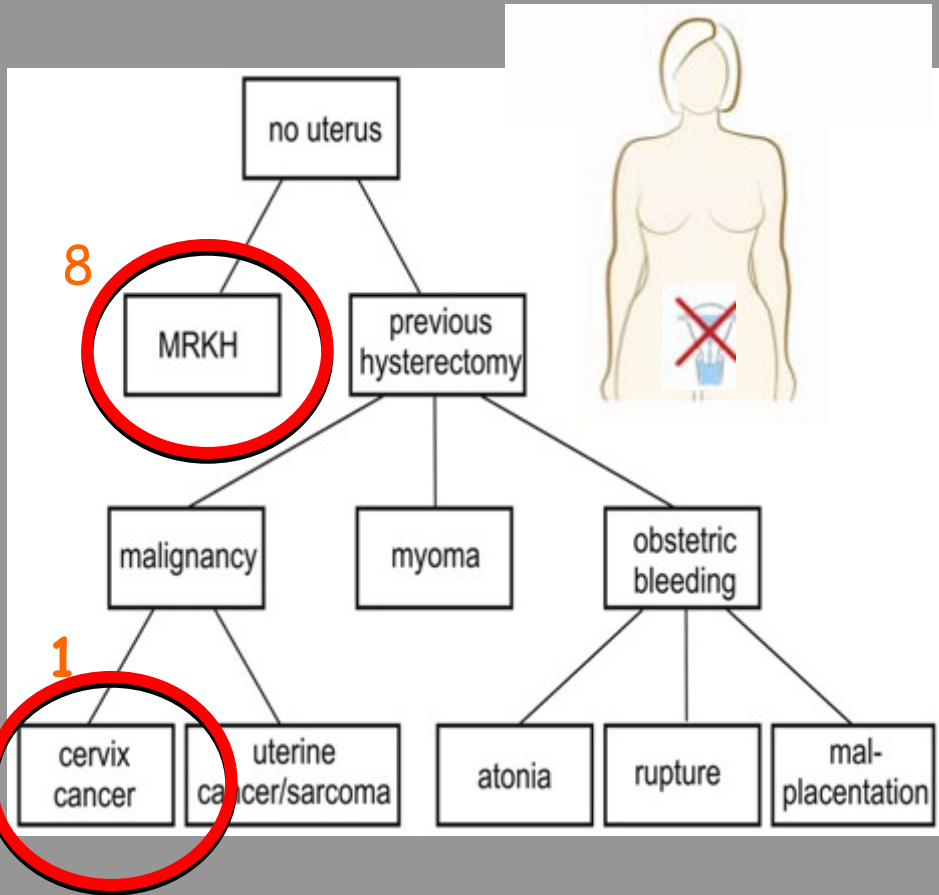
-paid entirely by private
research foundations

