JİNEKOLOJİK ENDOSKOPİ PLATFORMU

Uterus Transplantation

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6. MİNİMAL İNVAZİV JİNEKOLOJİK CERRAHİ KONGRESİ

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Kongre Merkezi,
Ataşehir - İSTANBUL

- Uterus tx indications
- Brief history
- Status in the World
- Where are we now, as Turkey?
- Future pespectives

Uterus transplantation

Uterine Factor Infertility

- UFI estimated to have a prevalence as high as 1/500 reproductive-aged women
- The prevalence of absolute UFI ~ 20,000 women of fertile age/ 100 million population

Table 1 Causes of uterine factor infertility that may be treatable by uterine transplantation

No uterus
Congenital uterine absence (Müllerian agenesis/Mayer-Rokitansky-Küster-Hauser (MRKH)-syndrome)
Hysterectomy
Cervical/uterine malignancy
Leiomyoma
Obstetric bleeding
Atony
Malplacentation (placenta accreta/percreta)
Uterine rupture
Uterus present
Leiomyoma
Adenomyosis
Multiple miscarriage/implantation failure
Radiation damage
Uterine malformation
Partly unicornuate uterus
Partly bicornuate uterus
Hypoplastic uterus
Cervical incompetence with multiple miscarriages
Post multiple conisation procedures
Post trachelectomy procedure
Intrauterine adhesions not treatable by hysteroscopic resection

Alternatives??

- Gestational surrogacy → genetic child

  →Not legal e.g. in Turkey

- Adoption

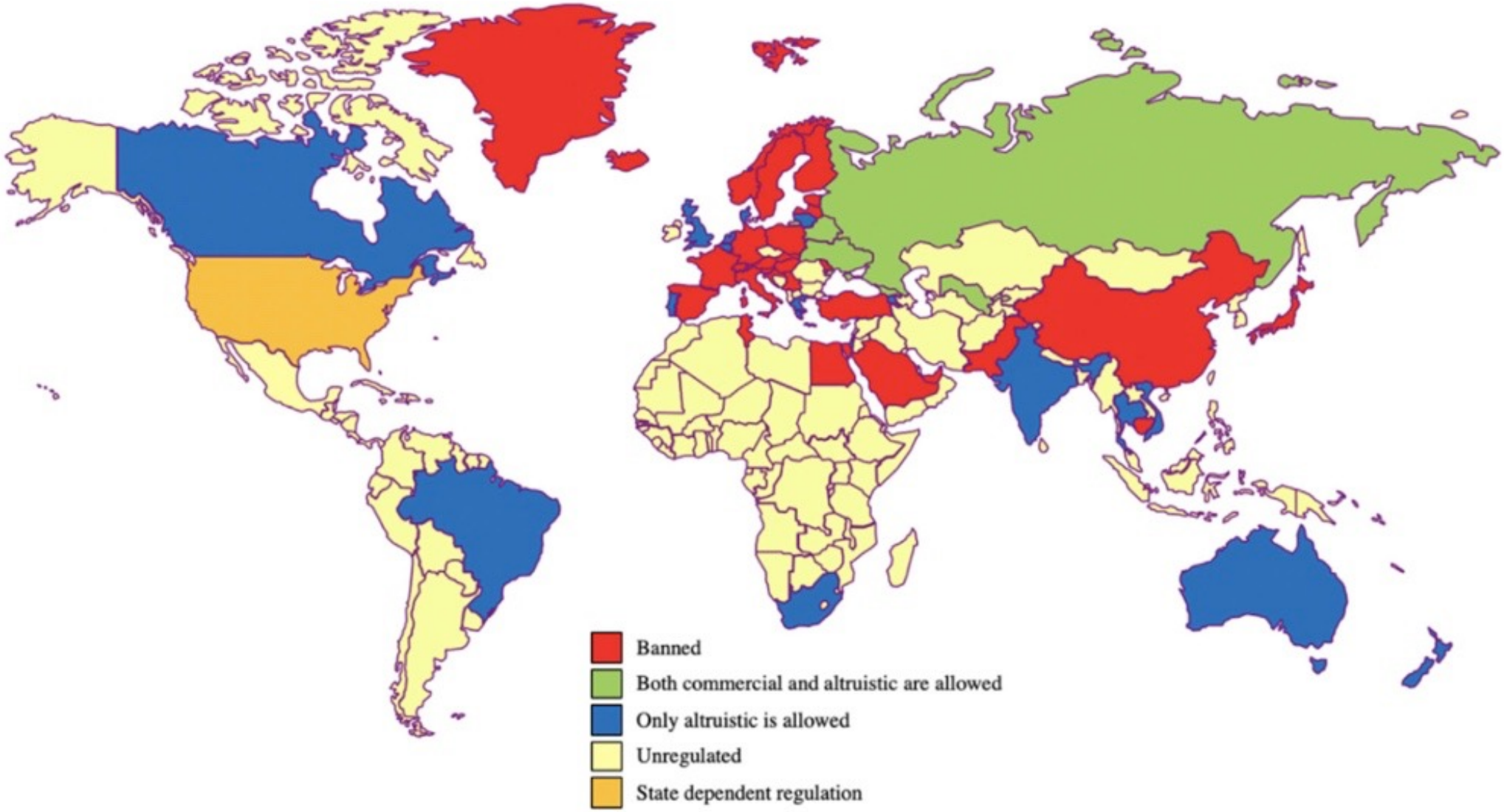


Figure 1. International variation of surrogacy law.

- Uterine transplantation is life propagating
- the first type of ephemeral organ transplantation
- Multidisciplinary approach
  - Transplant team (surgeon, immunologist, nephrologist)
  - Gyn oncologist
  - ICU specialist
  - Psychologist
  - Psychiastrist
  - MFM speacialist
  - Bioethicist

- UTx classified as a vascularized composite allograft transplantationsuch as hand and face
- Akdeniz University
  - 5 face transplants
  - 4 double hand
  - 2 uterus transplantation


CESAR DIAZ-GARCIA

Brief History

Eraslan et al
-1960s
-autotransplantation in dogs
-tubal transplantation

Arch Surg—Vol 92, Jan 1966

Replantation of Uterus and Ovaries in Dogs, With Successful Pregnancy

SADAN ERASLAN, MD; ROBERT J. HAMERNIK, MD;
AND JAMES D. HARDY, MD, JACKSON, MISS

Değerli Hocamız
Prof. Dr. Şadan ERASLAN

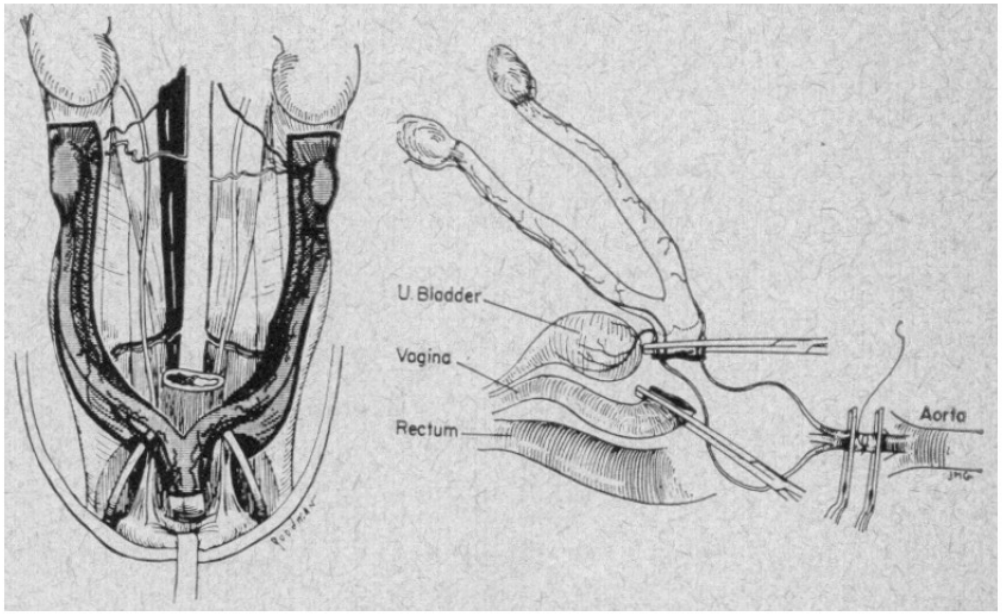


Fig 1.—*Left,* Incision of peritoneum and vagina with ovaries for total removal of organ. *Right* Completion of mobilization of uterus and ovaries.

Fig 2.—*Left,* Salpingogram which shows patency of uterine horns. *Right,* Aortogram of pregnant animal. *Arrow* indicates level of arterial anastomosis.

