Uterine transplantation and its complications

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Sydney

Disclosure of Relevant Financial Relationships

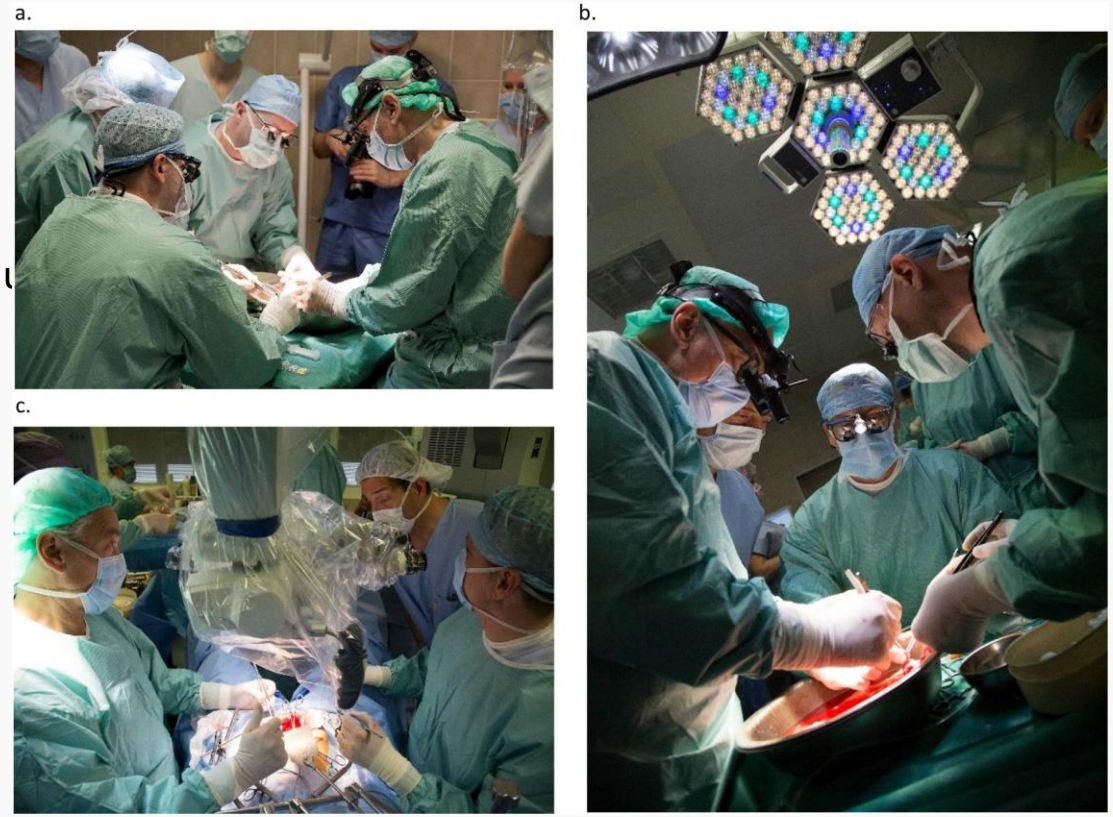
No relevant financial relationships.

W h a t I d o a t R P A H

1. G y n a e p a th o lo g y
2. R e n a l p a th o lo g y in c lu d in g tr a n s p la n ts
3. I t ’s n o t a s if th e y a re m u tu c o m p a tib le …
4. F e b 2 0 2 3 firs t R P A H u te r tr a n s p la n t

Outline

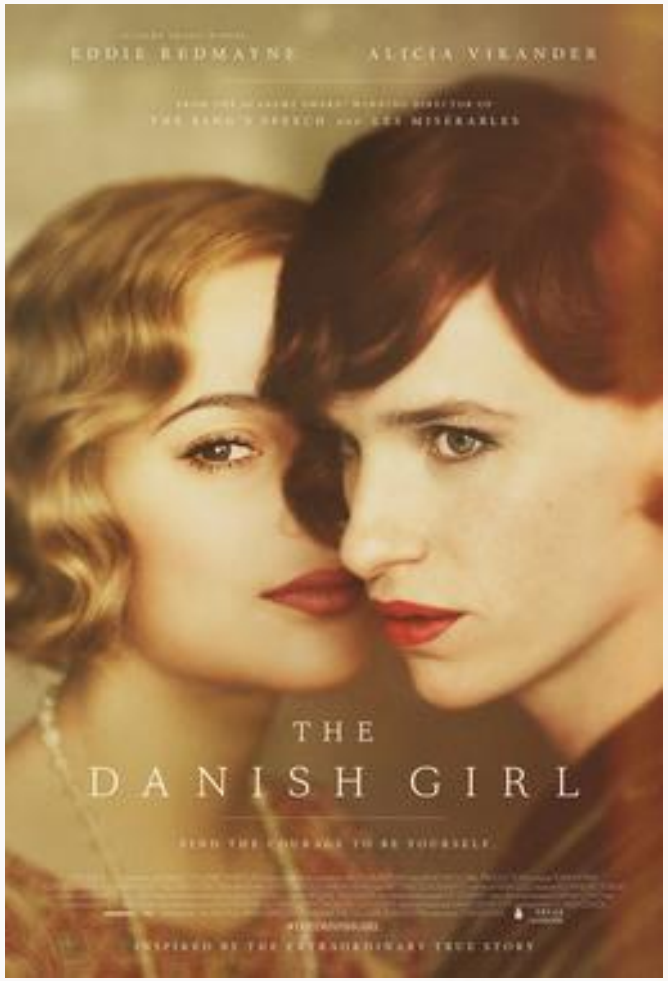
- History
- Who is eligible?
  - Uterine factor infertility
  - Mayer-Rokitansky-Kuster-Hau
- Does it work?
  - Scandinavian cohort, Prague
  - Dallas cohort, Penn cohort
- What are the comp
  - Bleeding
  - Infection
  - Rejection
  - Psychosocial



The Danish Gi

1930

- Lili Elbe
- First uterine transplant
- Died at 3 months post op



History

- 2000 Saudia Arabia – removed day 99 vascular thrombosis
- 2011 Turkey – no live infant
- 2013 Sweden – first live infant

I. Kisu *et al.*

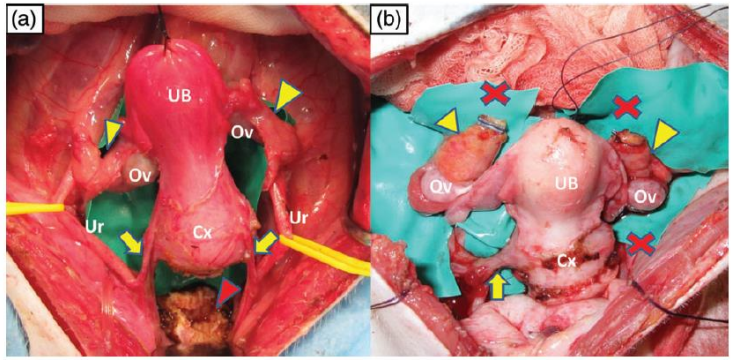


Figure 2 (a) Uterus after vascular dissection. The vaginal canal (red triangle) was cut and the uterus was connected to the pelvis with the bilateral ovarian vessels (yellow triangle) and uterine vessels (yellow arrow) alone. (b) Uterus with nutritional support from unilateral uterine vessels alone. The left uterine and bilateral ovarian vessels of the uterus and vaginal canal were cut. Cx, cervix; Ov, ovary; UB, uterine body; Ur, ureter.

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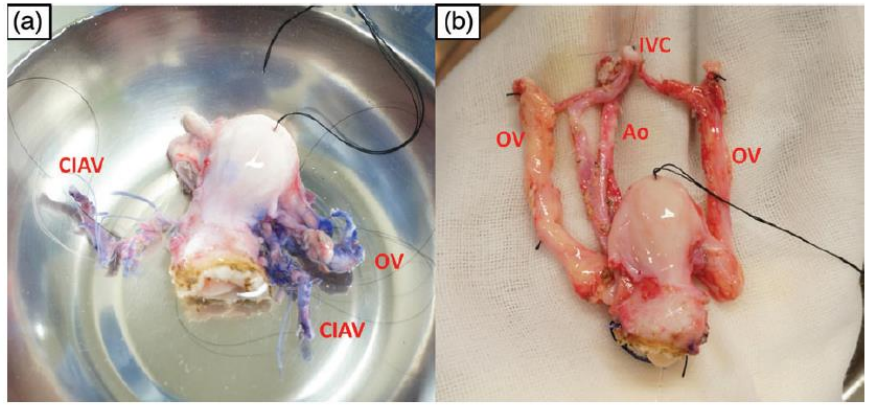


Figure 4 Grafted uterus. Uterus with common iliac vessels (a) or abdominal aorta/inferior vena cava (b) were removed from a donor. Ao, aorta; CIAV, common iliac artery and vein; OV, ovarian vein.

