

“Uterus Transplantation”

Transplantace dělohy v ČR a ve světě

Jiri Fronek

13. Prague ONCO

26.-28. ledna 2022



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I have no disclosures ...



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Uterus Transplantation (UTx)

- Introduction of the method
- History
- Czech uterus transplant trial
 - Indications
 - Preparations and workup
 - Surgery and follow-up
 - Results and childbirhts
- World-wide experientce
- Ethical and other considerations
- Future and possible demand



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Uterus Transplantation (UTx)

- Youngest solid organ transplant method
- Aim is not the transplant but childbirth
- Recipient medically fit and healthy person
- For AUFI patients, 3 groups of indications:
 - MRKH
 - Post hysterectomy
 - Non-functioning uterus
- Temporary transplantation
- Surgery difficult
- Immunosuppression risks
- Alternative to IVF, adoption, surrogacy, ...
- Real demand unknown



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No	Year	Institution	Country	Donor type	Child born	Graft removal	
1	2000	Jeddah	Saudi Arabia	Live	0	Ex	
2	2011	Antalya	Turkey	DBD	0	No	
3	2012	Goteborg	Sweden	Live	2	After birth	
4		Goteborg	Sweden	Live	n/a	Ex	
5		Goteborg	Sweden	Live	2	After birth	
6		Goteborg	Sweden	Live	0	No	
7		2013	Goteborg	Sweden	Live	1	No
8	Goteborg		Sweden	Live	1	No	
9	Goteborg		Sweden	Live	1	No	
10	Goteborg		Sweden	Live	1	No	
11	Goteborg		Sweden	Live	n/a	Ex	
12	2015	?	China	Live	0	?	
13	2016	Cleveland	USA	DBD	0	Ex	
14		IKEM Prague	Czech republic	Live	0	No	
15		IKEM Prague	Czech republic	DBD	n/a	Ex	
16		IKEM Prague	Czech republic	DBD	0	Ex	
17		Dallas	USA	Live	n/a	Ex	
18		Dallas	USA	Live	n/a	Ex	
19		Dallas	USA	Live	n/a	Ex	
20		Dallas	USA	Live	1	After birth	
21		Sao Paolo	Brazil	DBD	n/a	Ex	
22		Sao Paolo	Brazil	DBD	0	No	
23		Tubingen	Germany	Live	0	No	
24		IKEM Prague	Czech republic	Live	0	No	
25		Dallas	USA	Live	0	No	
26		2017	IKEM Prague	Czech republic	DBD	0	No
27			IKEM Prague	Czech republic	Live	0	No
28	IKEM Prague		Czech republic	DBD	0	No	
29	?		China	Live	0	?	
30	Goteborg		Sweden	Live	0	No	
31	Goteborg		Sweden	Live	0	No	
32	Pune		India	Live	n/a	Ex	
33	Pune		India	Live	n/a	Ex	
34	Dallas		USA	DBD	0	No	
35	Dallas		USA	Live	0	No	
36	Dallas		USA	DBD	n/a	Ex	
37	IKEM Prague		Czech republic	Live	n/a	Ex	
38	IKEM Prague		Czech republic	Live	0	No	

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Czech uterus transplant trial

ClinicalTrials.gov Identifier: NCT03277430

- Two-arm study comparing 10 LD and 10 DD UTx
- Preparations since 2012
- Ministry of health permission for unverified clinical method 7/2015
- Recipient having husband or partner, min 10 cryopreserved embryos prior to UTX
- Temporary Tx - Maximum 2 pregnancies or 5 years with the graft
- Hypothesis:
 - The outcomes from deceased and live donor UTx are equal
- First UTx 30/4/2016
- 10/20 UTx done
- 3 children born

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Type of recipients, indications

- Indication in general: AEFI
 - MRKH
 - Post hysterectomy
 - Non-functioning uterus
- CZ Utx trial:
 - All 10 recipients were MRKH syndrome
 - All except one had laparoscopic Vecchietti neo-vagina formation
 - All have their own ovaries
 - All have husband or long-term partner

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Uterus Transplantation (UTx)

- Patients referral, eligibility questionnaire
- Recipients workup, similar to for example kidney transplantation
- Immunology, crossmatches, ...
- Renal function and anatomy
- Gynecology assessment – vagina size and type, ovaries and reserve
- Live donor workup
- Deceased donor assessment on demand ...
- Surgery planned for live donor cases
- Activation on waiting list for deceased donor cases