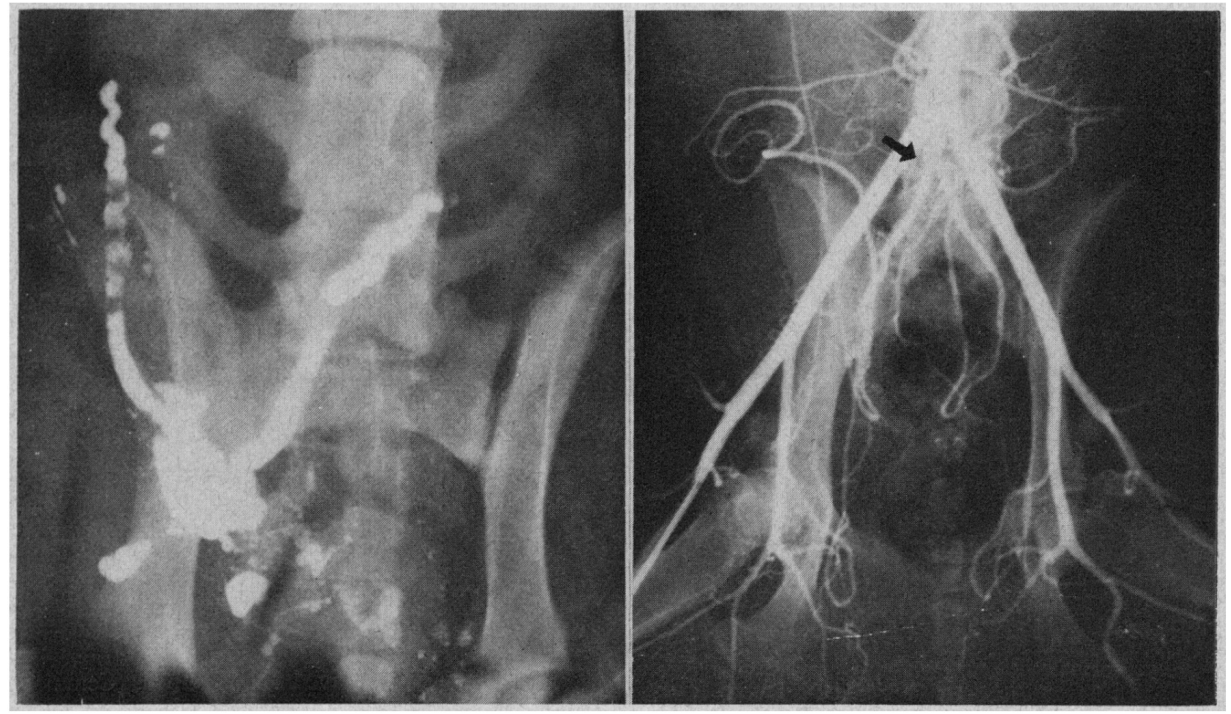
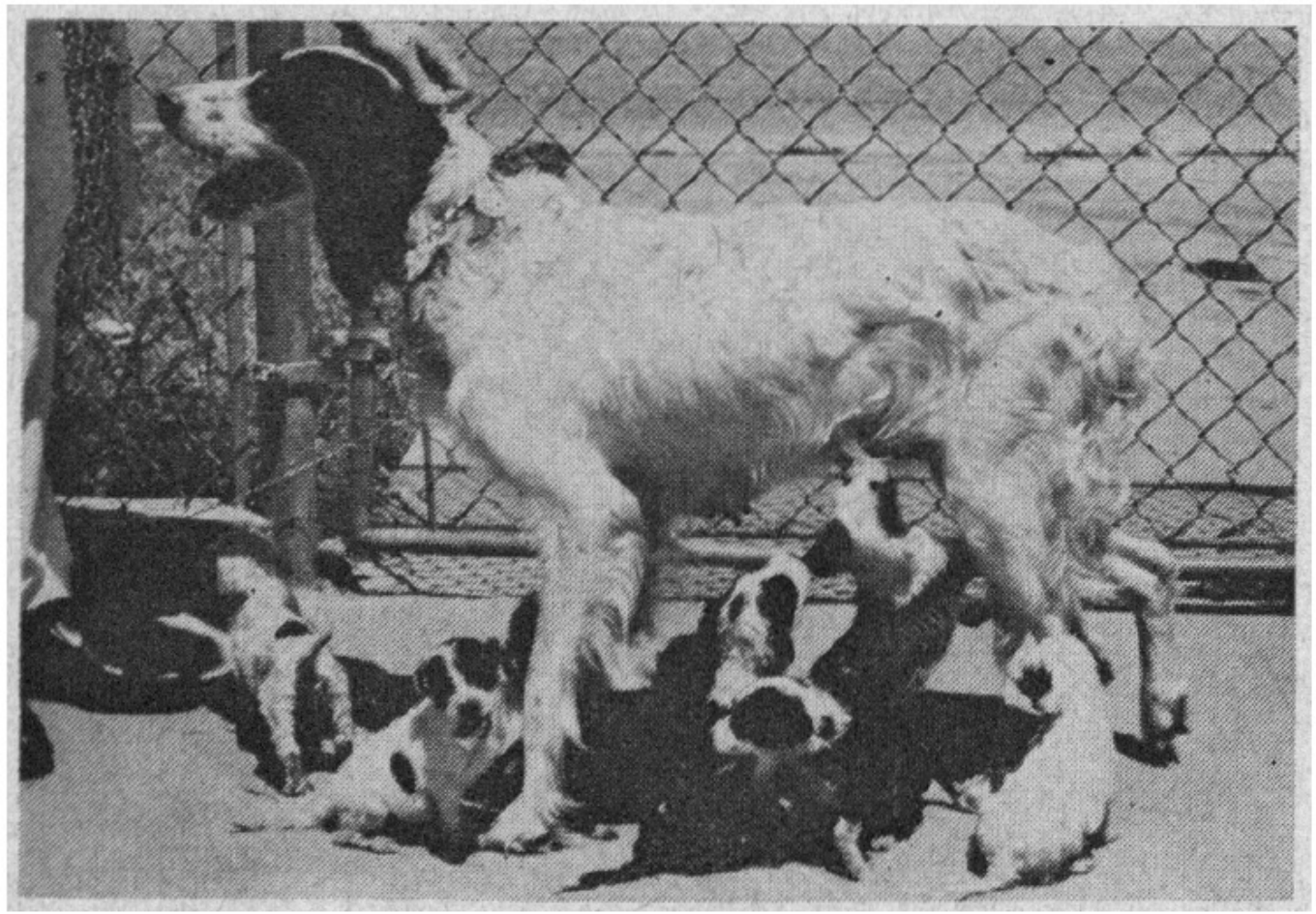
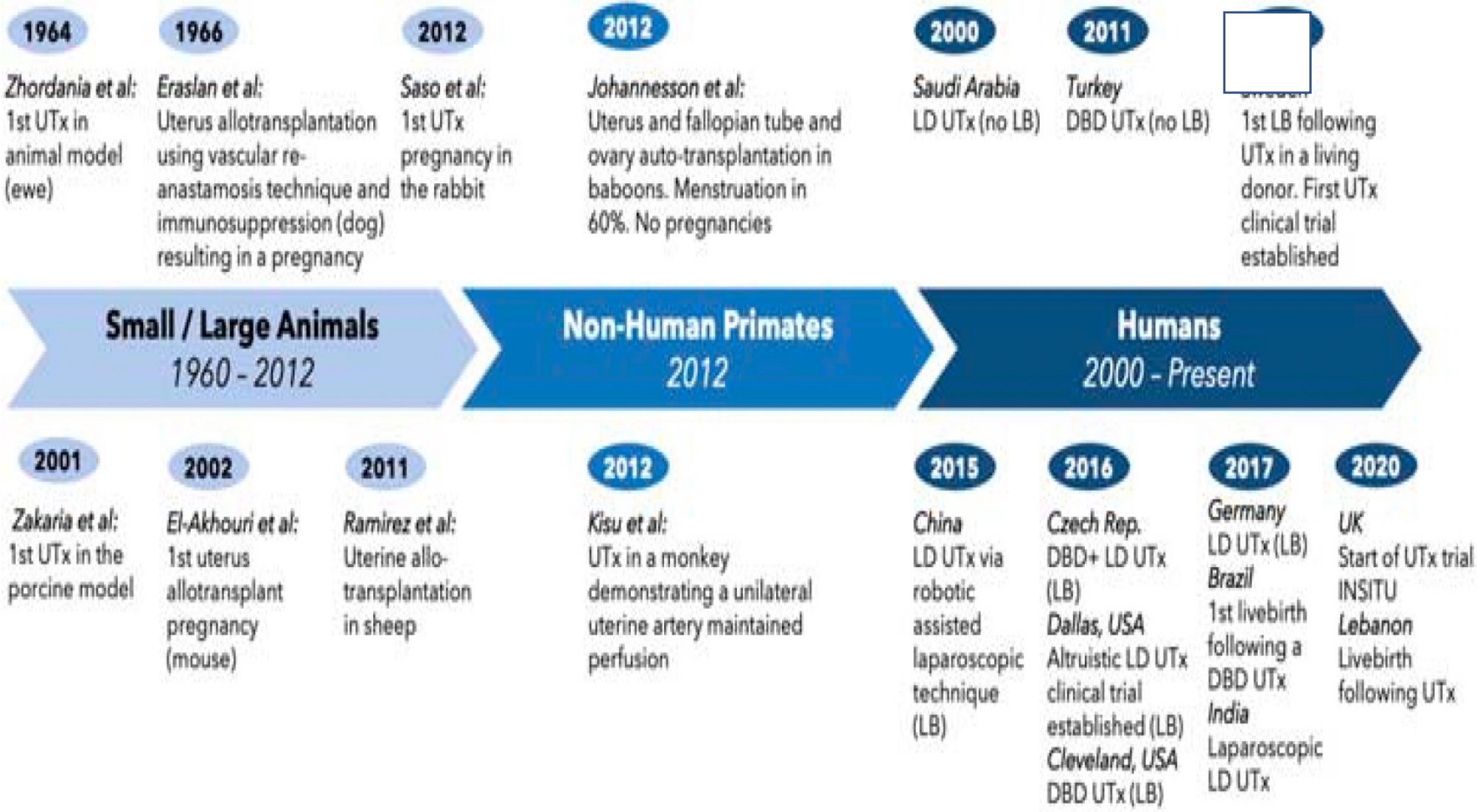
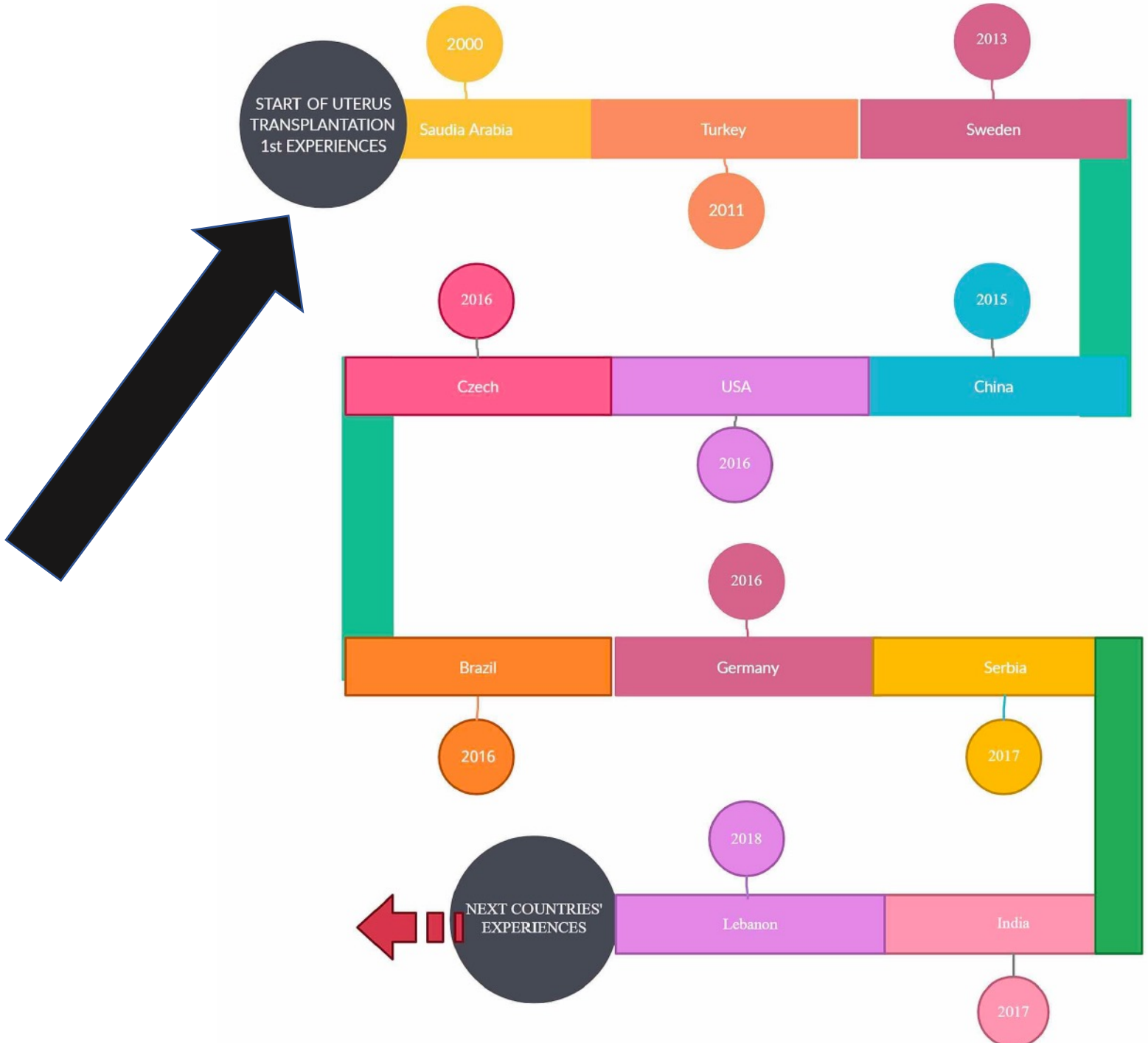