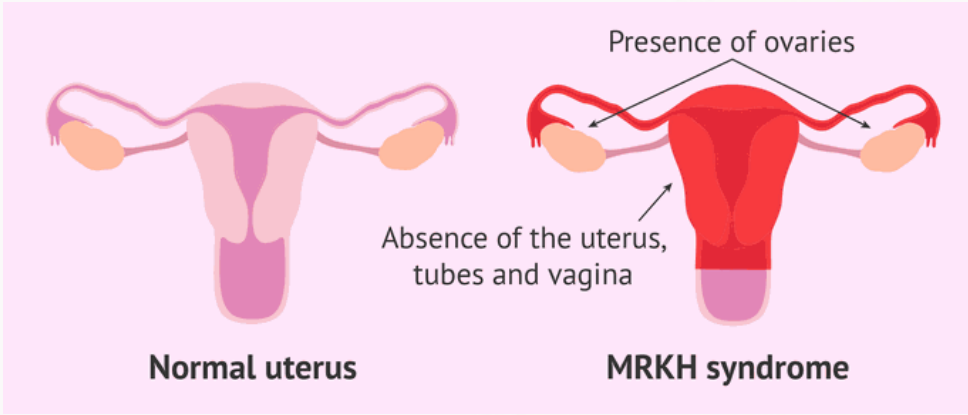
Is UTx new

- 90 cases worldw
- Most continents
- 50 live births

Liza Johannesson (Gynecologic surgeon)
Giuliano Testa (Transplant surgeon)

M R K H

- M a y e r-R o k i t a n s k y-K u s t e r-H a u s e r s y n d r o m e
- R a r e c o n g e n i t a l d i s o r
- E f f e c t s f e m a l e r e p r o d
- A f f e c t s 1 i n 4 5 0 0 f e m a
- C o n g e n i t a l l y a b s e n t o r s m a l l u t e r u s



Donor-Recipient relationships

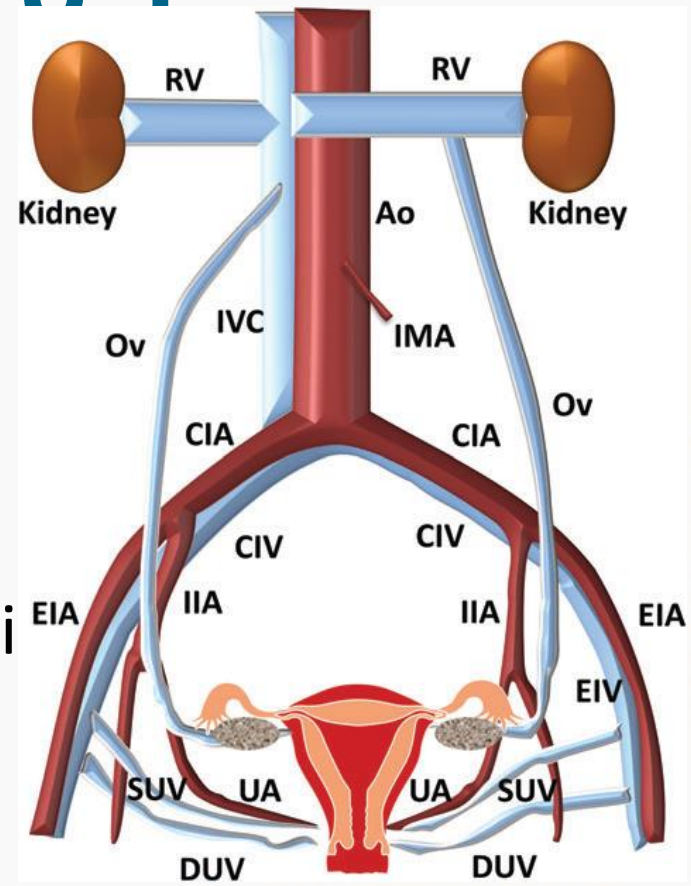
- Related donor
  - Mother, sister
- Unrelated known donor
  - Friend
- Unrelated unknown (non-directed) donor
  - Most altruistic
  - Arguably most likely to break down
  - Currently remain unknown to either otherwise per other solid organ transplants in Australia

Eligibility of recipient

- Absolute Uterine Factor Infertility (UFI)
- Good health
- Non-smoker
- Age range
- Adequate AMH
- Comprehensive ID serology, UEC, FBC, TFT, imaging, CSTs

E lig ib ility o f d o n o r

- B M I
- A g e
- C S T h is to ry
- N o s u rg ic a l o r m e d ic a l h is
- C T p e lv is u te rin e a rte ry d i
- M R I fo r p e lv ic v e in s



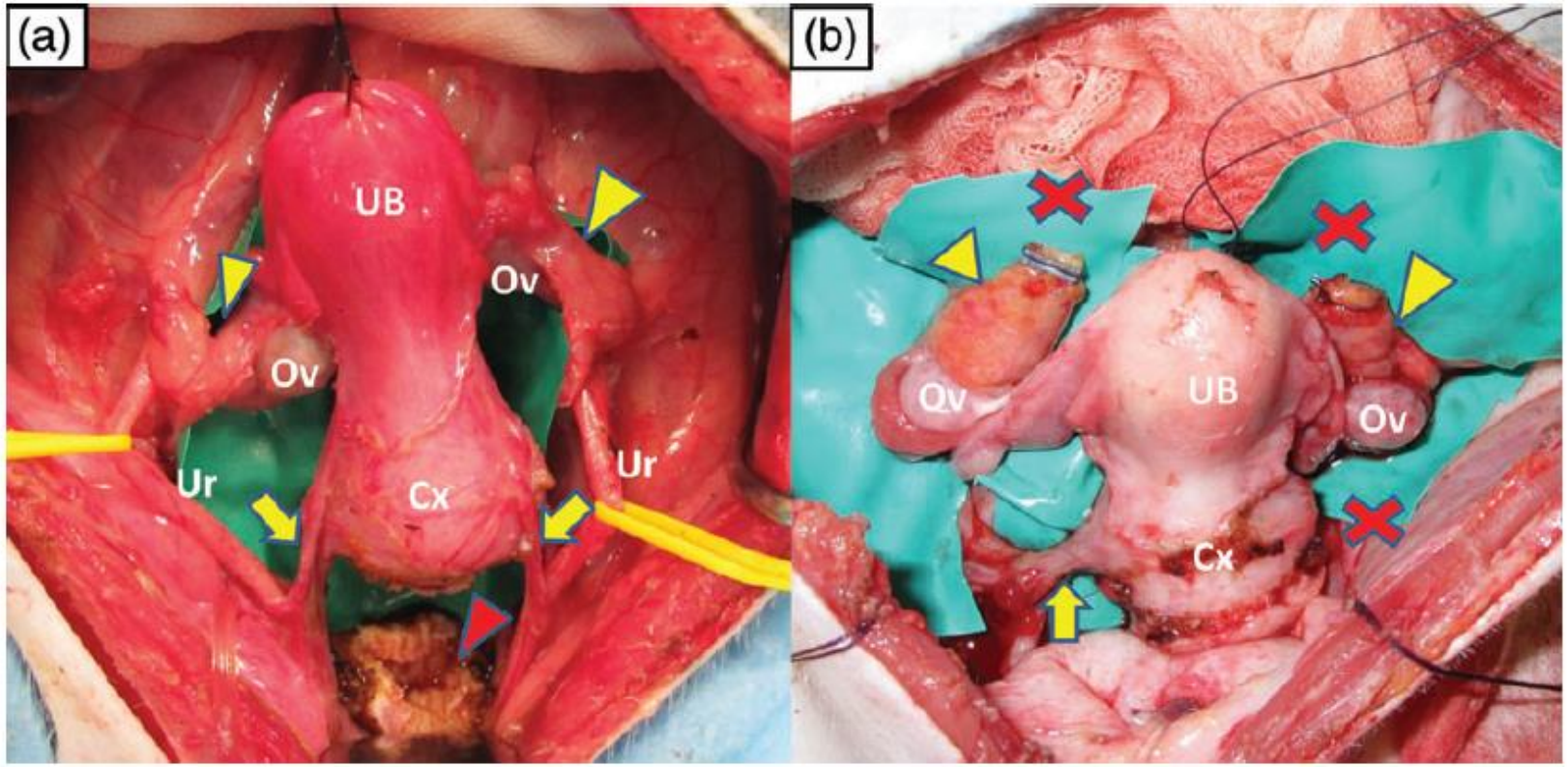


Figure 2 (a) Uterus after vascular dissection. The vaginal canal (red triangle) was cut and the uterus was connected to the pelvis with the bilateral ovarian vessels (yellow triangle) and uterine vessels (yellow arrow) alone. (b) Uterus with nutritional support from unilateral uterine vessels alone. The left uterine and bilateral ovarian vessels of the uterus and vaginal canal were cut. Cx, cervix; Ov, ovary; UB, uterine body; Ur, ureter.