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Uterus transplantation - surgery

- All procedures in IKEM hospital
- All donor and recipient surgeries performed by transplant surgeon
- Deceased donors donated also other organs e.g. Liver, pancreas, kidneys, ...
- All surgeries open procedures

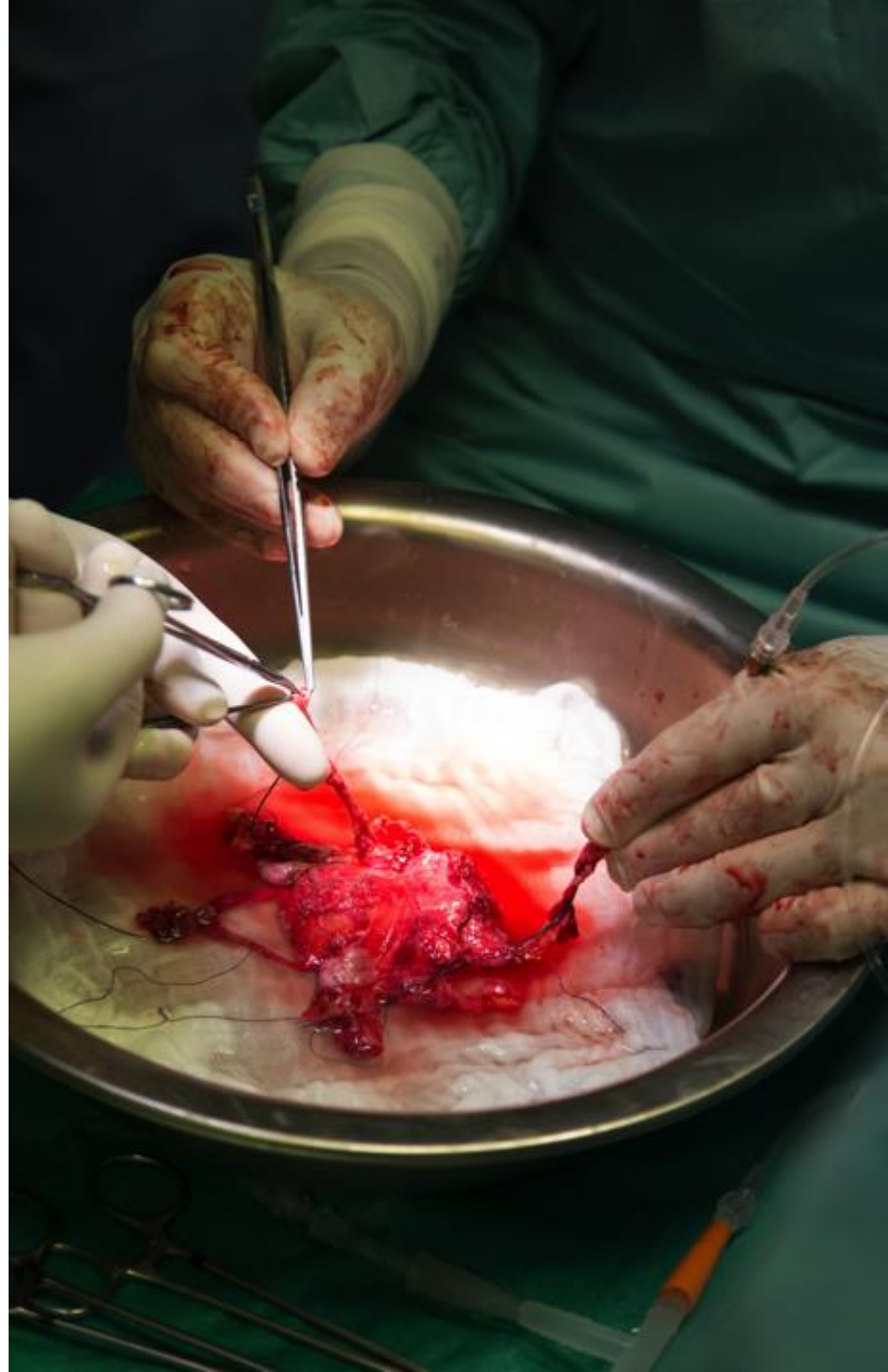
Uterus transplant graft Ischemic and op. times