Fig 4.—Animal with puppies six weeks following delivery. This represents second postreplant pregnancy for this animal, abortion having followed exploratory laparotomy in first instance.




1964
Zhordania et al:
1st UTx in animal model (ewe)
1966
Eraslan et al:
Uterus allotransplantation using vascular re-anastamosis technique and immunosuppression (dog) resulting in a pregnancy
2012
Saso et al:
1st UTx pregnancy in the rabbit
2012
Johannesson et al:
Uterus and fallopian tube and ovary auto-transplantation in baboons. Menstruation in 60%. No pregnancies
2000
Saudi Arabia
LD UTx (no LB)
2011
Turkey
DBD UTx (no LB)
1st LB following UTx in a living donor. First UTx clinical trial established
Small / Large Animals
1960 - 2012
Non-Human Primates
2012
Humans
2000 – Present
2001
Zakaria et al:
1st UTx in the porcine model
2002
El-Akhouri et al:
1st uterus allotransplant pregnancy (mouse)
2011
Ramirez et al:
Uterine allo-transplantation in sheep
2012
Kisu et al:
UTx in a monkey demonstrating a unilateral uterine artery maintained perfusion
2015
China
LD UTx via robotic assisted laparoscopic technique (LB)
2016
Czech Rep.
DBD+ LD UTx (LB)
Dallas, USA
Altruistic LD UTx clinical trial established (LB)
Cleveland, USA
DBD UTx (LB)
2017
Germany
LD UTx (LB)
Brazil
1st livebirth following a DBD UTx
India
Laparoscopic LD UTx
2020
UK
Start of UTx trial INSITU
Lebanon
Livebirth following UTx


START OF UTERUS TRANSPLANTATION 1st EXPERIENCES
2000
Saudia Arabia
Turkey
2011
2013
Sweden
2016
Czech
USA
2016
2015
China
2016
Brazil
Germany
2016
Serbia
2017
2018
NEXT COUNTRIES' EXPERIENCES
Lebanon
India
2017


(2012)
SWEDEN*
17 LD-Utx, 10 Livebirths
(First Livebirth from LD-UTx in 2014)
(2018)
BELGIUM
1 DD, No Livebirth
(2016)
CZECH REPUBLIC*
10 (5LD-5DD) Utx, 3 Livebirths
(2016)
GERMANY*
4 LD-Utx, 2 Livebirths
(2017)
SERBIA
1 LD-Utx, 1 Livebirth
(2011)
TURKEY
2 DD-Utx, 2 Livebirths
(First technically successful Utx in 2011)
(2018)
FRANCE*
2 LD-Utx, 1 Livebirth
(2020)
SPAIN
2 LD-Utx, No Livebirth
(2020)
ITALY
1 DD-Utx, 1 Livebirth
(2015)
CHINA
3 LD-Utx, 1 Livebirth
(2019)
MEXICO
Donor type: NA
(2018)
LEBANON
1 LD-Utx, 1 Livebirth
(2017)
INDIA
6 LD-Utx, 1 Livebirth
(2016)
USA*
Dallas Trial 20 UTx (LD + DD) – 14 Livebirths
Cleveland 8 Utx (DD) – 5 Livebirths
Philadelphia: 3 UTx (LD + DD) – 2 Livebirth
(Largest Livebirth Series up-to-date)
(2016)
BRAZIL
2 DD-Utx, 1 Livebirth
(First livebirth from DD-UTx in history)
(2000)
S. ARABIA
(First LD-UTx in history - failure)
Year in parenthesis – timing of first UTx and/or clinical trial
*Countries with published clinical trials

Table 2. Uterus transplantation trials and cases, with rates of surgical success and major post-operative complications of live donors.

Trials (city)*	From year	Type of case	# cases	# Surgical successes	# LD cases	# LD post-op complications	Reference
Sweden	2012	Laparotomy LD	9	7 (78%)	9	1 (11%)	Brännström *et al.* (2014)
USA (Cleveland)	2016	DD	8	6 (75%)	n/a	n/a	Richards *et al.* (2021)
Czech Republic	2016	Laparotomy LD	5	4 (80%)	5	2 (40%)	Fronek *et al.* (2021)
		DD	5	3 (60%)	n/a	n/a	
USA (Dallas)	2016	Laparotomy LD	13	8 (62%)	13	2 (15%)	Testa *et al.* (2020)
		Robotic LD	5	5 (100%)	5	2 (40%)	
		DD	2	1 (50%)	n/a	n/a	
Germany	2016	Laparotomy LD	4	4 (100%)	4	0 (0%)	Brucker *et al.* (2020)
India	2017	Laparoscopy LD	4	4 (100%)	4	0 (0%)	Puntambekar *et al.* (2018, 2019)
Sweden	2017	Robotic LD	8	6 (75%)	8	1 (13%)	Brännström *et al.* (2020a,c)
Single cases (city)*	**Year**	**Type of case**	**# cases**	**# Surgical successes**	**# LD cases**	**# LD post-op complications**	**Reference**
Saudi Arabia	2000	Laparotomy LD	1	0 (0%)	1	0 (0%)	Fageeh *et al.* (2002)
Turkey	2011	DD	1	1 (100%)	n/a	n/a	Ozkan *et al.* (2013)
China	2015	Robotic LD	1	1 (100%)	1	0 (0%)	Wei *et al.* (2017)
Brazil (Sao Paulo)	2016	DD	1	1 (100%)	n/a	n/a	Ejzenberg *et al.* (2019)
Lebanon	2018	Laparotomy LD	1	1 (100%)	1	0 (0%)	Akouri *et al.* (2020)
France	2019	Robotic LD	1	1 (100%)	1	1 (100%)	Ayoubi *et al.* (2022)
Spain	2020	Robotic LD	1	1 (100%)	1	0 (0%)	Carmona *et al.* (2021)
Brazil (Barretos)	2021	Robotic LD	1	1 (100%)	1	0 (0%)	Vieira *et al.* (2021)
All cases		**Type of case**	**# cases**	**# Surgical successes**	**# LD cases**	**# LD post-op complications**	
		Laparotomy LD	33	24 (73%)	33	5 (15%)	
		Robotic LD	17	15 (88%)	17	4 (24%)	
		Laparoscopy LD	4	4 (100%)	4	0 (0%)	
		DD	17	12 (71%)	n/a	n/a	
Totals		**All types**	**71**	**55 (77%)**	**54**	**9 (17%)**	

* City indicated if more than one city in a country. LD, live donor; DD, deceased donor.

Livebirths of Uterus Transplantation

By February–2023, search from peer–reviewed publications and/or internet databases identified 45 livebirths have been born to 40 UTx women following a viable pregnancy course and five women gave birth to consecutive siblings in 84 procedures so far *(see supplemental table)*.