Timeline

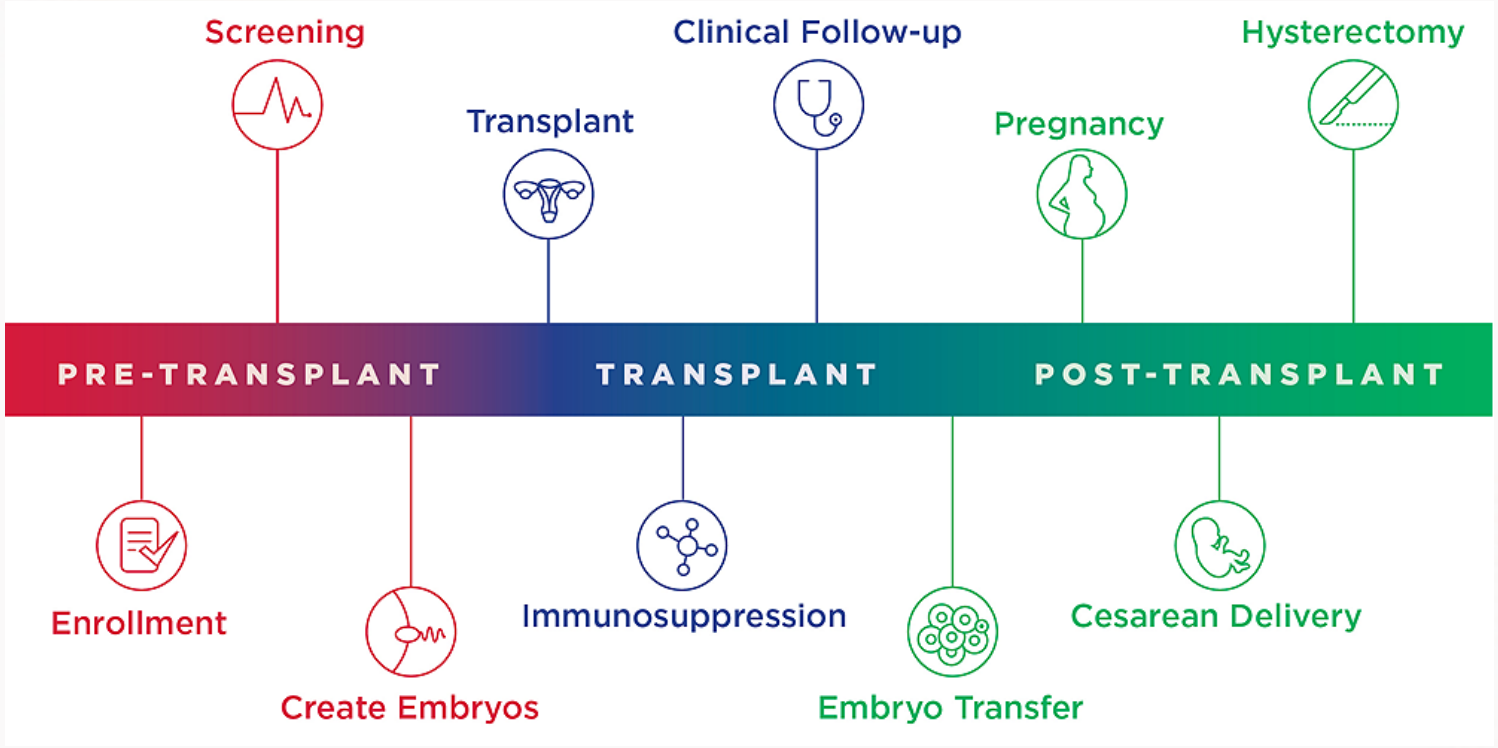


Image courtesy: https://www.pennmedicine.org/for-patients-and-visitors/find-a-program-or-service/transplant-institute/uterus-transplant

Rejection

Monitoring of Human Uterus Transplantation With Cervical Biopsies: A Provisional Scoring System for Rejection

J. Mölne, V. Broecker, J. Ekberg, O. Nilsson, P. Dahm-Kähler, M. Brännström

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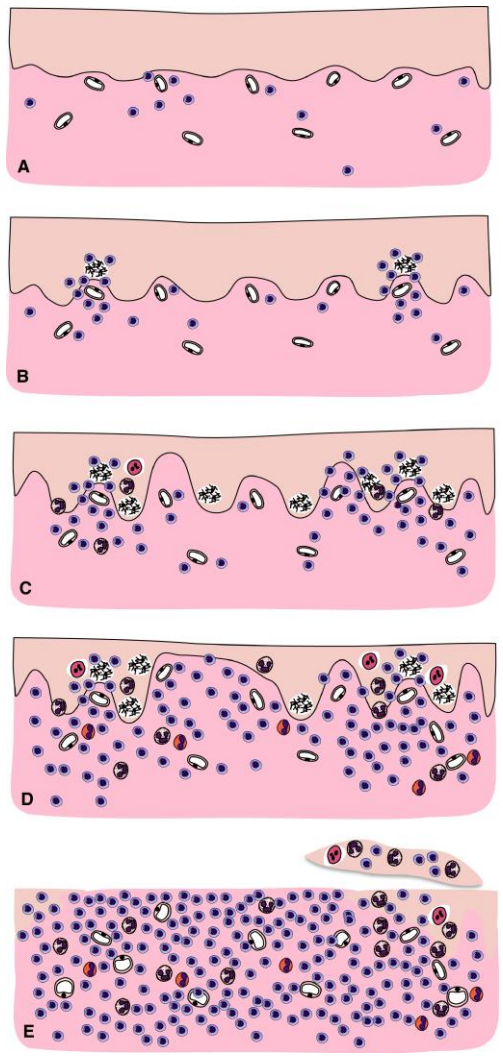


Schematic illustrations of rejection patterns and grading system in cervical biopsies.

(A) Normal cervical biopsy with few inflammatory cells.

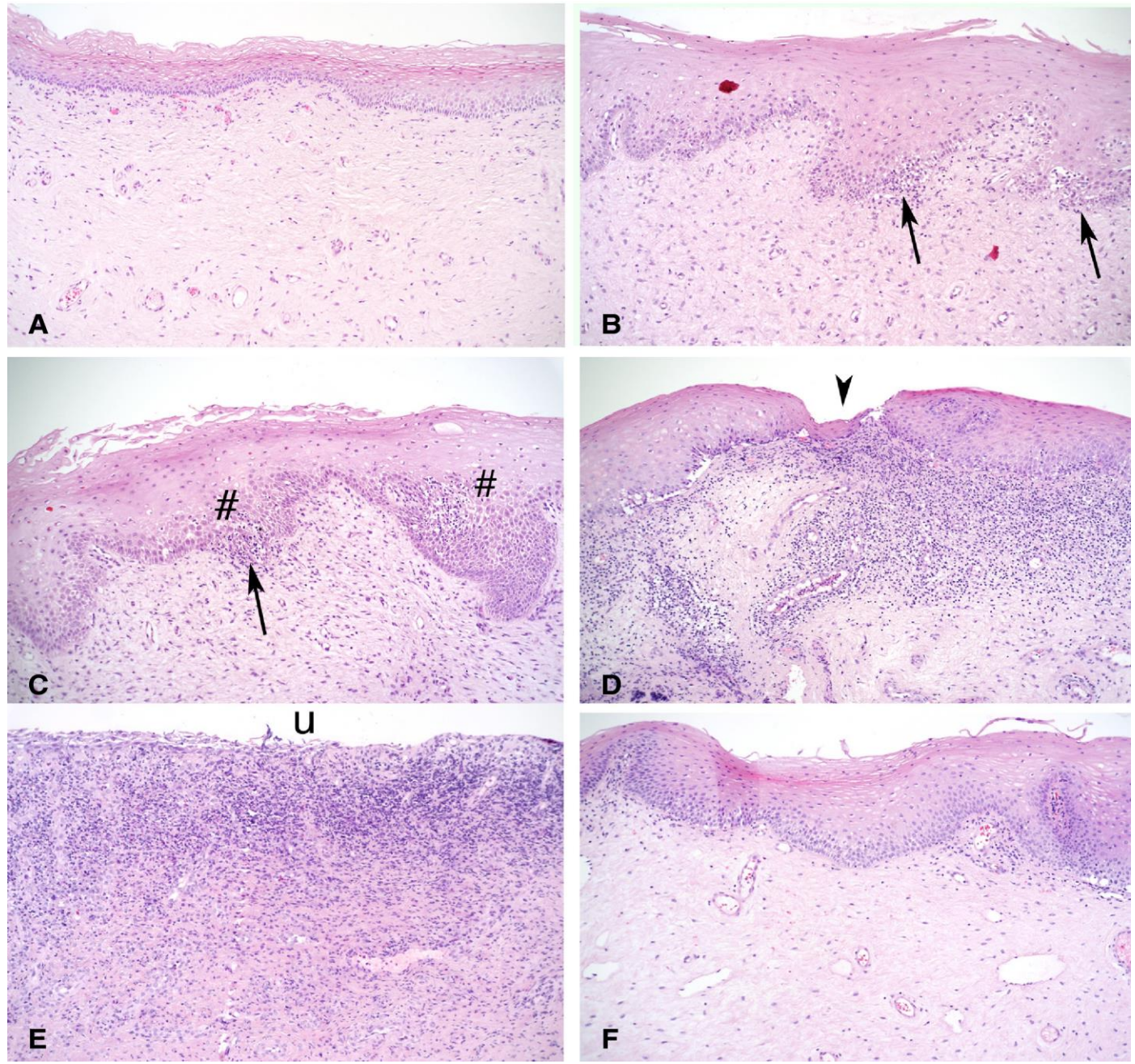
(B) **Borderline** changes. Small nests of inflammatory cells, dominated by lymphocytes, can be seen at the stromal–epithelial interface.