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

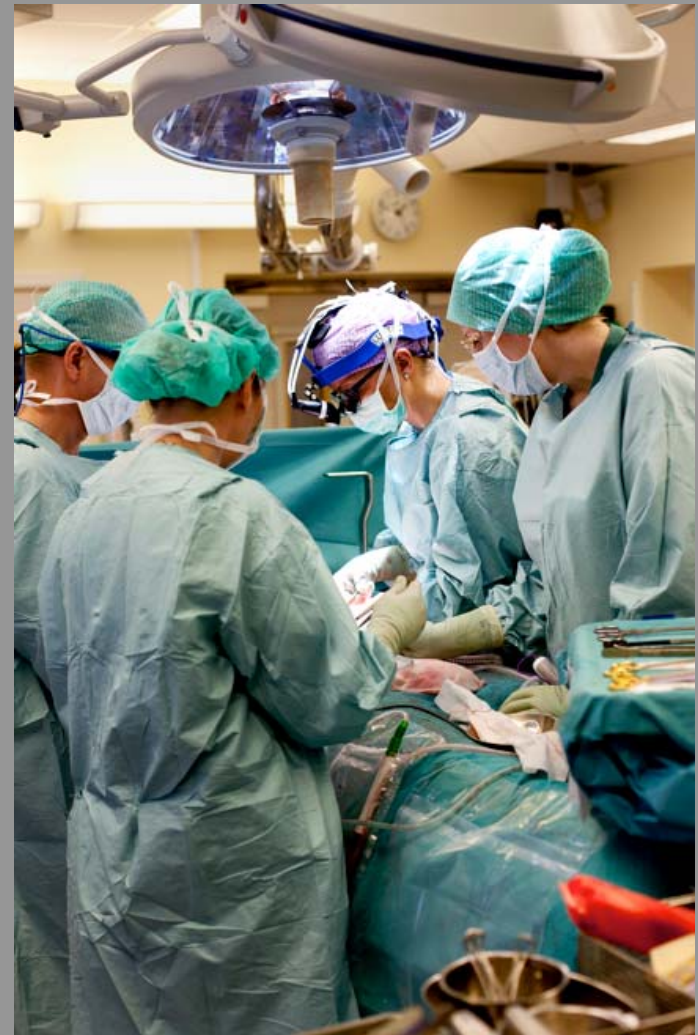


- mother (5)
- older sister (1)
- mother's sister (1)
- mother-in-law (1)
- family friend (1)

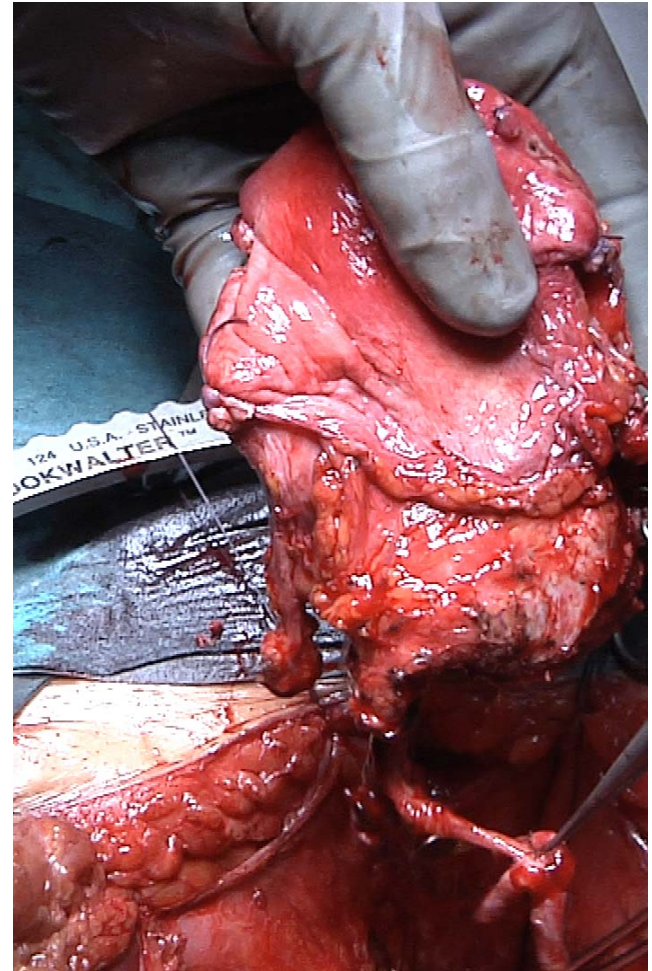
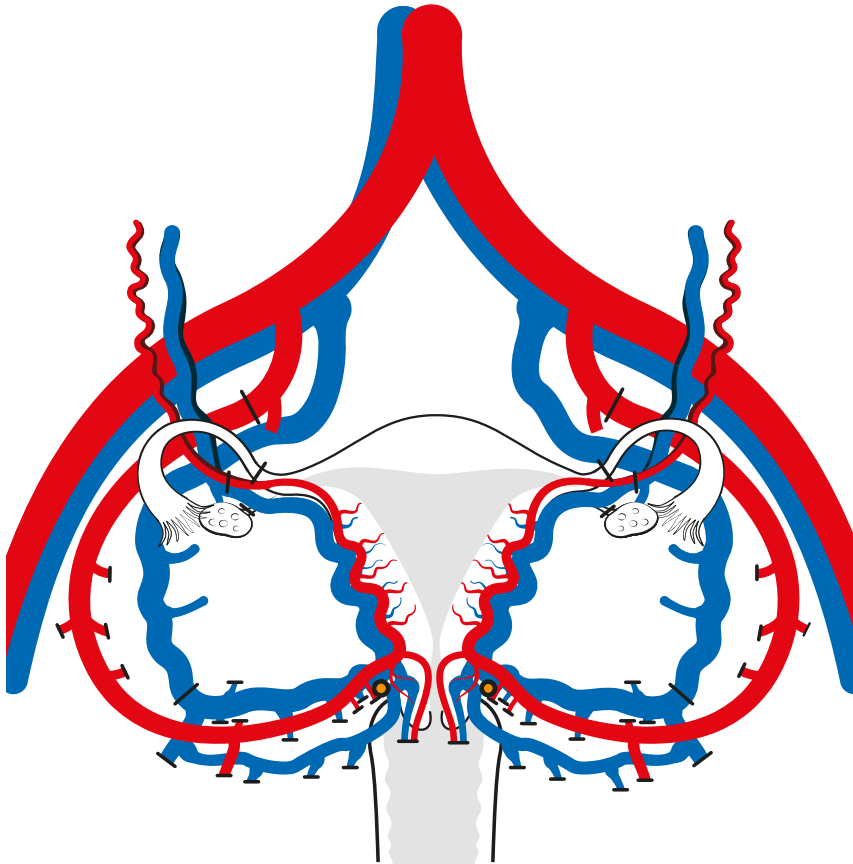
- extensive investigation of patients, partners and donors for >12 months
 - psychologist (multiple visits)
 - transplant counsellor
 - physician
 - anesthesiologist (x2)
 - gynecologist (x3)
 - transplant surgeon
- blood tests, MRI, TVU, virology