Supplemental Table. Antenatal and neonatal outcome in uterus transplantation

UTx year	Donor type LD/ DD	Cause of infertility	Donor age *(year)*	Recipient age *(year)*	Antenatal complication	sex	Indication for delivery	Gestational age *(week)*	Birthweight *gr (p)*	Height *(cm)*	HC *(cm)*	Apgar Score[a]	Neonatal complication	NICU stay *(day)*	Gestational age at discharge *(week)*
2011								**TURKEY**							
	DD	MRHK	22 Non-directed	21	PTL, PE, PPROM (10w), IUGR, oligohydramnios	M	PE, PTL, IUGR	28 0/7	760 (9)	34	24	7-8-8	RDS (CPAP), SGA, sepsis, BPD, inguinal hernia, hip dysplasia	79	39 2/7
	DD	MRHK	37 Non-directed	34	GDM, PTL, PPROM (36h), hypothyroidism	F	PTL	29 0/7	1720 (99)	40	29	7-8-8	RDS (CPAP), LGA, hypoglycemia	47	35 5/7
2014								**SWEDEN**							
	LD	MRHK	52 Mother	35	PE, single kidney, anemia	M	PE	31 6/7	1775 (52)	40,0	-	9-10-10	RDS, jaundice	16	33 2/7
	LD	MRHK	58 Mother	28	anemia, OC	M	OC	34 4/7	2335 (45)	44,0	-	9-10-10	RDS	5	35 2/7
	LD	MRHK	54 Mother	32[b]	-	M	per protocol	35 1/7	2700 (76)	46,0	-	8-8-8	RDS	7	36 1/7
	LD	MRHK	54 Mother	32	-	F	per protocol	37 0/7	2600 (30)	44,0	-	9-10-10	-	-	
	LD	MRHK	50 Mother	32	PE, single kidney, PPROM, OC, p. previa	M	PE, OC	34 5/7	3074 (94)	47,0	-	3-7-10	RDS, LGA PPV at delivery	2	35 0/7
	LD	MRHK	61 Mother	27[b]	PE, single kidney	F	PE	35 3/7	2552 (58)	46,0	-	9-10-10	-	-	
	LD	MRHK	61 Mother	27	-	M	per protocol	35 6/7	2745 (55)	48,0	-	9-10-10	-	2	36 1/7
	LD	MRHK	53 Mother	27[b]	-	F	per protocol	37 1/7	2676 (34)	45,0	-	9-10-10	-	-	
	LD	MRHK	53 Mother	27	-	F	per protocol	38 0/7	3078 (52)	47,0	-	9-10-10	-	-	
	LD	MRHK	62 Mother	33	minor vaginal hemorrhage	M	per protocol	36 1/7	2894 (62)	48,0	-	9-10-10	mild RDS (CPAP)	5	37 0/7
2015								**CHINA**							
	LD	MRHK	43 Mother	22	SCH, PTL	M	PTL	33 6/7	2000 (29)	-	-	10-10-10	-	-	
2016								**USA[c]**							
	LD	MRHK	34 Non-directed	30	sCrea↑, SCH	M	sCrea↑	33 1/7	1995 (44)	43,0	31	8-9	RDS (CPAP)	33	37 6/7
	LD	MRHK	36 Non-directed	28	-	F	per protocol	36 6/7	2920 (76)	34,0	49	9-9	clitoromegaly anterior caudally displaced urethra	Newborn nursery	
	LD	MRHK	36 Non-directed	28	-	F	per protocol	38 0/7	3370 (74)	50,5	34,5	9-9	-	-	
	DD	MRHK	33 Non-directed	36	GHT	F	per protocol	38 0/7	3470 (82)	48,5	36,5	9-9	-	-	
	LD	MRHK	39 Non-directed	25	GDM	F	per protocol	35 6/7	2860 (74)	44,0	33	8-8	RDS (CPAP)	7	36 6/7
	LD	MRHK	35 Non-directed	24	PTL, single kidney, CI	F	PTL	30 6/7	1770 (83)	43,0	28	7-8	RDS (CPAP)	38	36 2/7
	LD	MRHK	32	20	-	M	per protocol	37 2/7	3140 (62)	47,0	35	8-8	hypoglycemia	6	38 1/7

	LD	MRHK	Non-directed 32	20	.PTL	F	PTL	36 6/7	-						
	LD	MRHK	Non-directed 39	31	-	M	per protocol	37 0/7	2960 (51)	47,0	35	8-9	TTN (no need for O_2)	3	37 3/7
	LD	Hyster-ectomy leiomyoma	Non-directed 43	31	p. accreta, PE	F	PE	36 6/7	2400 (18)	46,5	33	8-9	-	Newborn nursery	
	LD	MRHK	Non-directed 30	31	GHT, polyhydramnios	M	per protocol	37 0/7	3025 (29)	50,0	34	4-9	TTN	4	37 4/7
	LD	MRHK	Non-directed 38	33	PTL, p.previa, vaginal bleeding	M	PTL, p.previa	32 4/7	2350 (88)	45,0	32	7-8	PPV at delivery RDS (CPAP), preterm apnea anemia	29	36 5/7
	LD	MRHK	-			M	PPROM	37 0/7					-		
	LD	MRHK	Non-directed 38	30	PTL	F	PTL	35 6/7	2325 (29)	50,0	32	8-8	Apnea, O_2 therapy and stimulation	3	36 1/7
	DD	MRHK	-			F	-	34 2/7	1930 (26)	-		9-9	-		
	DD	MRHK			GDM, GHT PPROM		GHT, GDM	34 2/7	2480	-		8-9-9	-		
	DD	MRHK	?	30	GHT, *sCrea*↑	M	*sCrea*↑	34 6/7	2600 (80)	-		7-8		7	35 0/7
	DD	MRHK	-		-	-		37 1/7	3022	-		8/9	-		
2016	**CZECH REPUBLIC**														
	LD	MRHK	53 Mother	30	GDM, p.previa Vesicovaginal fistula, recurrent UTI, sCrea↑ *before* pregnancy	F	per protocol	35 3/7	2115 (20)	-		9-10-10	-	-	
	DD	MRHK	19 Non-directed	24	GDM (insülin use), vaginal stenosis, *sCrea*↑, leukopenia, Cl.difficile colitis with perforated appendicitis	M	per protocol	34 6/7	2740 (75)	-		7-9-9	-	-	
	LD	MRHK	48 Mother	26	GHT	F	per protocol	36 2/7	2300 (19)	-		10-10-10	-	-	
	GERMANY														
	LD	MRHK	23 Mother	23	PTL, PPROM	M	PTL	35 1/7	2180 (21)	45,0	-	9-10-10	hypoglycemia, hypothermia,	3	35 4/7 (2376 gr)
2017	**ITALY**														
	DD	MRHK	37 Mother	30	COVID	F	Fever (COVID)	34 0/7	1700 (14)	-			Resp-assistance	1	
	LD	Asherman	45 Mother	24	GHT, oligohydramnios, IUGR	F	oligo-hydramnios	34 0/7	1450 (4)	-			SGA, flood O_2	+	
2018	**LEBANON**														
	LD	MRHK	50 Mother	24	PTL, anemia	F	PTL	35 1/7	2620 (70)	47	-	9-10-10	-	-	
	SERBIA														
	LD	MRHK	38 Twin	38	-	M	-	38 0/7	2948 (32)	-					
2019	**FRANCE**														
	LD	MRHK	57 Mother	34	PTL, PE, sCrea↑	F	PE, PTL	32 4/7	1845 (54)	-		7/8	adrenal cyst, COVID, inguinal	48	39/7

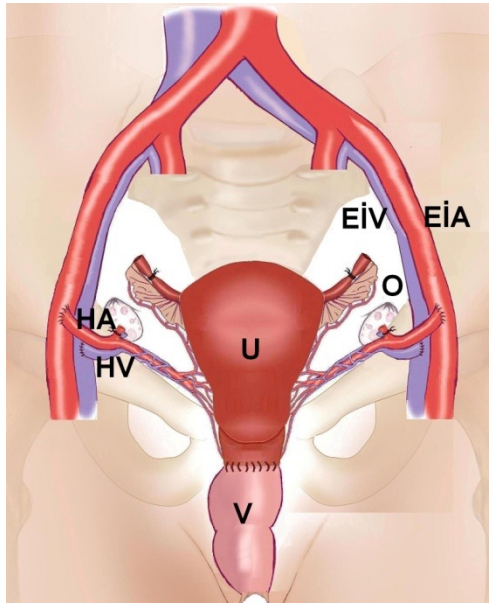
2020	**ITALY**													
	DD	MRHK	37 Mother	30	COVID	F	Fever (COVID)	34 0/7	1700 (14)	-		Resp-assistance	1	

Utx transplants

- Mostly live donor
- Live donor complication rate → 10 % (requiring further correcting surgery)
- RKMH, pp hysterectomy
- globally, 71% of Utx grafts have survived
- Pregnancies complicated by preeclampsia, cholestasis
- 76% of deliveries <37 weeks gestation