(C) **Grade 1** rejection. A mixed inflammatory infiltrate at the stromal–epithelial interface is dominated by lymphocytes. There is low-grade stromal inflammation and edema.

(D) **Grade 2** rejection. A moderate interface inflammatory infiltrate with intraepidermal influx of inflammatory cells is dominated by lymphocytes and has some neutrophils. There is often a reduced surface epithelial thickness and a marked mixed stromal inflammation with an edema.

(E) **Grade 3** rejection. There is a significant diffuse, mixed inflammatory cell infiltrate dominated by lymphocytes, with a presence of neutrophils and eosinophils. Apoptotic bodies, epithelial erosions/ulcerations, and focal necrosis can be seen. The stromal infiltrate (mixed) is intense and continuous.

Proposed grading system for uterine transplant (ectocervical biopsy)	
Indeterminate	At least two foci of interface inflammation Minimal spongiosis Minimal stromal inflammation predominantly lymphocytes Minimal vascular damage Zero to one epithelial apoptotic body
Mild	Two or more foci of interface inflammation Mild stromal inflammation (predominantly lymphocytes) One to two foci of perivascular inflammation with vascular damage Two or more epithelial apoptotic bodies
Moderate	Mild to moderate intraepidermal inflammatory infiltrate (predominantly lymphocytes admixed with neutrophils) Moderate spongiosis Impending ulcer formation Non-confluent epithelial apoptotic bodies Moderate stromal inflammation predominantly lymphocytes Multifocal perivascular inflammation with vascular damage
Severe	Severe mixed intraepidermal inflammatory infiltrate composed of lymphocytes, eosinophils and neutrophils Moderate to severe spongiosis Ulcer formation with fibrin deposition and dermo-epidermal junction Confluent epithelial apoptotic bodies Severe mixed stromal inflammation Diffuse perivascular inflammation with vascular damage


A
B
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Human Reproduction, Vol.28, No.1 pp. 189–198, 2013
Advanced Access publication on October 28, 2012 doi:10.1093/humrep/des381

human reproduction

ORIGINAL ARTICLE *Reproductive biology*

Preclinical report on allogeneic uterus transplantation in non-human primates

L. Johannesson[1,*], A. Enskog[2], J. Mölne[3], C. Diaz-Garcia[4], A. Hanafy[5], P. Dahm-Kähler[1], A. Tekin[6], P. Tryphonopoulos[6], P. Morales[7], K. Rivas[7], P. Ruiz[6], A. Tzakis[6], M. Olausson[8], and M. Brännström[1]

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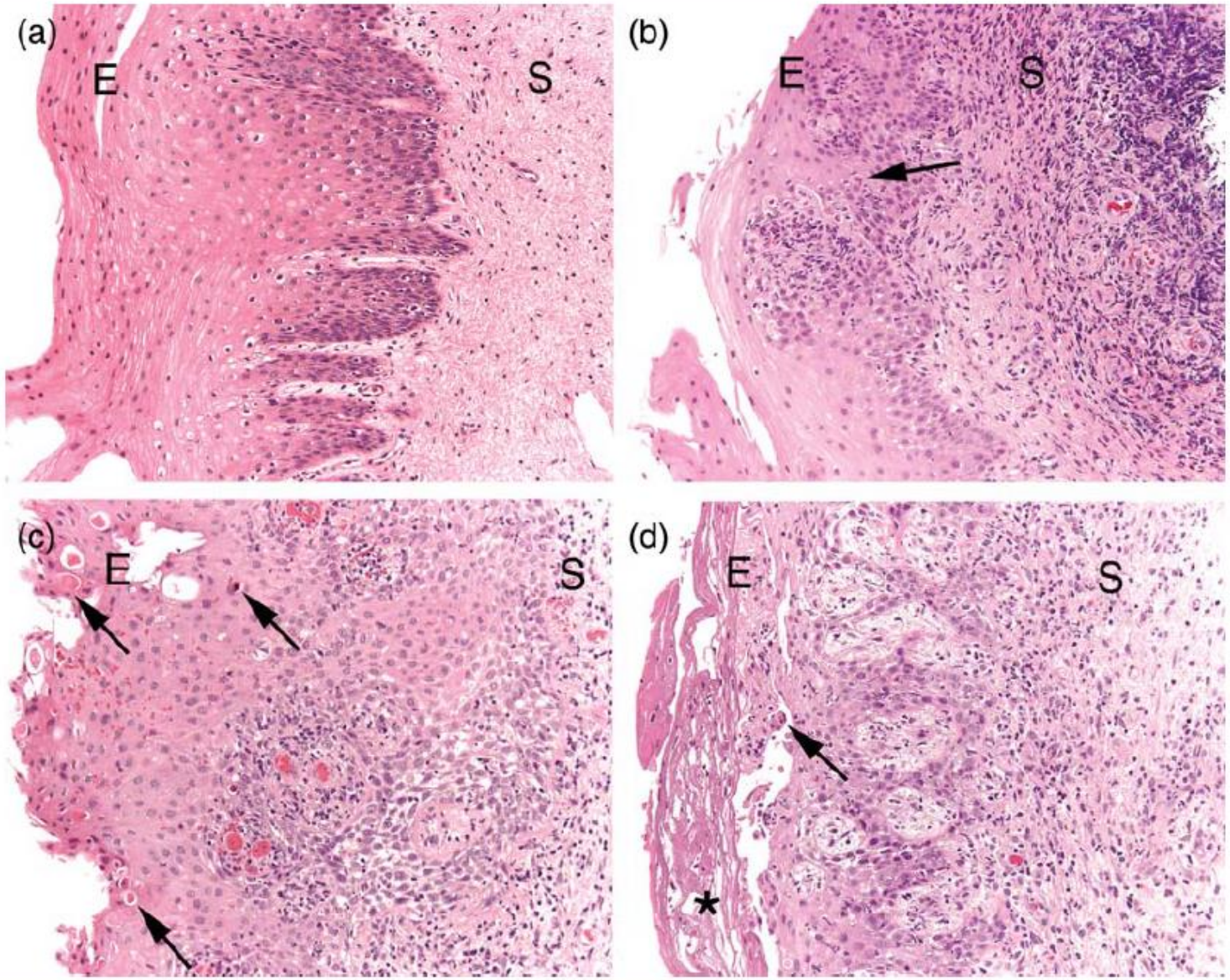


Figure 4 Representative light micrographs of cervical biopsy samples showing; (**a**) Grade 0: Normal morphology, (**b**) Grade 1: Mild rejection, (**c**) Grade 2: Moderate rejection and (**d**) Grade 3: Severe rejection. For definitions of the classification of uterine rejection, see Table III. Epithelium (E); stroma (S); apoptotic bodies (arrow) and necrosis and loss of endothelium (*) are marked. Magnification ×20.