Case No.	LD	Utx	CIT	anast	
1	5:23	3:29	6:23	2:22	
2		4:05	6:34	1:40	graft ex
3		4:10	2:26	1:03	
4	6:09	3:49	4:43	1:24	
5		4:54	9:09	1:31	
6	7:11	4:56	5:04	1:59	
7		3:53	4:03	1:05	chron rej
8	5:26	3:36	3:54	1:10	graft ex
9	5:32	3:36	4:48	1:04	
10		5:19	5:07	1:21	

Czech Uterus transplant trial Early Complications

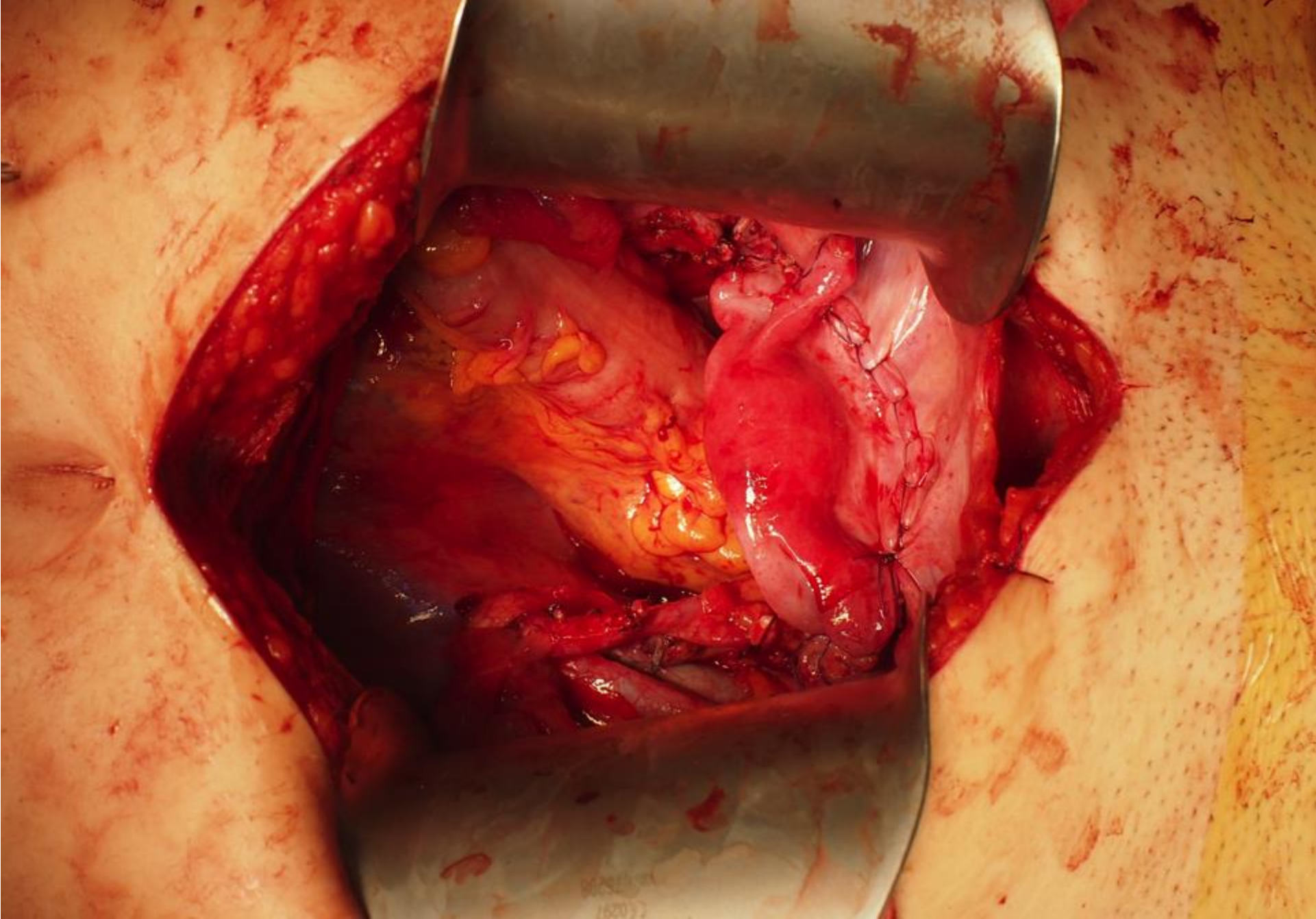
Case	LD	bleeding	thrombosis	infection	leukopenia	stenosis	
1	1					1	
2		1	1				graft ex
3					1		
4	1				1		
5				1	1	1	
6	1				1	1	
7		1	1		1	1	chron rej
8	1			1			graft ex
9	1						
10						1	

Ex-vivo hypothermic HTK
Perfusion via both uterine
arteries, both uterine veins
tied off, ovarian veins used
For graft venous drainage
...