First Successfull Uterus Tx From Cadaver

- Turkey in 2011
- Deceased donor
- MRKH synd
- Postop 20 days menstruation



External iliac arteries and veins and Uterine arteries and uterin veins

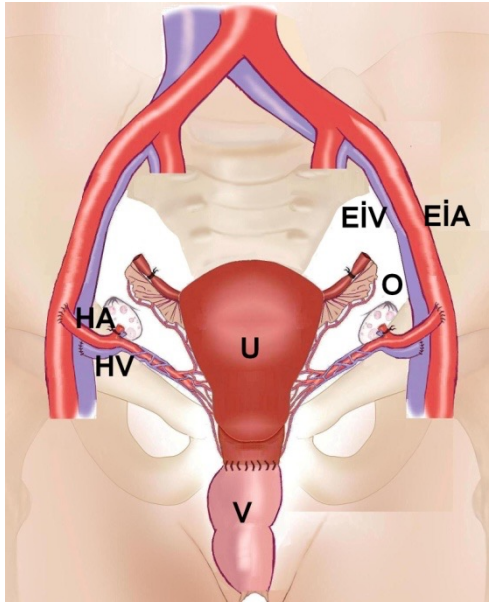
End to side anastomoses

Sacrouterine ligament

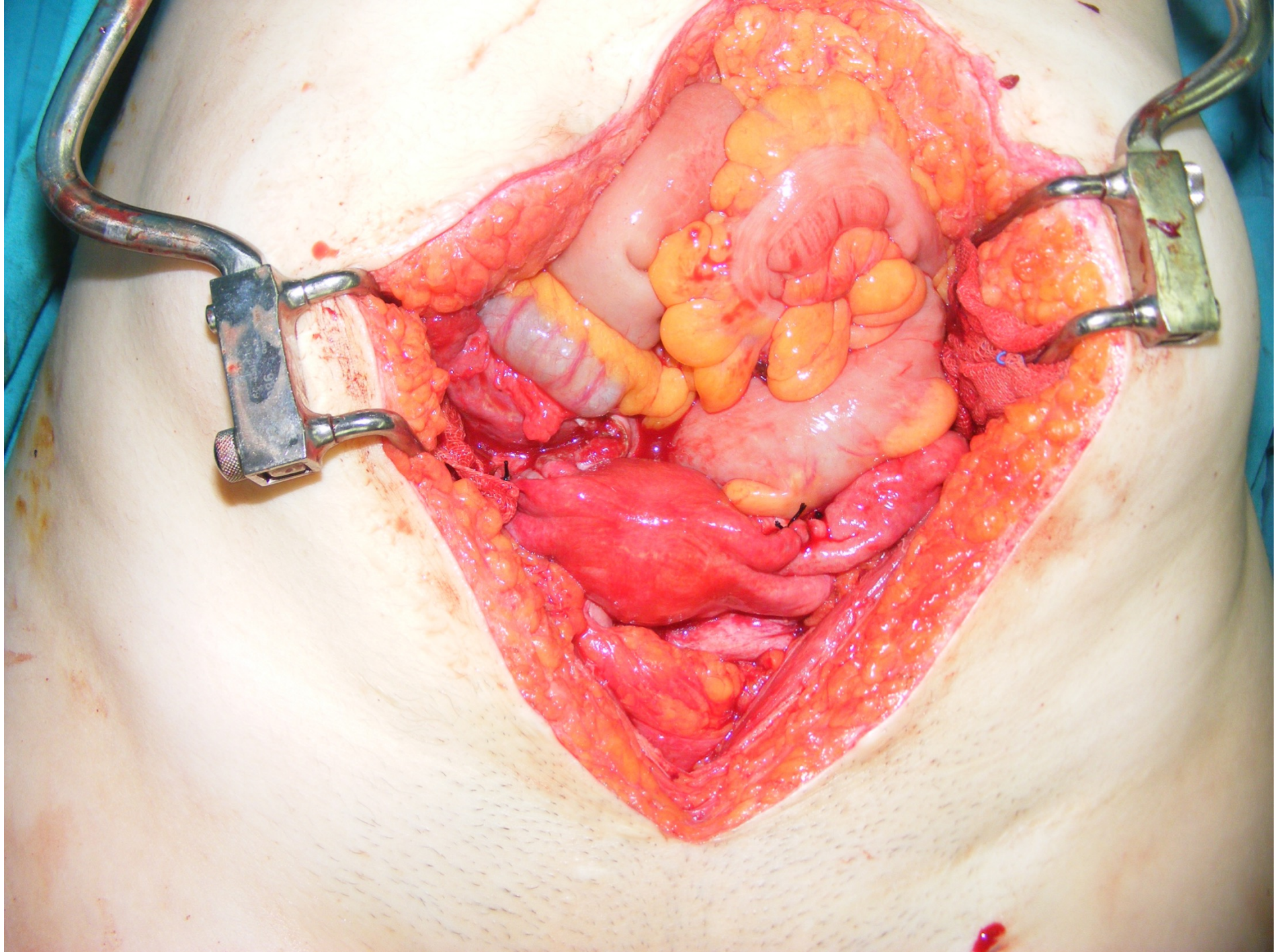
Round ligament

Vagino-neovaginal anastomoses

Vesicouterine peritoneal reflection



The entire procedure →8 hours
2 hours→allograft procurement
30 minutes for transfer and the
(remaining time for uterus implantation)



Immunosuppressive protocol

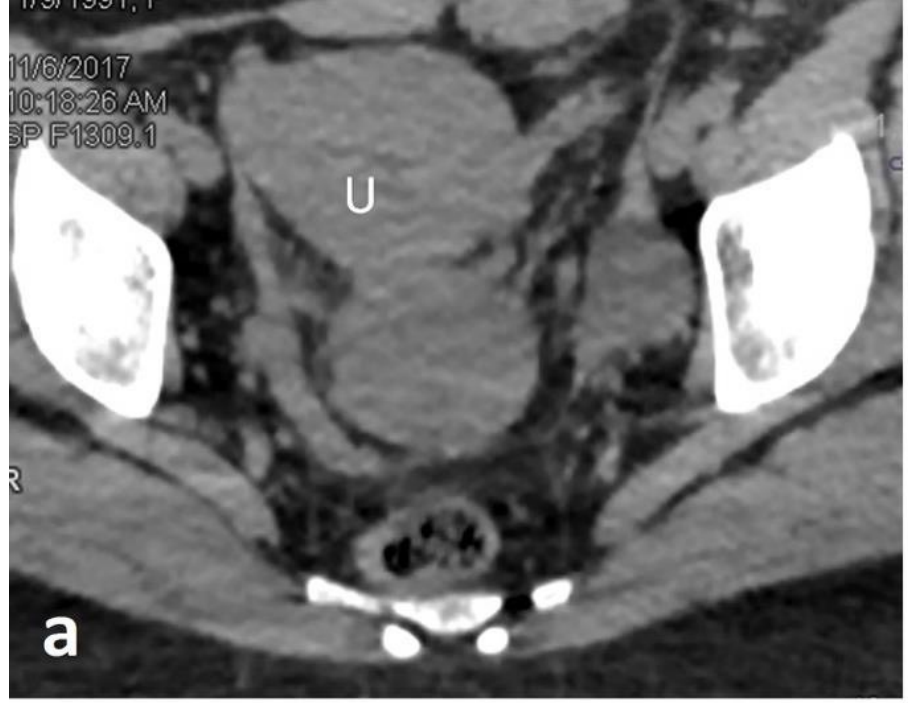
- Induction phase
  - ATG: 100-300mg/day for 10 days
    - prednisolone: 1000 mg IV on day 1; then slowly tapered to 20 mg/day

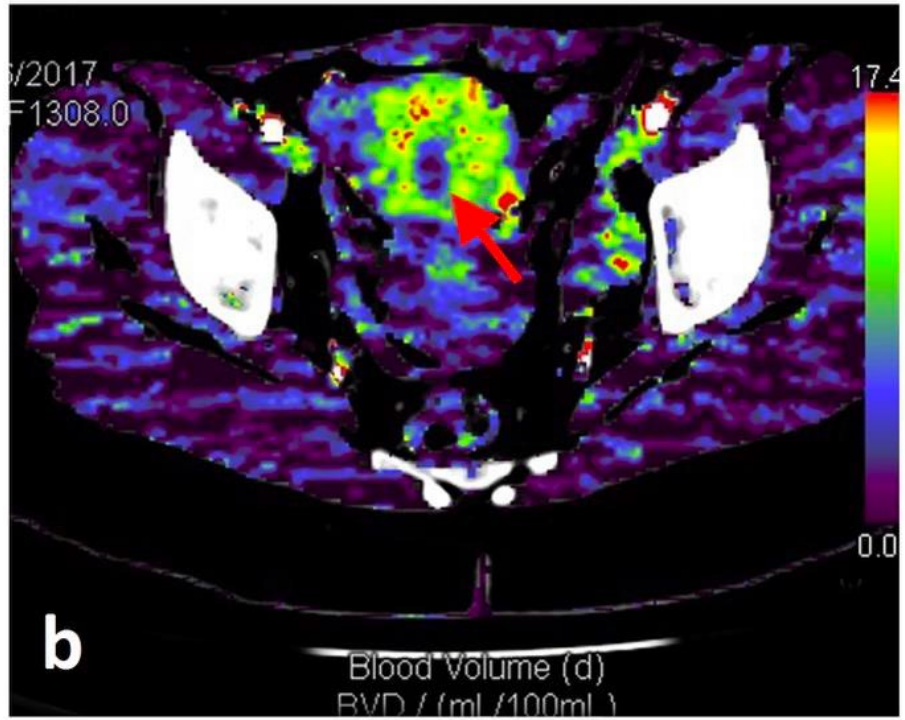
- The maintenance
    - tacrolimus (Prograf, 0.2 mg/kg/day with blood levels between 15 and 20 µg/ml in the first month, 12-15 µg/ml in the second month)
    - Mycophenolate mofetil (Cell Cept, 2 g/day)
    - prednisolone: 10 mg/day

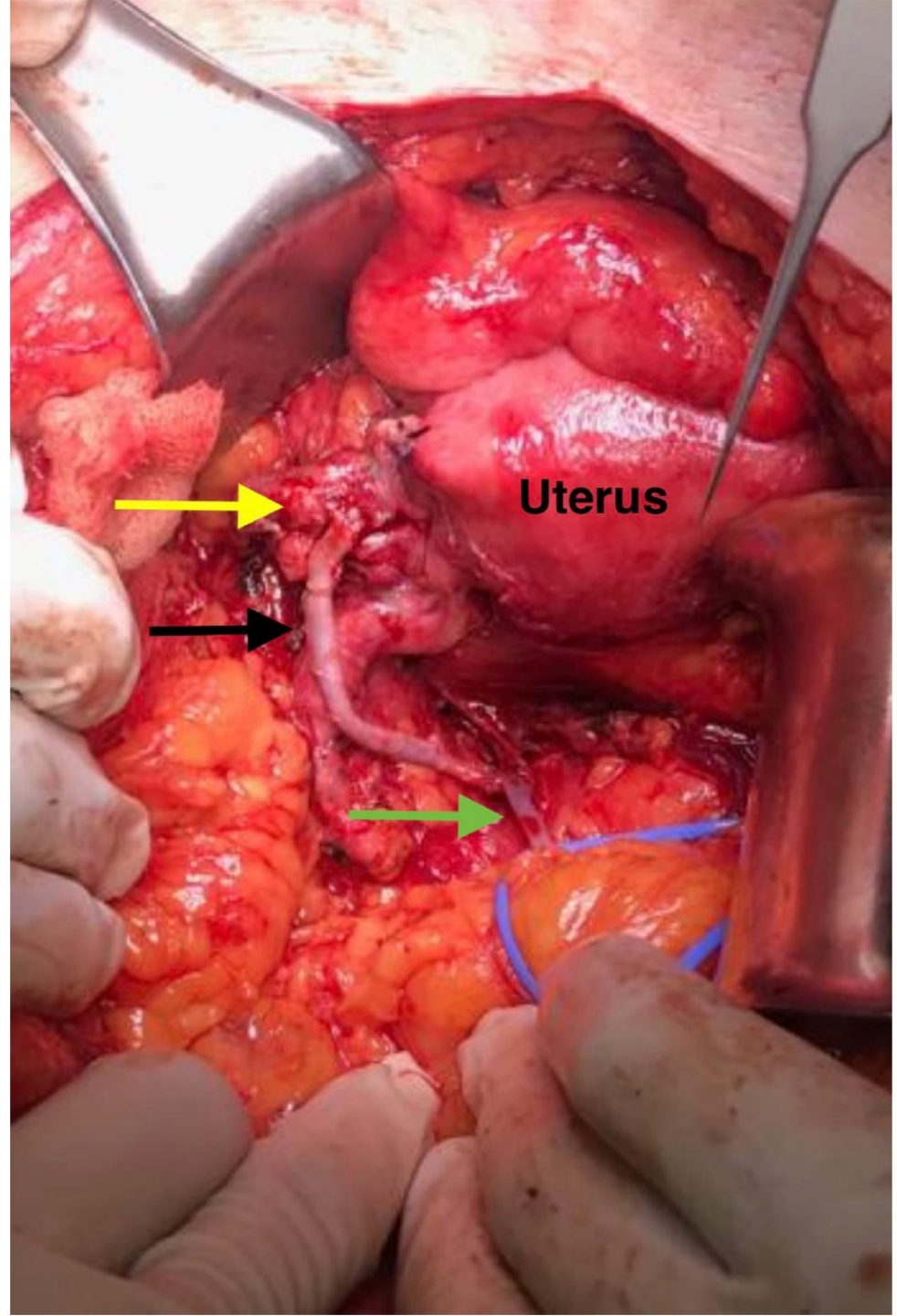
Induction therapy		Maintenance therapy							
	Intraop	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Thymoglobulin	1·5 mg/kg	60 mg							
Methylprednisolone	1 g	200 mg	160 mg	120 mg	80 mg	40 mg			
Tacrolimus			3 mg every 12 h	4 mg every 12 h		5 mg every 12 h	6 mg every 12 h		
Mycophenolate mofetil			720 mg every 12 h						
Prednisone							20 mg	20 mg	20 mg