10 surgeons (2 patients in partially parallel surgery)

- 4 gynecology surgeons
- 3 transplant surgeon
- 3 gynecologists



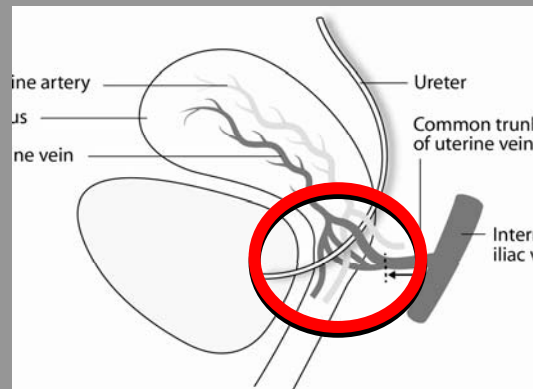
Donor surgery



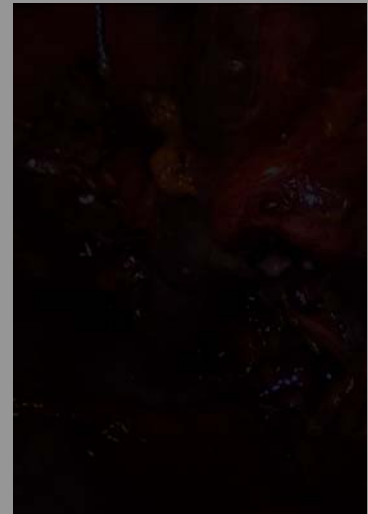
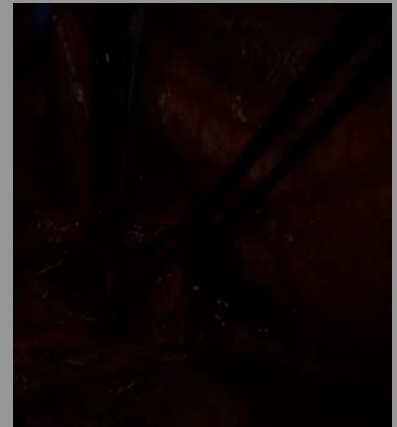
Donor surgery