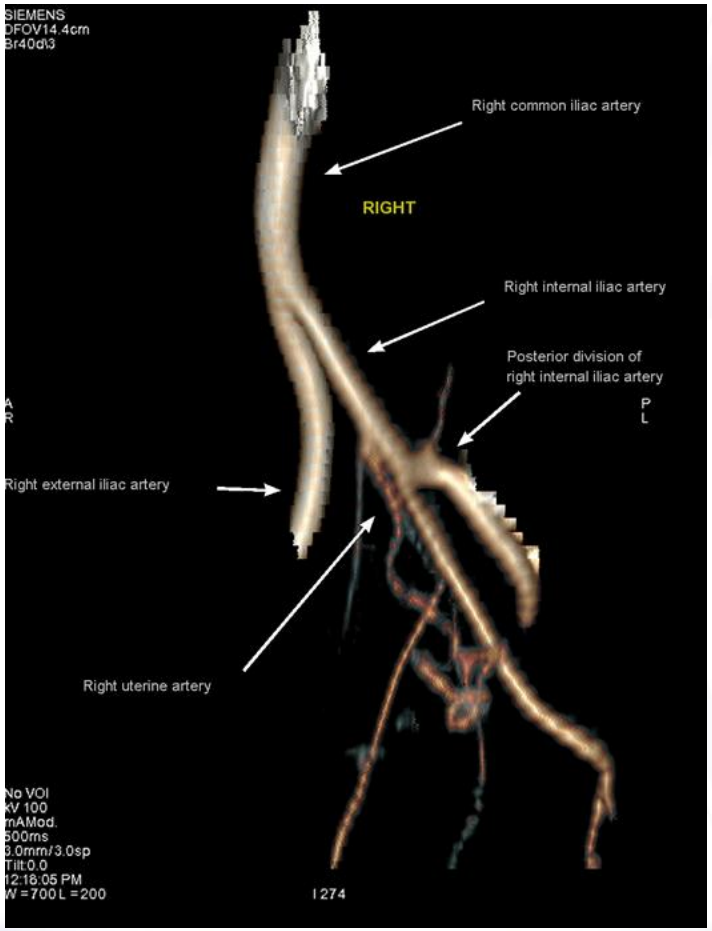
Case study – Feb 2023

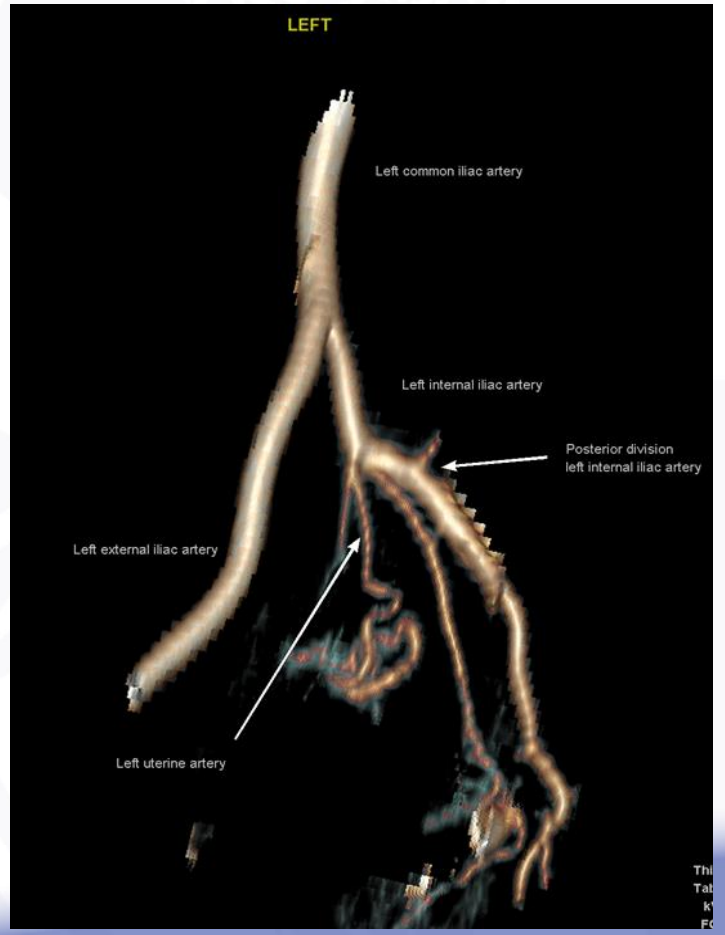
- 25 year old female, dance teacher
- MRKH (Mayer-Rokitansky-Kuster-Hauser syndrome) dx age 18
- Donor is mum's cousin's friend, 47 year old school teacher
- Extensive counselling
- Donor recipient surgery 16 hours with team from Dallas and local transplant surgeons