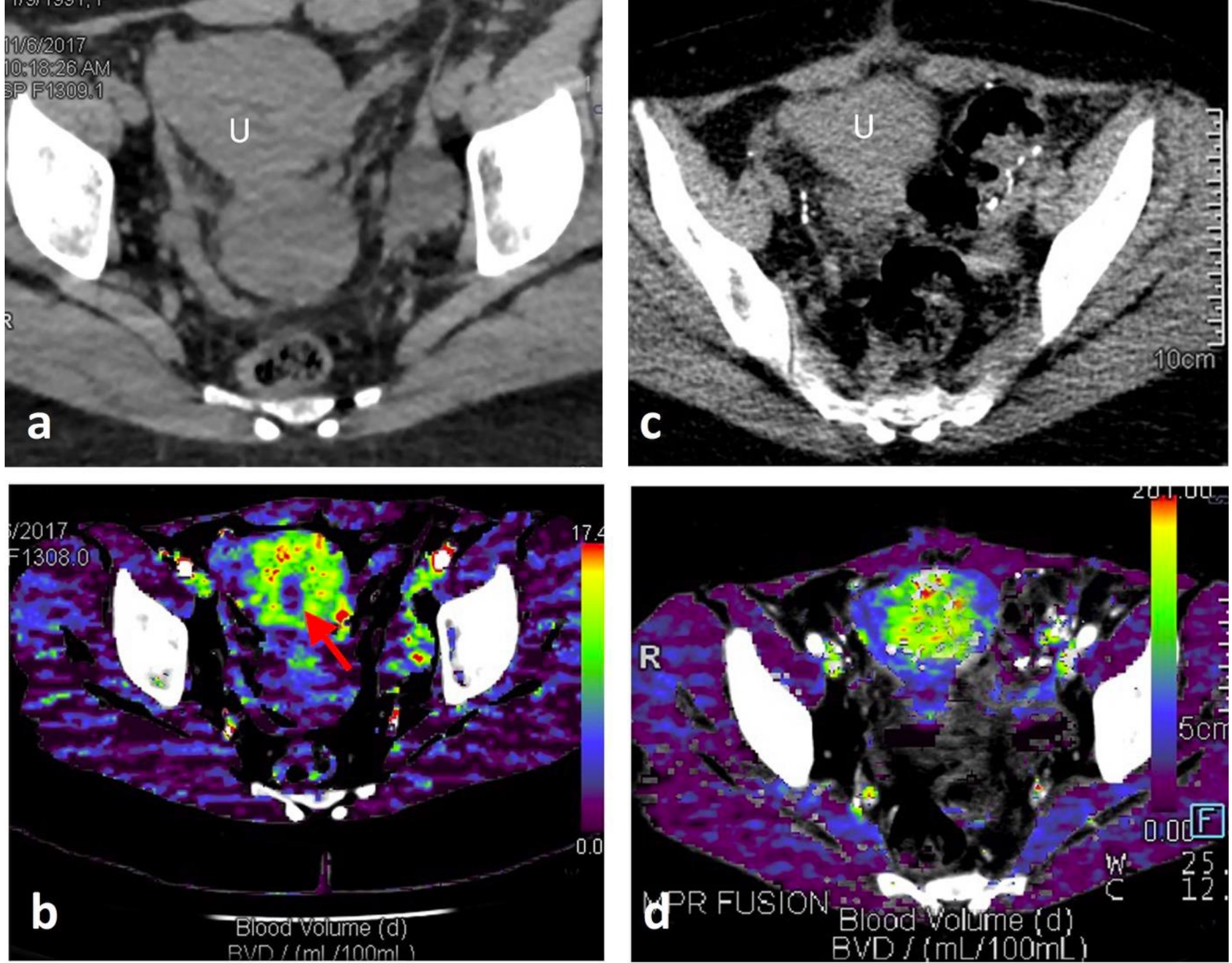
Totally 7 pregnancy

- 1 live birth
- 1 chemical pregnancy
- 5 missed abortus(7-8-9 week)


11/6/2017
10:18:26 AM
SP F1309.1
U
R
a

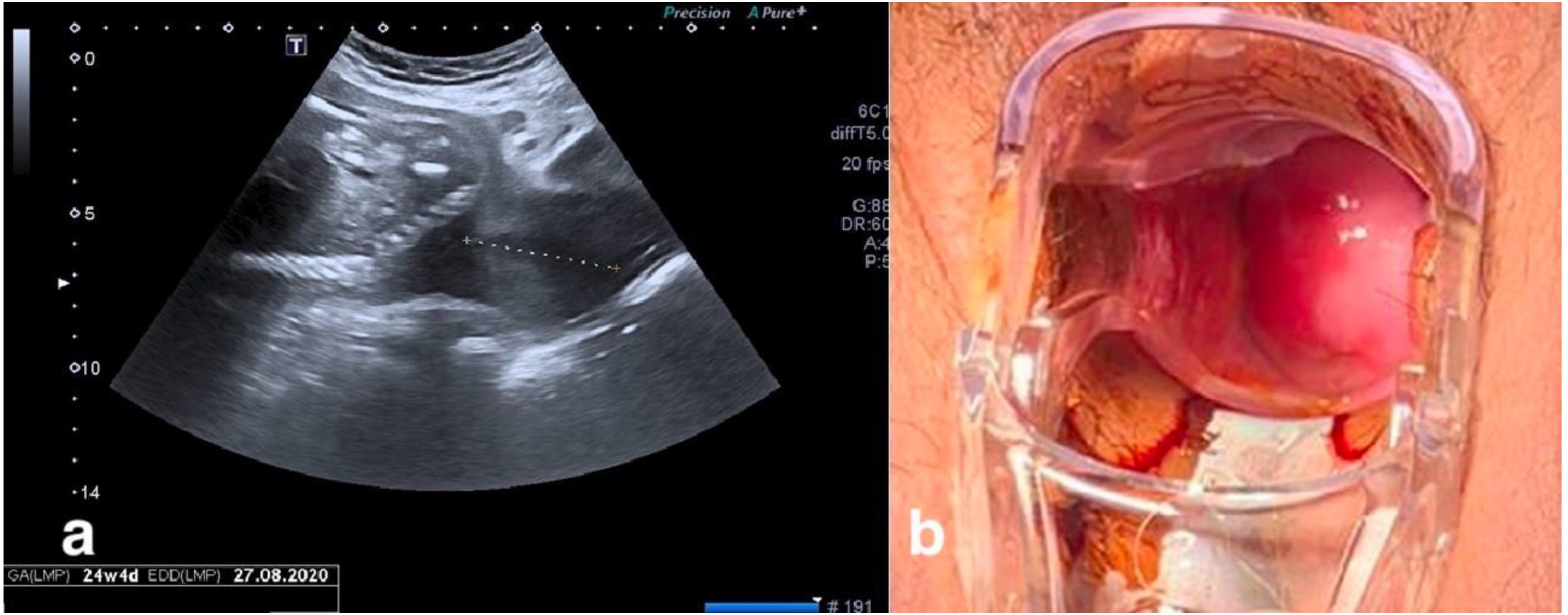

/2017
F1308.0
17.4
0.0
b
Blood Volume (d)


Uterus

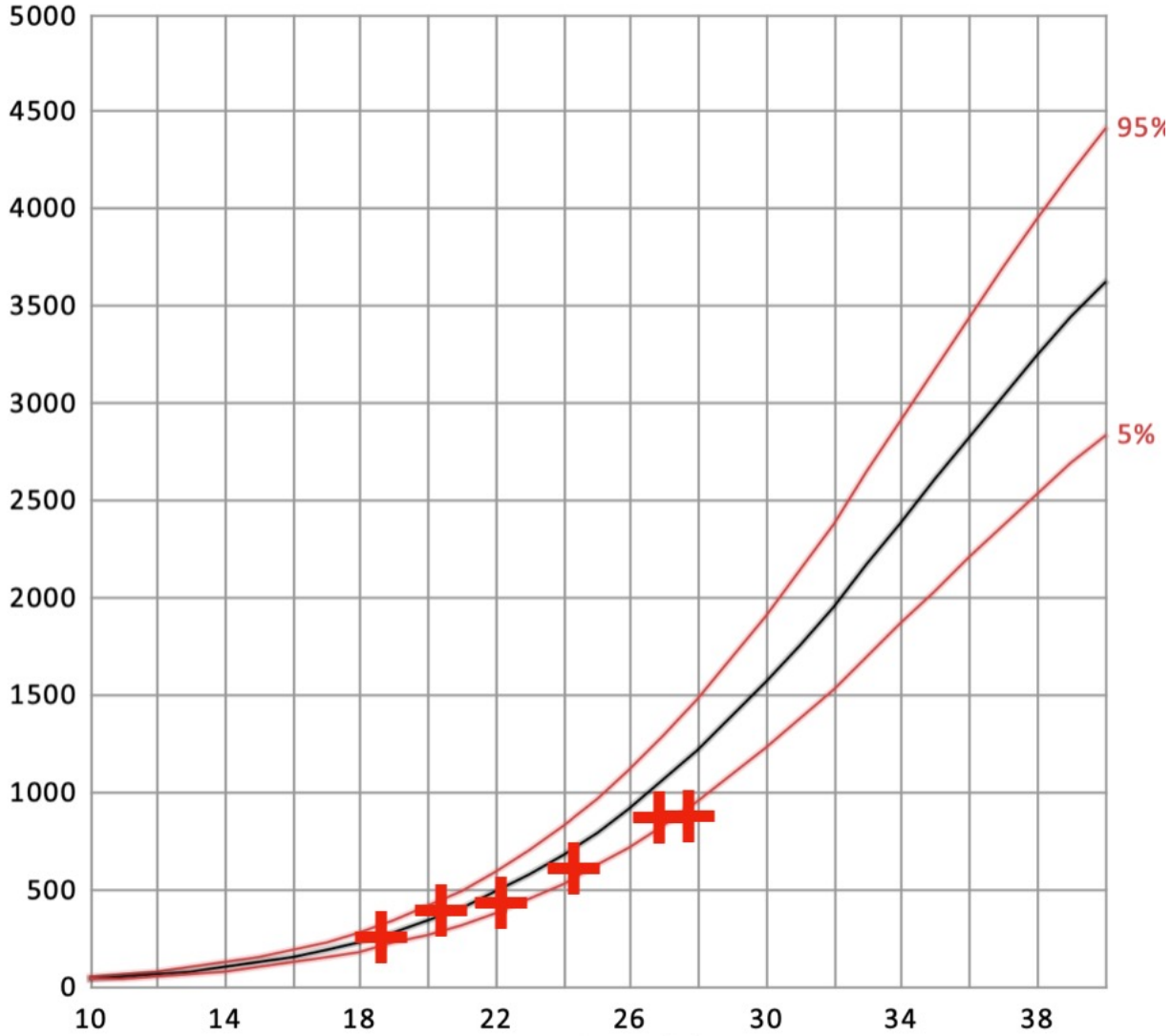

11/6/2017
10:18:26 AM
SP F1309.1
U
a
U
10cm
c
/2017
F1308.0
17.4
0.0
b
Blood Volume (d)
BVD / (mL/100mL)
R
5cm
0.0
F
W
C
25
12
PR FUSION
Blood Volume (d)
BVD / (mL/100mL)
d