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The usual UTx time scale ...

- Patient/live donor referral, assessment, if eligible ...
- IVF stage I
- Need for at least 10 cryopreserved embryos prior to the Utx
- Uterine transplantation
- Follow up
- IVF stage II
- Pregnancy
- Delivery
- Graft hysterectomy
- Life-long follow-up at the transplant center

The results

• Tx	10
• Graft removal	
• Early (Thrombosis)	2
• late (infection/rejection)	2
• After delivery	2
• Recipients for transfer	7
• Still being transferred 11/2021	4
• No. of transfers	... (50+)
• Ongoing gravidity	0
• Abortion total	2+
• Early. ...	
• Advanced gr.	2
• Delivery	3
• 29/8/2019 boy, deceased donor	
• 11/11/2019 girl, living donor	
• 7/1/2021 girl, living donor	

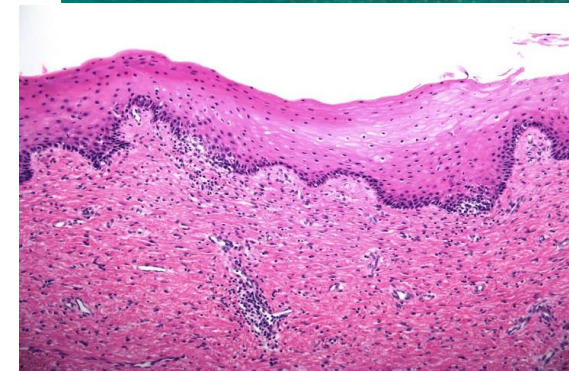
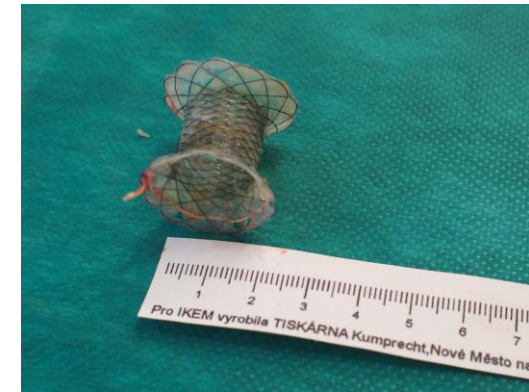


Table 7. Pregnancy outcomes of 10 consecutive uterus transplantations.

Case	Donor	Grav.	Par.	Menop.	Menses (Day)	Embryo Transfers (Day Post-Transplant)	Miscarriage Days to ET/Gest. Day	Live Birth (Day)
1	LD1	2	2	yes	45	8× (551, 641, 711, 858, 947, 977, 1031, 1482→P)		1713, girl, 35 w + 3
2	DD1	N/R	1	yes	N/A	N/A Graft loss, day 7	-	-
3	DD2	0	0	no	103	11× (245, 322, 405, 537, 638→M, 908, 1204, 1234, 1268, 1368→M, 1533→M)	3× (638/48, 1368/42, 1533/49)	
4	LD2	2	2	yes	133	11× (340, 417, 459, 578, 648, 814, 921, 963, 1095, 1192, 1322)		
5	DD3	0	0	no	58	4× (414, 443, 627, 725→LB)		950, boy, 34 w + 6
6	LD3	2	1s.c.	yes	35	5× (463, 582, 676, 1200, 1236)		
7	DD4	N/R	1	yes	no	N/A Graft loss, day 213	-	-
8	LD4	4	3	no	N/A	N/A Graft loss, day 15	-	-
9	LD5	2	2	no	86	5× (282, 373, 490→LB, 1079, 1114)		721, girl, 36 w + 2
10	DD5	N/R	N/R	no	26	6× (433, 469 (2 emryos), 503, 645, 719→M, 964)	1×, 719/137	