Recipient prior to transplant

Recipient pre transplant

Donor Imaging



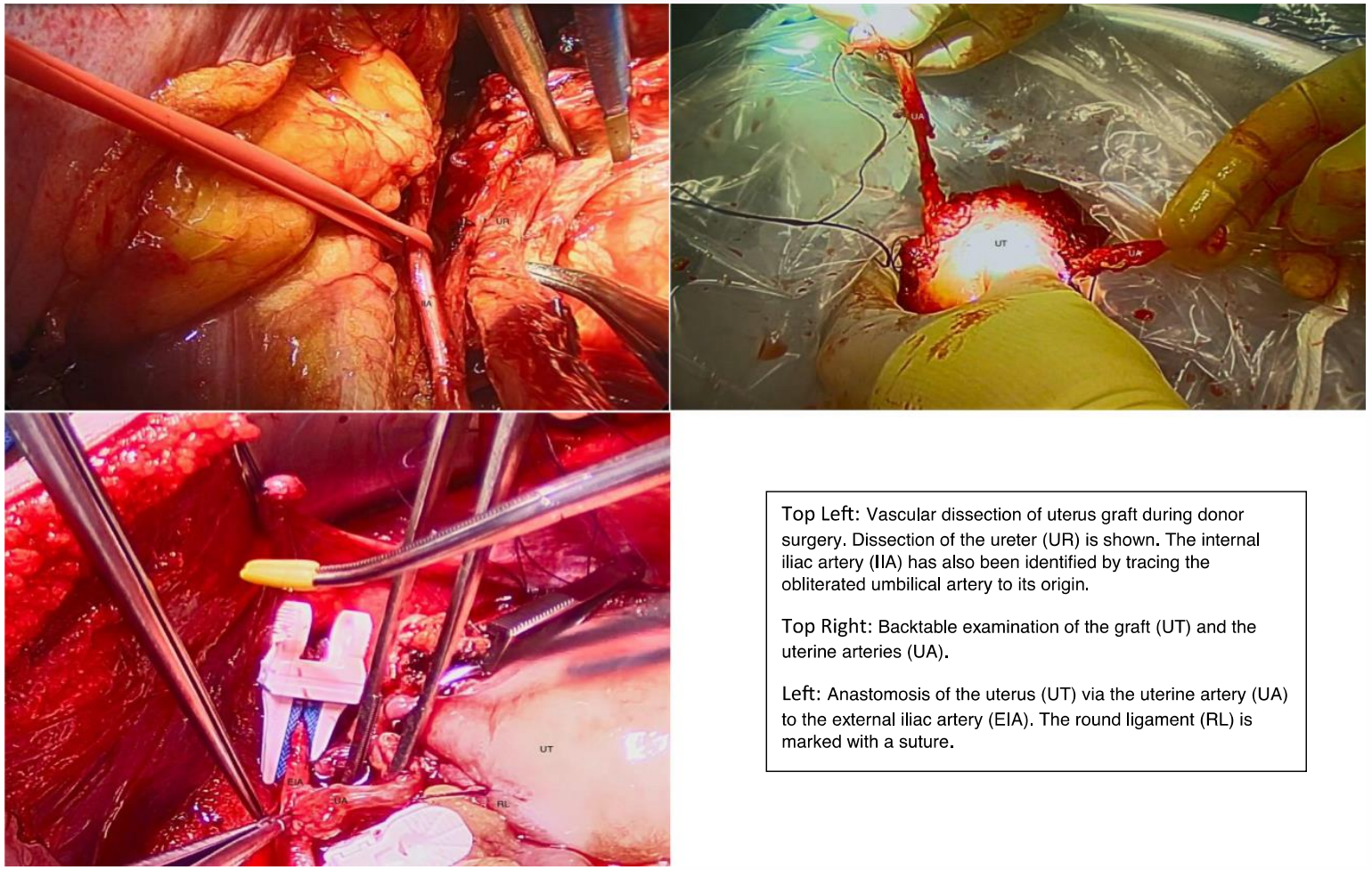


Had to sacrifice of posterior branches of internal iliac artery

– can lead to gluteal claudication

RPA | Uterus Transplant Trial

Transplant

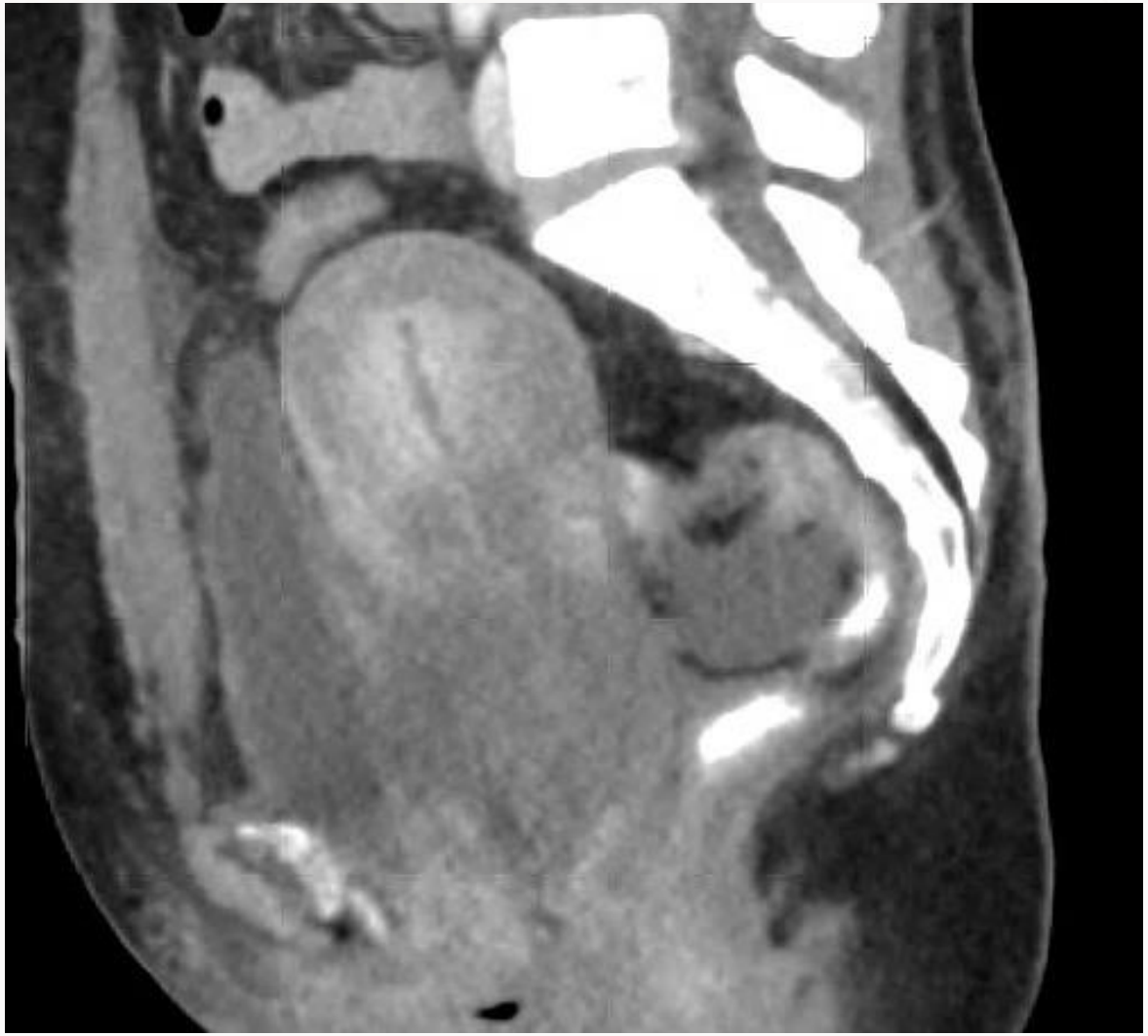


Top Left: Vascular dissection of uterus graft during donor surgery. Dissection of the ureter (UR) is shown. The internal iliac artery (IIA) has also been identified by tracing the obliterated umbilical artery to its origin.

Top Right: Backtable examination of the graft (UT) and the uterine arteries (UA).

Left: Anastomosis of the uterus (UT) via the uterine artery (UA) to the external iliac artery (EIA). The round ligament (RL) is marked with a suture.

FIGURE 1 Images of donor surgery, back table, and recipient surgery.



Posttransplant recipient
-Day 8
-Cervical oedema
-Uterine oedema

Post transplant recipient

Complicating patient factors

- Probably has PCOS
  - Anovulatory
  - Ovarian stimulation
- Intermediate risk of CMV reactivation
  - Patient is positive for IgG
  - Mother is positive for IgG
  - Prophylaxis for 3 months post transplantation
  - Risk of reactivation

In flight complications

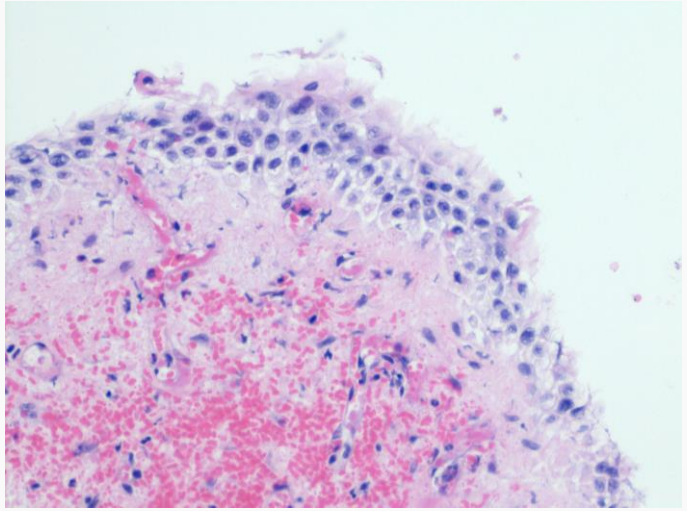
- Anaemic, ongoing haemolysis from Tac
- 30cm clot in arm on clexane
- 4/6 HLA mismatch
- Class II DSA sup front

Criteria for preservation/reperfusion injury	
Minimal	No histopathologic alteration in ectocervix
Mild	Minimal to mild stromal oedema Mild spongiosis
Moderate	Moderate stromal oedema Moderate spongiosis Mild capillary sludging with neutrophils Mild separation of squamous epithelium from underlying stroma
Severe	Marked stromal oedema Marked spongiosis Moderate capillary sludging with neutrophils Moderate to marked separation of squamous epithelium from underlying stroma

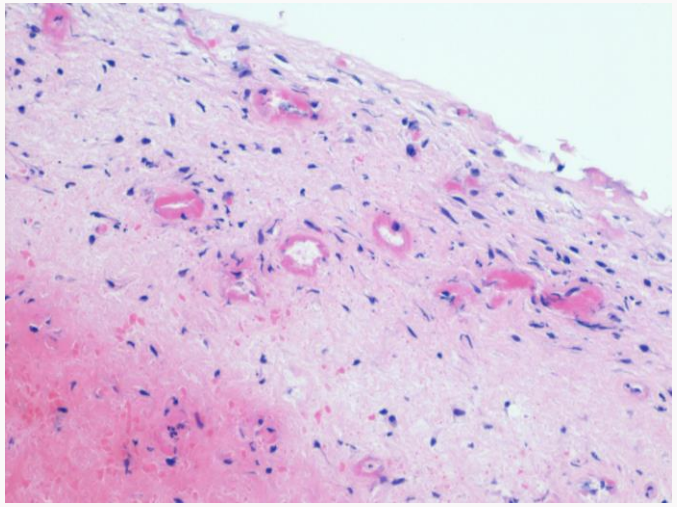
Criteria for interface inflammation
At least 15 lymphocytes (including activated lymphocytes) involving dermo-epidermal junction
Mild spongiosis of the involved squamous epithelium
Presence of focal haemorrhage around the involved squamous epithelium
Minimal to mild tissue separation
Apoptosis may be present or absent