- ET after revision surgery
- Pregnancy progressed well beyond 9 w
- PPROM at 19 weeks

Cervical length 24 weeks



Estimated fetal weight

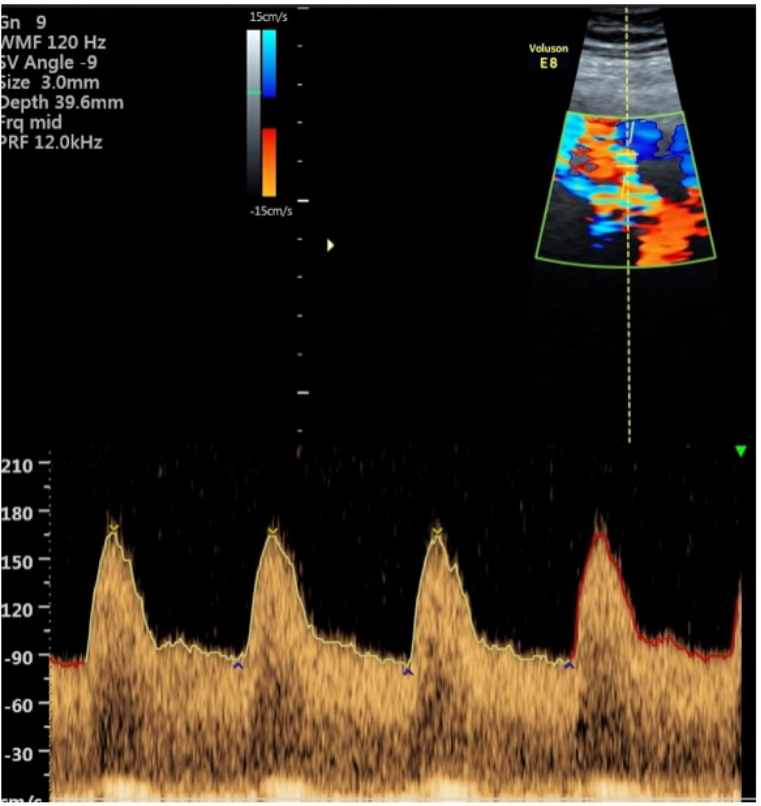


Gestational week

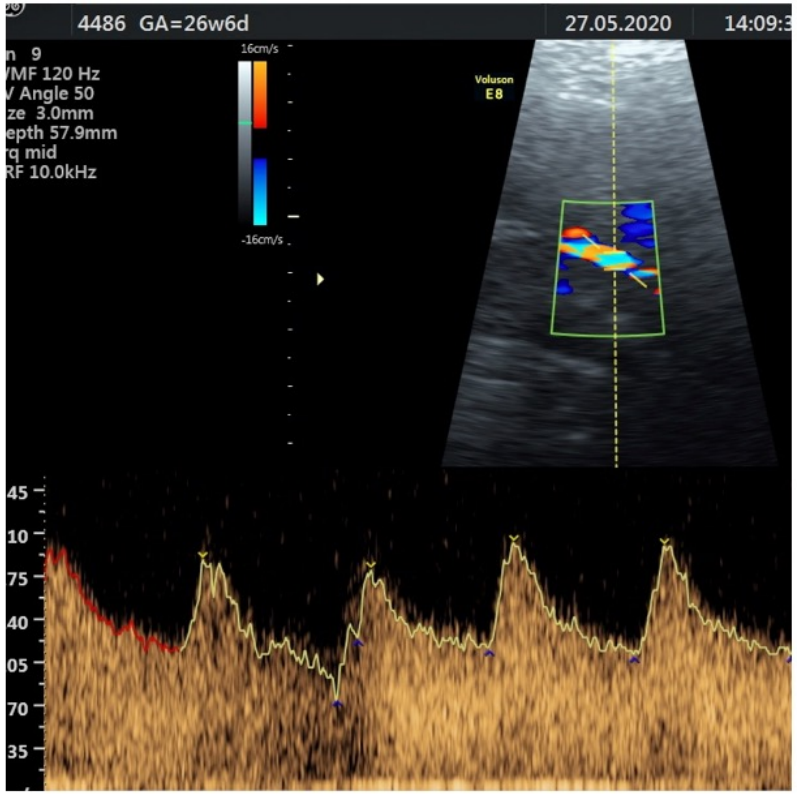
-Beginning of IUGR 24 weeks

- Gest HT at 27 weeks (no proteinuria)