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

- time consumption
 - ureteric dissection
 - isolation of uterine veins

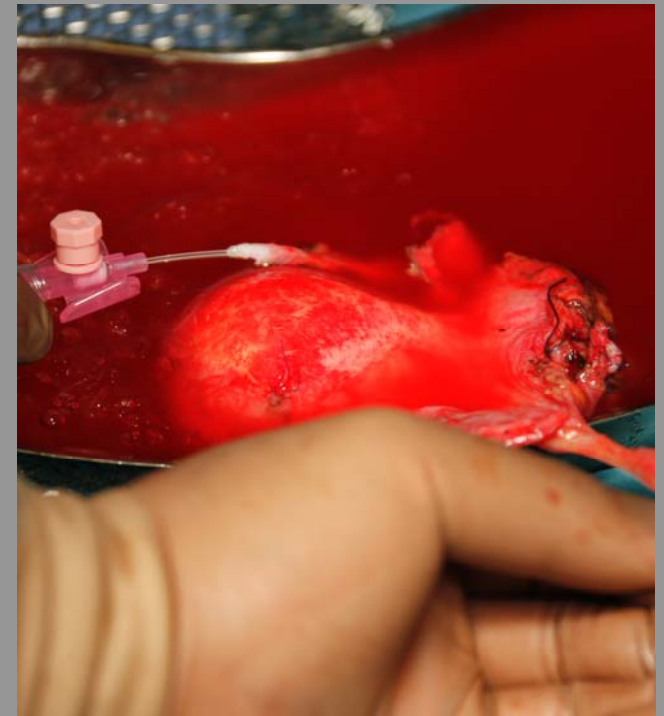
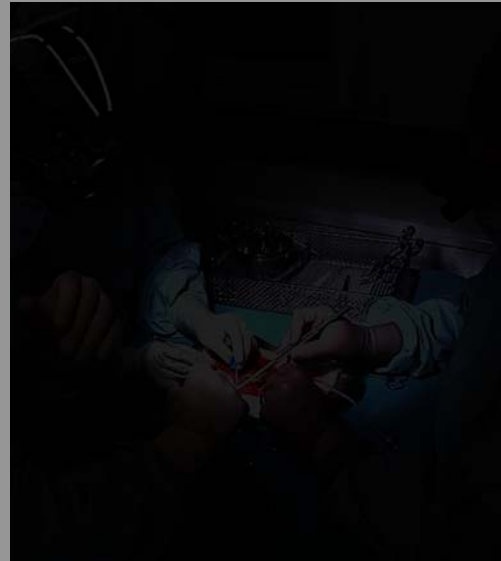
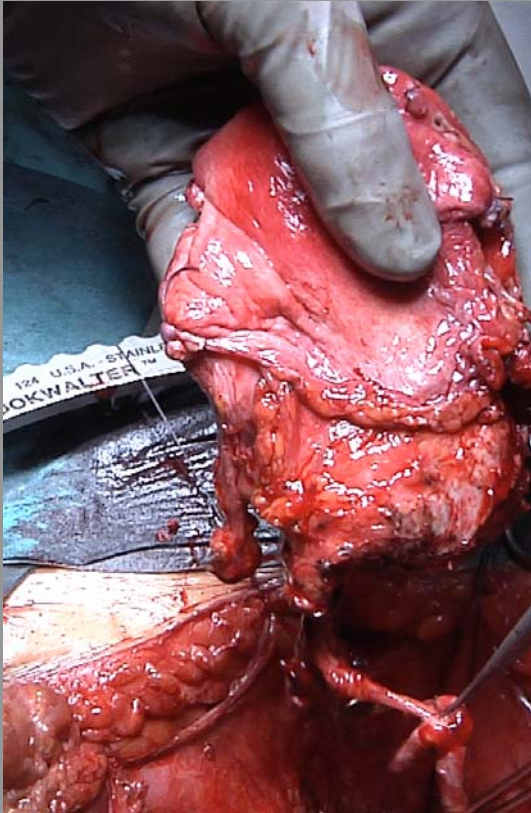