First biopsies

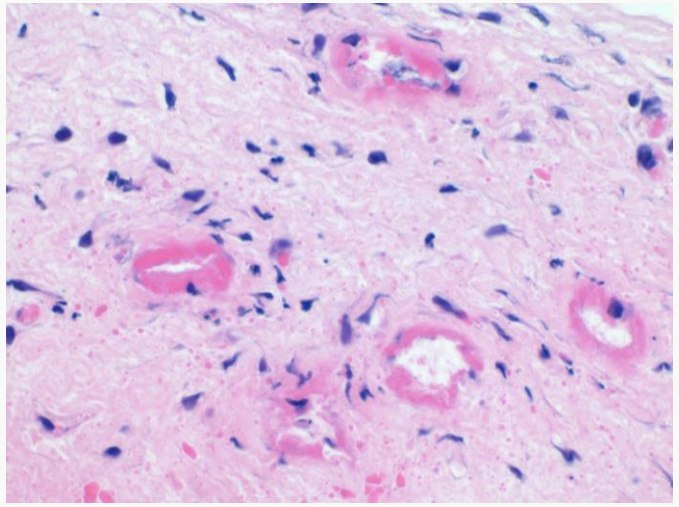
Surface disruption



Ischemia x 20 mag

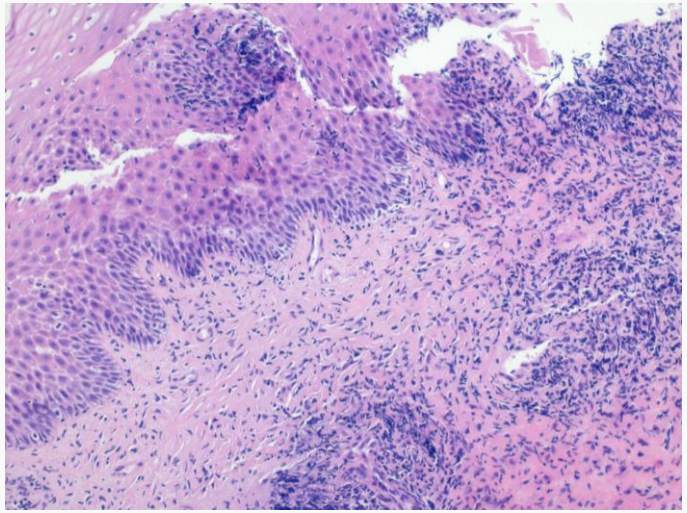


Ischemia x40 mag

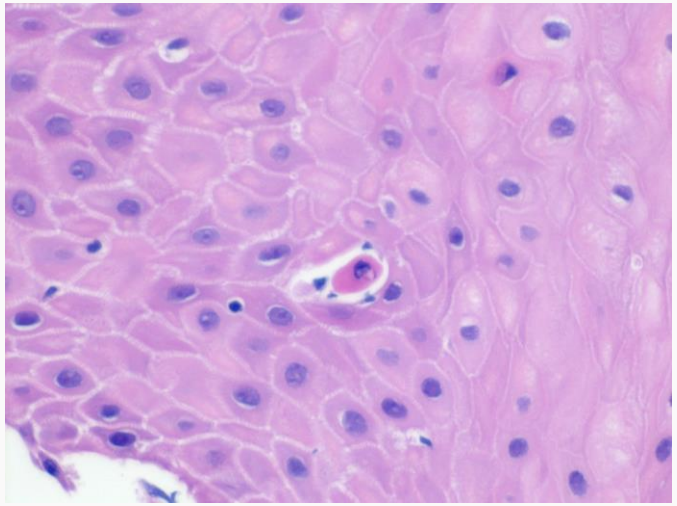


Rejection @ 9 weeks

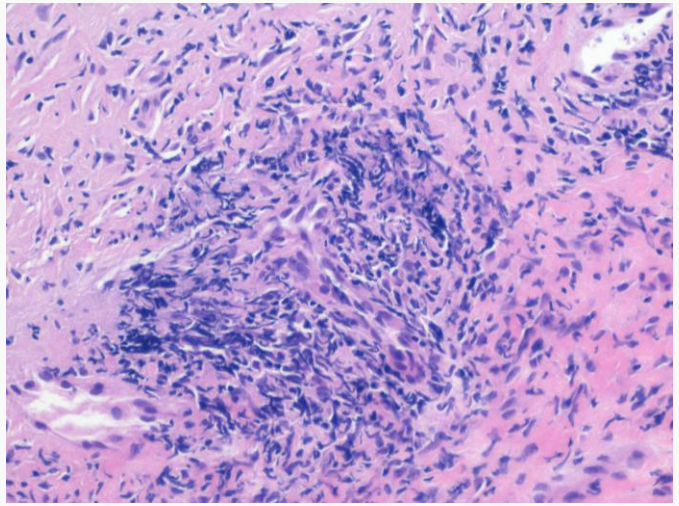
Stromal inflammation



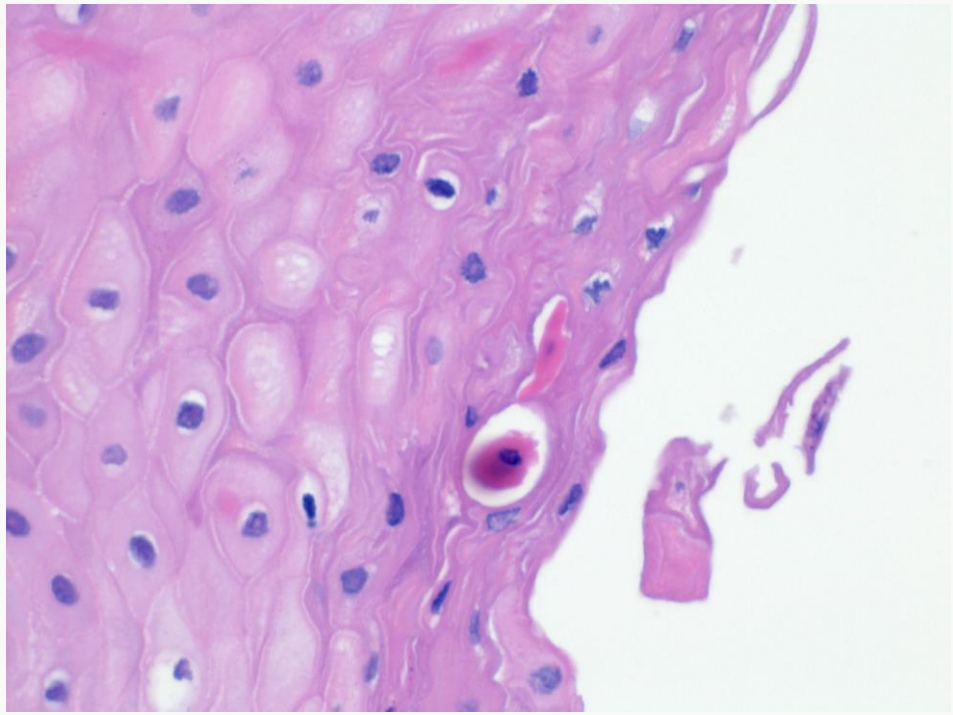
Apoptosis



Perivascular lymphoid



Apoptosis



Rejection experience from Dallas

Generally, there are 3 time points where rejection episodes are likely to occur:

1. During the first month post-transplant;
2. During the stimulation leading up to embryo transfer (ET);
3. After the delivery of a baby.

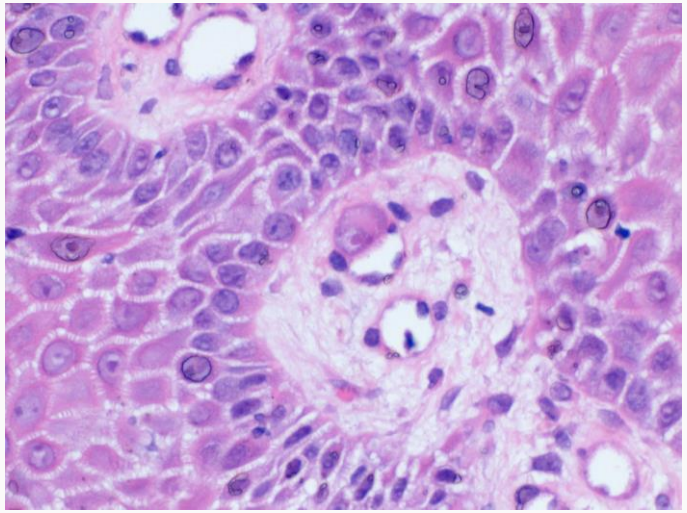
Clinically stabilized

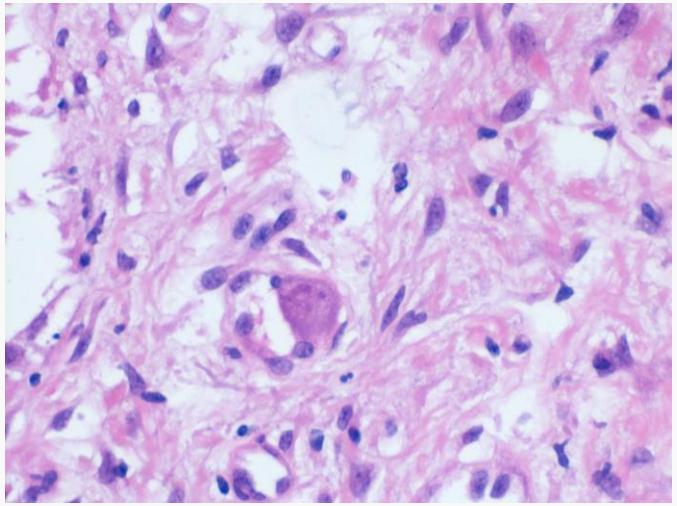
Worked up for first embryo transfer after counselling

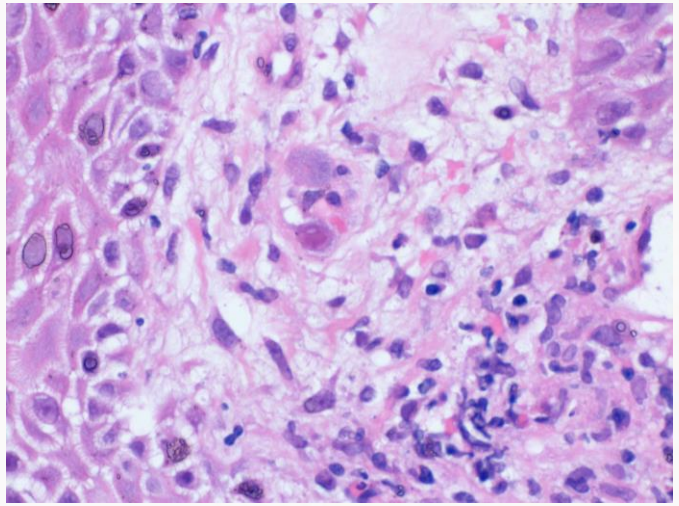
Embryo transfer 1 (ET1)

- Sept2023 – pregnancy confirmed
- Miscarriage
- Logarithmic record of CMV copies – 100,000 copies per ml
  - Reduced appetite, malaise, dropped WCC
- Second ET delayed March 2024