The complications

- Plan for 20 DBD+LD, 10 UTx done – 5 DBD, 5 LD
- 4/10 grafts removed (LD/DBD, 7D thrombosis, chronic rejection)
- 5/8 Vaginal anastomosis stenosis (stenting)
- 1/8 One re-operation for ves-vag phistula
- 5/8 Leucopenia (viral infections (HSV), over-immunosupression?, ...)
- Rejection: 130+ biopsies, 2 severe, 1 moderate (same patient), 30! Mild rejections, 20! Border line changes, ...
- AZA after rejection episode
- One conversion from TAC to Envarsus



Uterus transplantation - summary

- Smallest organ ever transplanted (3x3x5 cm)
- Tiny vessels, microsurgery, op. microscope
- Ideally anastomosing all 6 vessels, if uterine or ovarian veins no good only one of those but both sides
- Vaginal anastomosis deep in the inherited absence cases, narrow in some ...
- No function to be measured after Tx
- Regular ultrasound doppler and cervix biopsies

Immunosuppression:

- Thymo/TAC/MMF/ster
- Steroid 3W withdrawal, MMF 3+M withdrawal
- Long term TAC monotherapy with levels 5-10

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The world experience

- First attempts ... Saudi, Turkey
- First Trial ... Sweden 9 cases, second trial in place now
- Czech, Prague 10 cases
- USA Cleveland
- USA Dallas
- Germany Tübingen
- Some more centres, mostly small numbers 1-3 cases
- More programs in preparation ...

ISUTx – International Society for Uterine Transplantation

Formed January 2016 in Gothenburg, Sweden

Youngest transplant society

Since 2021 under TTS (The Transplantation Society)

First funding president:

Mats Brannstrom

First president elect 2019-2021

Jiri Froněk

Second President elect 2022-2023

Jiri Froněk

World registry:

80+ Utx

40+ childbirths

18 in europe

3 CZ

All children born healthy

- **Froněk, J.**, L. Janousek, J. Kristek, J. Chlupac, M. Pluta, R. Novotny, J. Maluskova, and M. Olausson. "Live Birth Following Uterine Transplantation from a Nulliparous Deceased Donor." [In eng]. *Transplantation* 105, no. 5 (May 1 2021): 1077-81.
- **Froněk, Jiri**, Jakub Kristek, Jaroslav Chlupac, Libor Janousek, and Michael Olausson. "Human Uterus Transplantation from Living and Deceased Donors: The Interim Results of the First 10 Cases of the Czech Trial." *Journal of Clinical Medicine* 10, no. 4 (2021): 586.

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Ethical considerations I.

Live donor:

- Not life saving organ, but ...
- Ovaries/age/atherosclerosis/long-term risks
- Will for own child
- The recipients partner

Deceased donor:

- Med/gyn history on the day of retrieval,
- Retrieval hysteroscopy and cervix cytology 24/7
- Family consent form?

UTx recipient:

- MRKH + renal anomalies, otherwise healthy recipient
- Age limitations
- immunosuppression toxicity
- Long-term risks

Ethical considerations II.

- The child:
 - Aim is the healthy child after „normal“ pregnancy ...
 - Always Cesarean section
 - All children born till now healthy
 - Risks not clear: abortion, inherited disease, anomalies, early death
- Multidisciplinary team
- Tx chir, gyn, IVF, immunology, pathology, psychologist, ...

Other considerations

Pending difficulties ...

- Age restrictions
- Donated eggs/sperm
- Trans-gender recipient
- Solo mother without partner/husband?
- Financial issues
- Infertility is a stigma in many countries ...
- Surrogacy ethically and medically difficult, illegal in some countries

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Future – possible demand for UTx

- Demand up to 300/per mil
- in CZ possibly 3000+ potential patients
- Safety and efficacy still to be proven (first 100 world cases to be reviewed)
- The needs:
 - Funding
 - More referring centres
 - Inter-disciplinary cooperation

Uterus transplantation (UTx)

- On the forum of Prague ONCO ...
- One of the indications for UTx is uterus absent
- In case of cervical cancer, after hysterectomy, no other own children, long-term in the malignancy remission ...
- Such woman may benefit from uterine transplantation, keep it in mind for those patients please ...

Thank you for attention

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