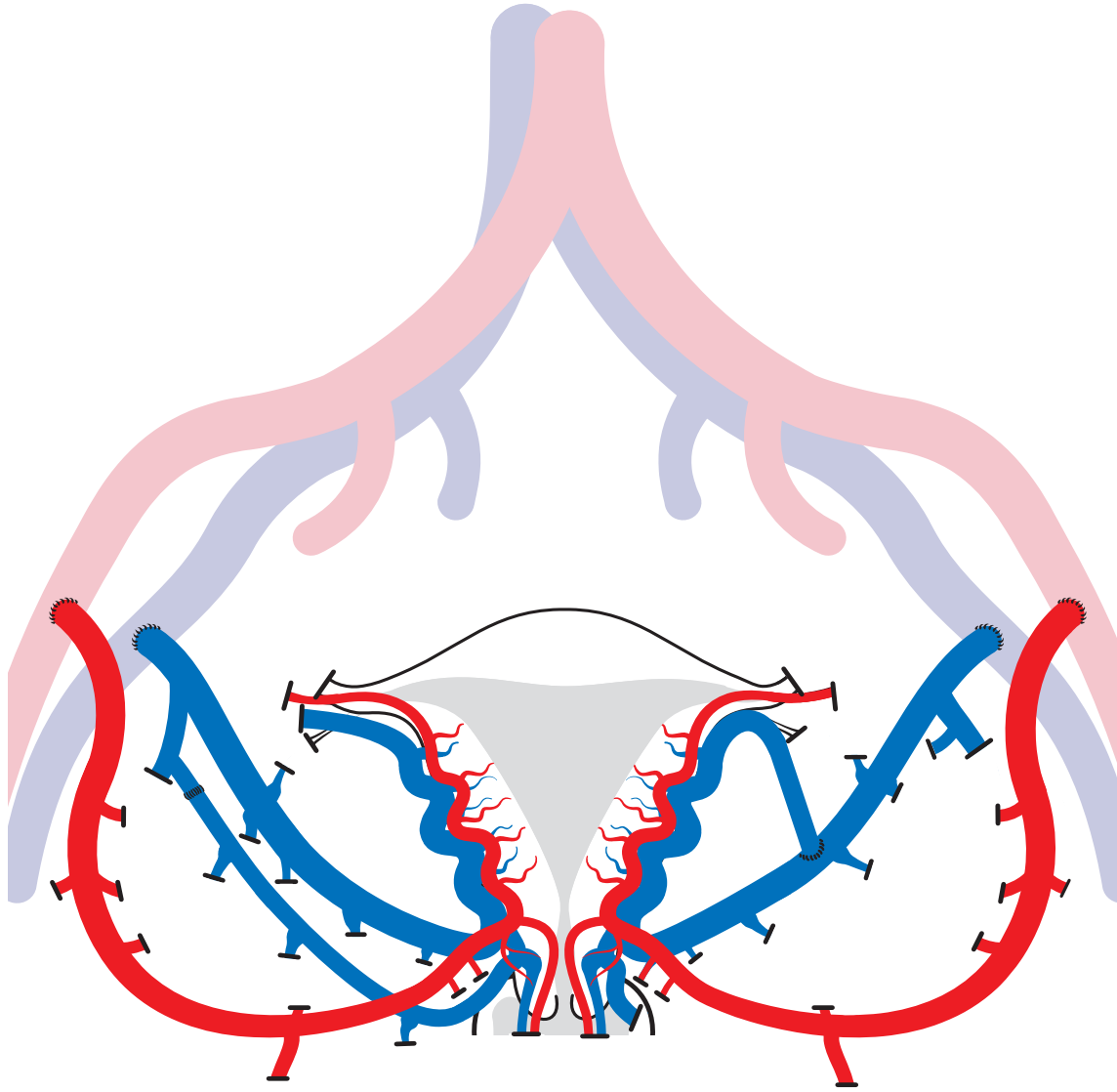
- no blood transfusions
- no ICU
- 4-5 days hospital stay