Cervix biopsies @ 10 months

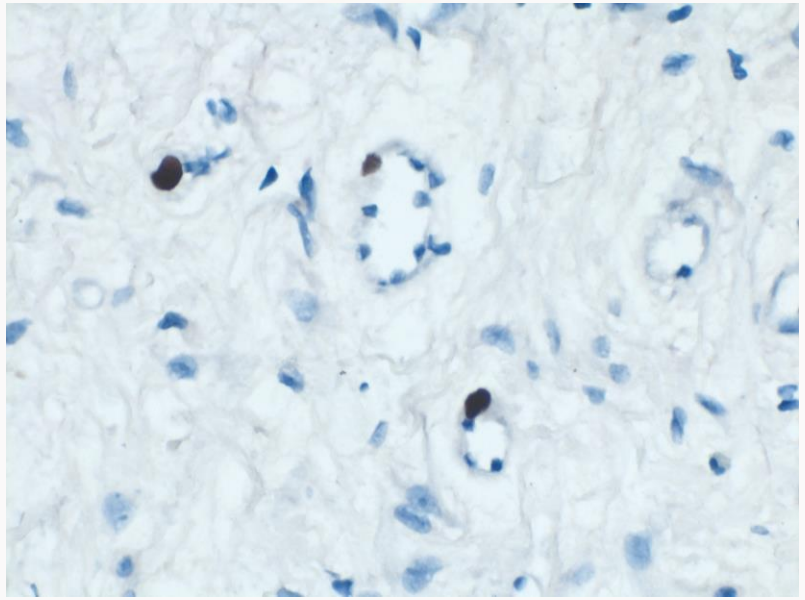






CMV – Dec 2023

IHC



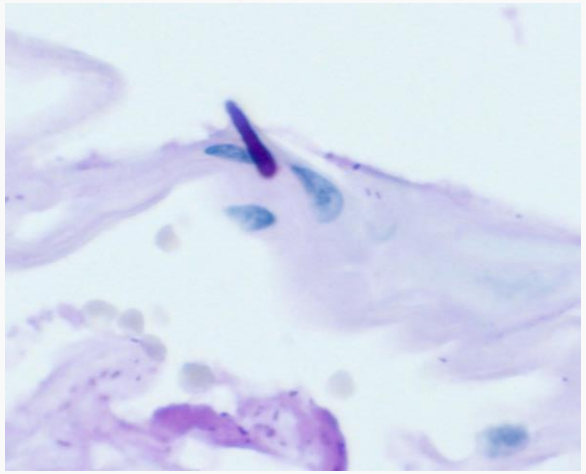
Viral load

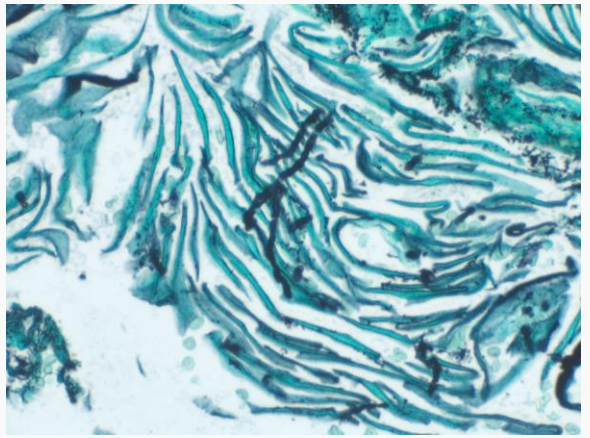
- CMV very high levels
- Valganciclovir therapy well prior to ET
- Cease just prior to ET due to teratogenic effects

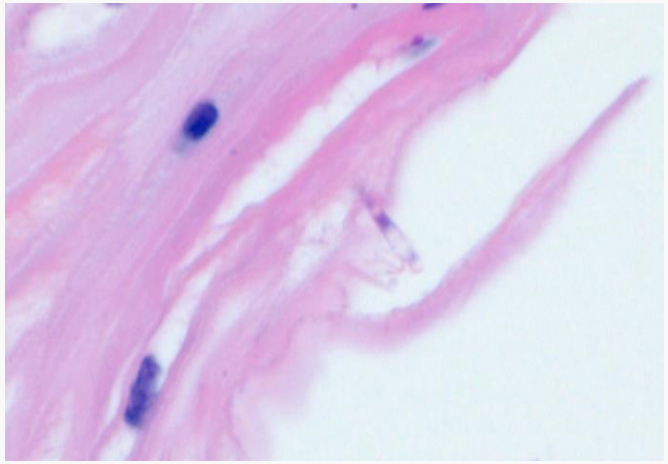
Jan 2024

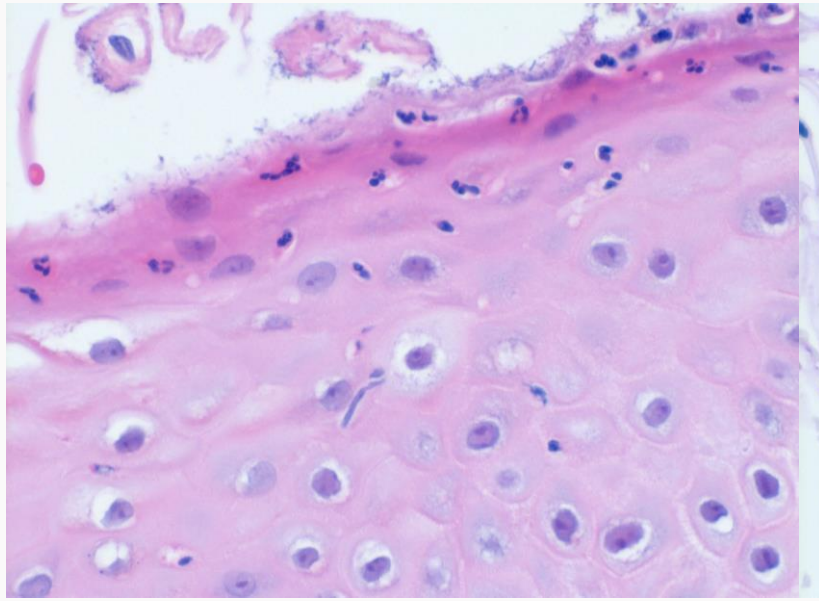
Cervix biopsies

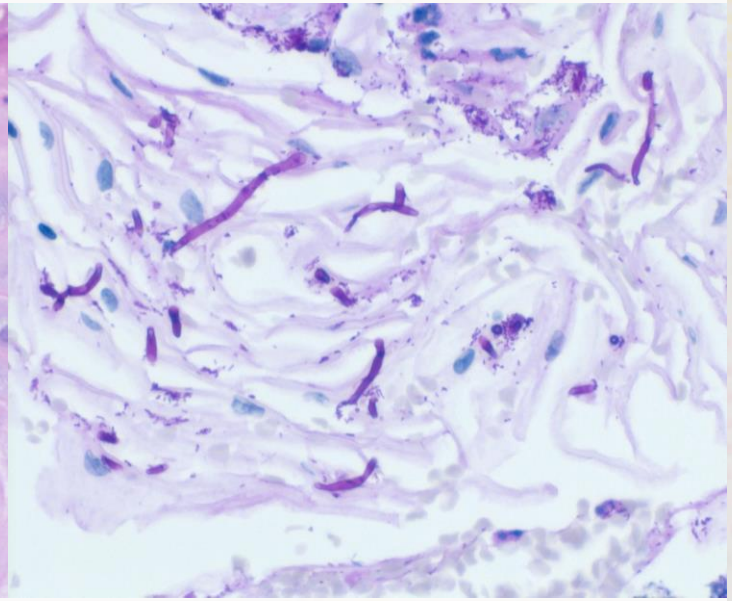
- Fungal elements
- Mixed bacterial colonies











Embryo Transfer 2 (ET2)

- March 2024
- No pregnancy
- Biopsies show no rejection

Complications

- PCOS
- CMV levels
- Donorspecific antibodies
- Rejection
- Fungalinfection

ET3 April 2024

- No pregnancy
- 12 embyros left
- Patient reporting low mood

Ethical debate

“Medical advances in treating infertility and helping women to get pregnant have sparked widespread ethical debate, with some critics saying scientists shouldn't "play God". Others question the morality of spending huge sums to enable women to get pregnant when they have the option to adopt.”

Donor complications

- Loss of bladder function – incontinence
- Fistula
- Hydronephrosis
- Psychological-regret

Future directions

- Potential pair – MRKH recipient, donor had a seizure, recipient withdrawal, donor still keen
- Potential pair – MRKH recipient, lymphadenopathy for workup in donor, probably low grade lymphoma, donor excluded
- Potential pair – hysterectomy for endometriosis at 25 and hereditary angioedema, recipient excluded due to risk
- Potential complete androgen insensitivity syndrome (AIS) genetic male -

Future directions

- Recipients with prior malignancy
  - Completion hysterectomy for CIN / cervical cancer – 5 years?
  - Hysterectomy at 3 years for embryonal sarcoma – 20 years?
  - Postirradiation sarcomas

- **L**: In Dallas and other centres, they do not have a no blanket rule, however they included a patient who had stage 1b cervical cancer 7 years prior to the transplant. She has delivered two babies. Most centres would accept these kinds of patients.

Future directions

- Transgender patients

G: Cooperated with the Rush centre in Chicago, which is a large transgender centre. Including transgenders is not supported in Dallas, and it is not possible to perform these surgeries. In the Rush centre, there been a proposal that female to male transgender people would be the person donating to a male to female transgender.

L: There is also a huge centre in Belgium, who have been looking into this. They have removed a uterus from a female to male transgender, and in the future may potentially look at transplanting the uterus into a trans female. Surgically it is possible, as is achieving a pregnancy, however the ethical component remains the challenging factor

Disclosure

- First successful delivery late 2023 POW
- Second successful delivery due May POW
- Third case underway

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