Flushing ex vivo

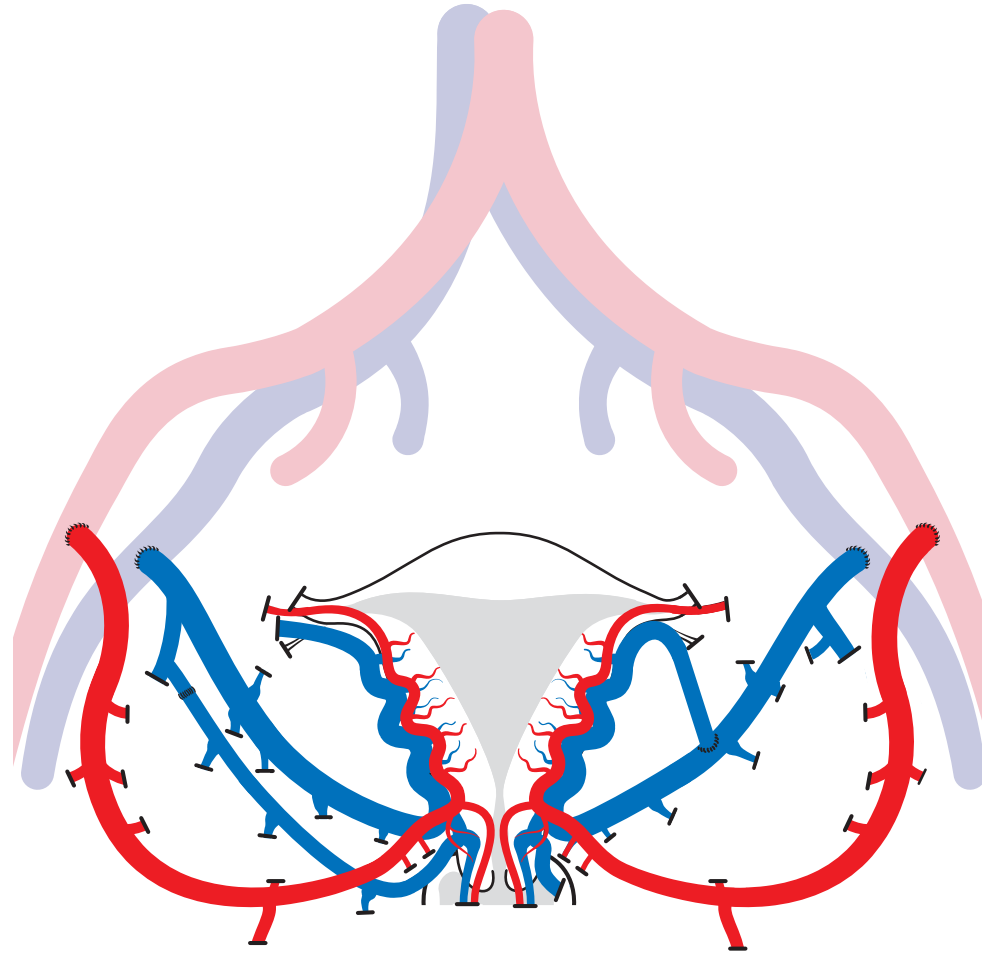
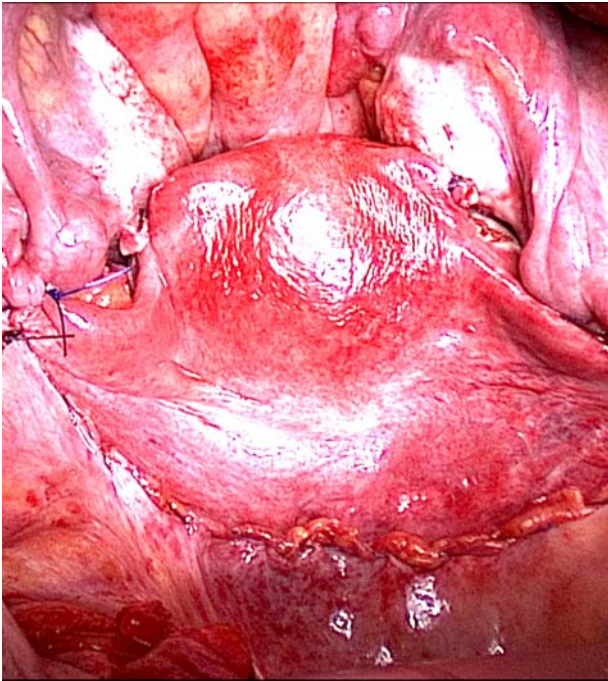
- CUSTODIOL PRESERVATION SOLUTION
- ICE SLUSH
- BACKTABLE PREPARATION OF VESSELS





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)

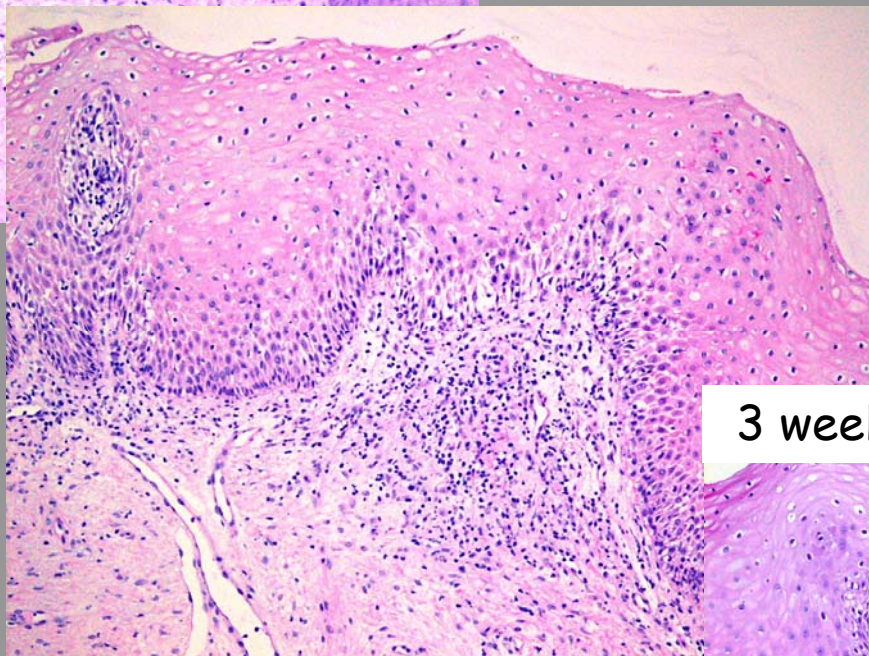
5 - (1 every 3d week)

- 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 Dahm-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 Mölne 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