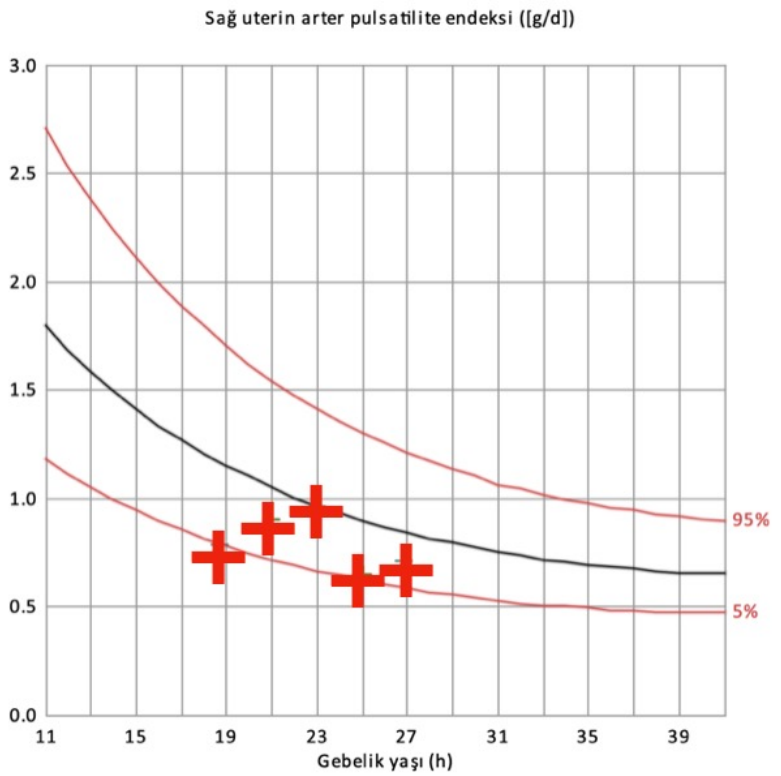
Doppler



Right uterine artery

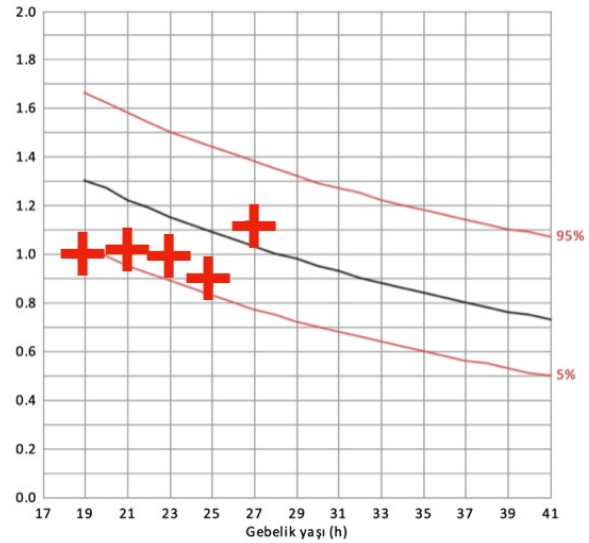


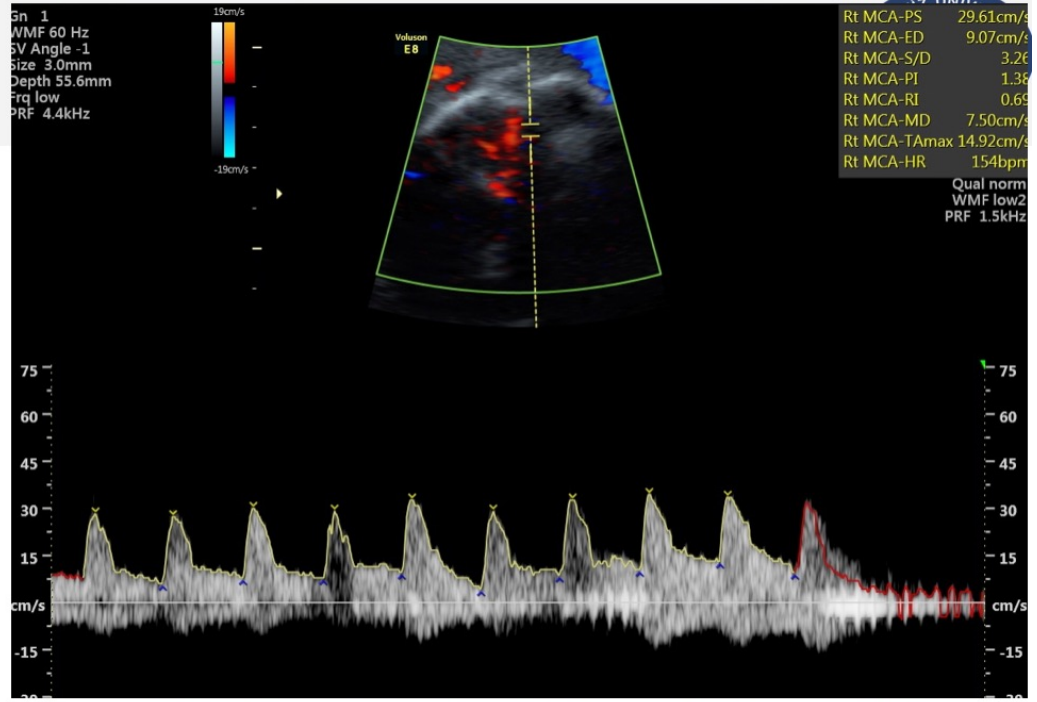
Left uterine artery



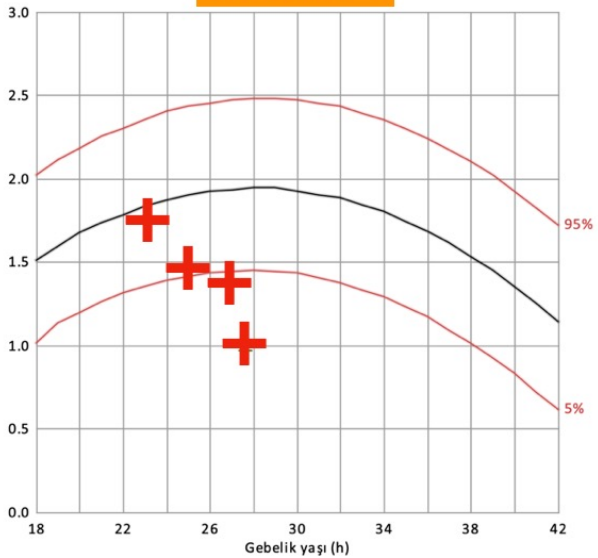
Right uterine artery PI

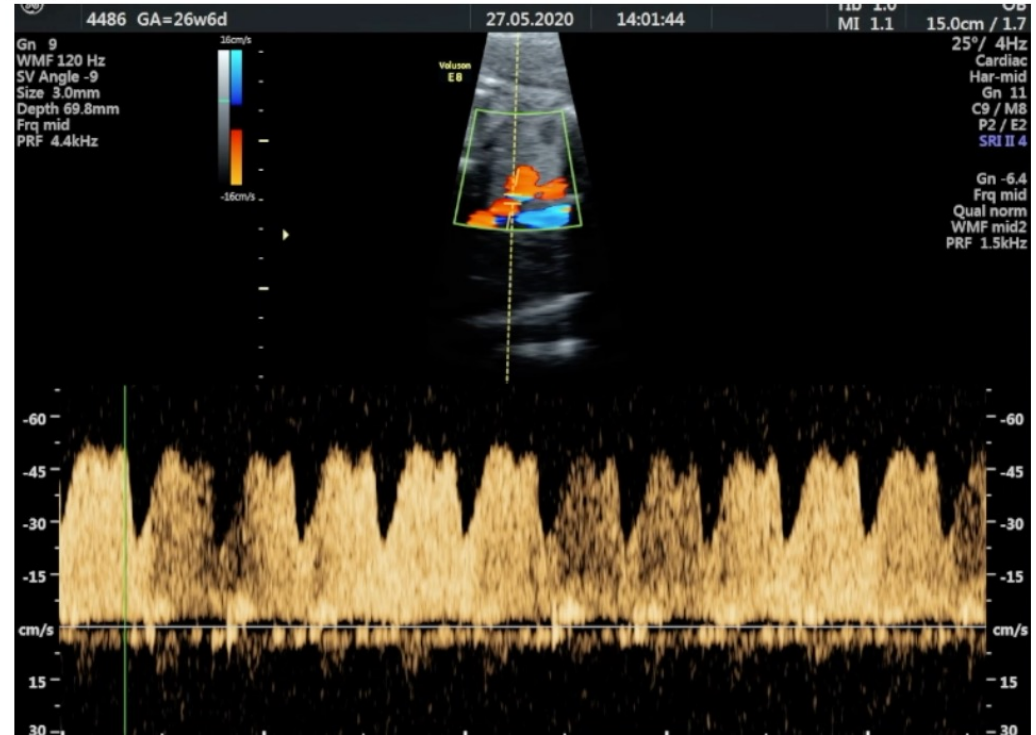
Umbilikal Arter PI



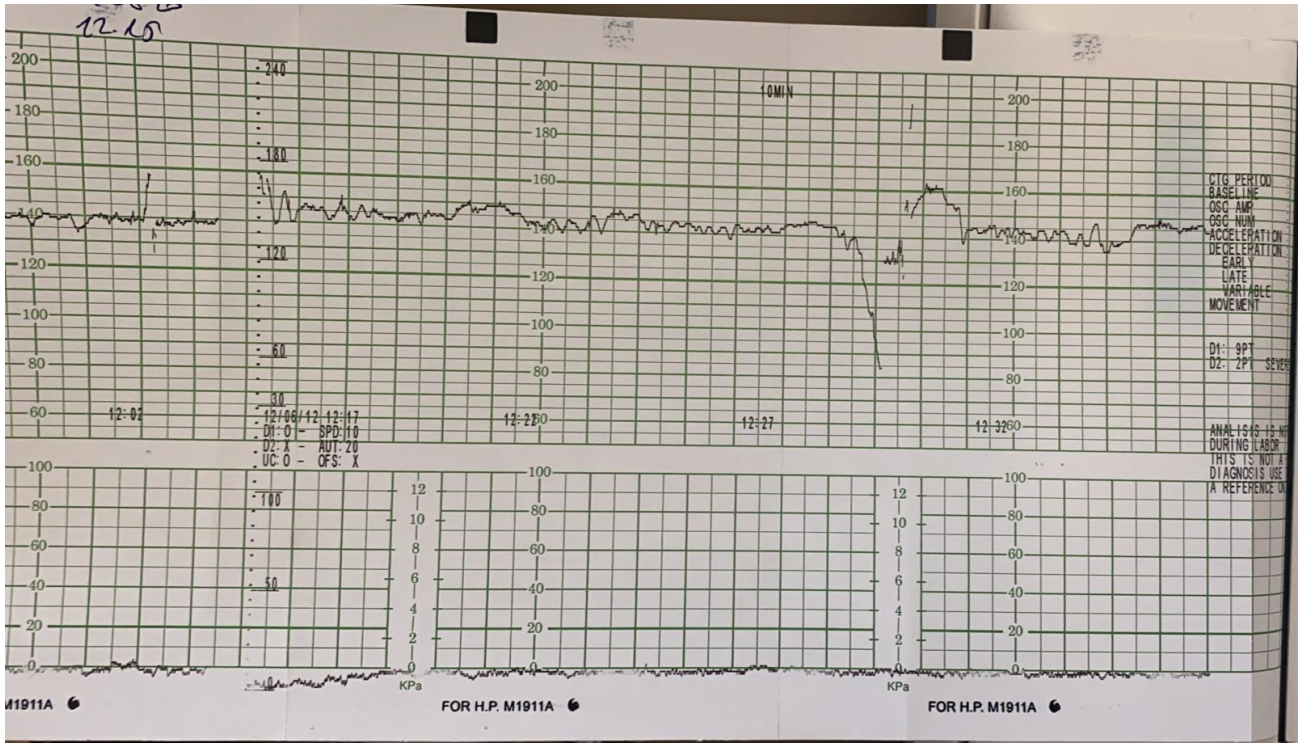


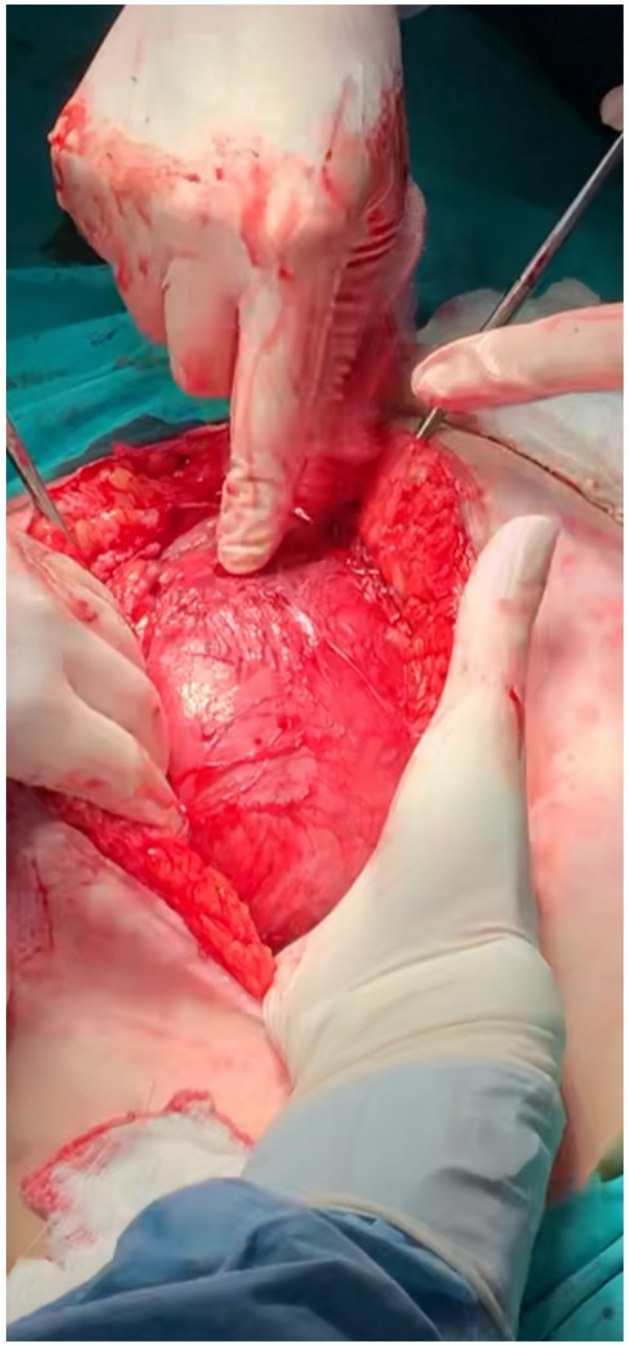
Sağ orta MCA PI eksi ([g/d])

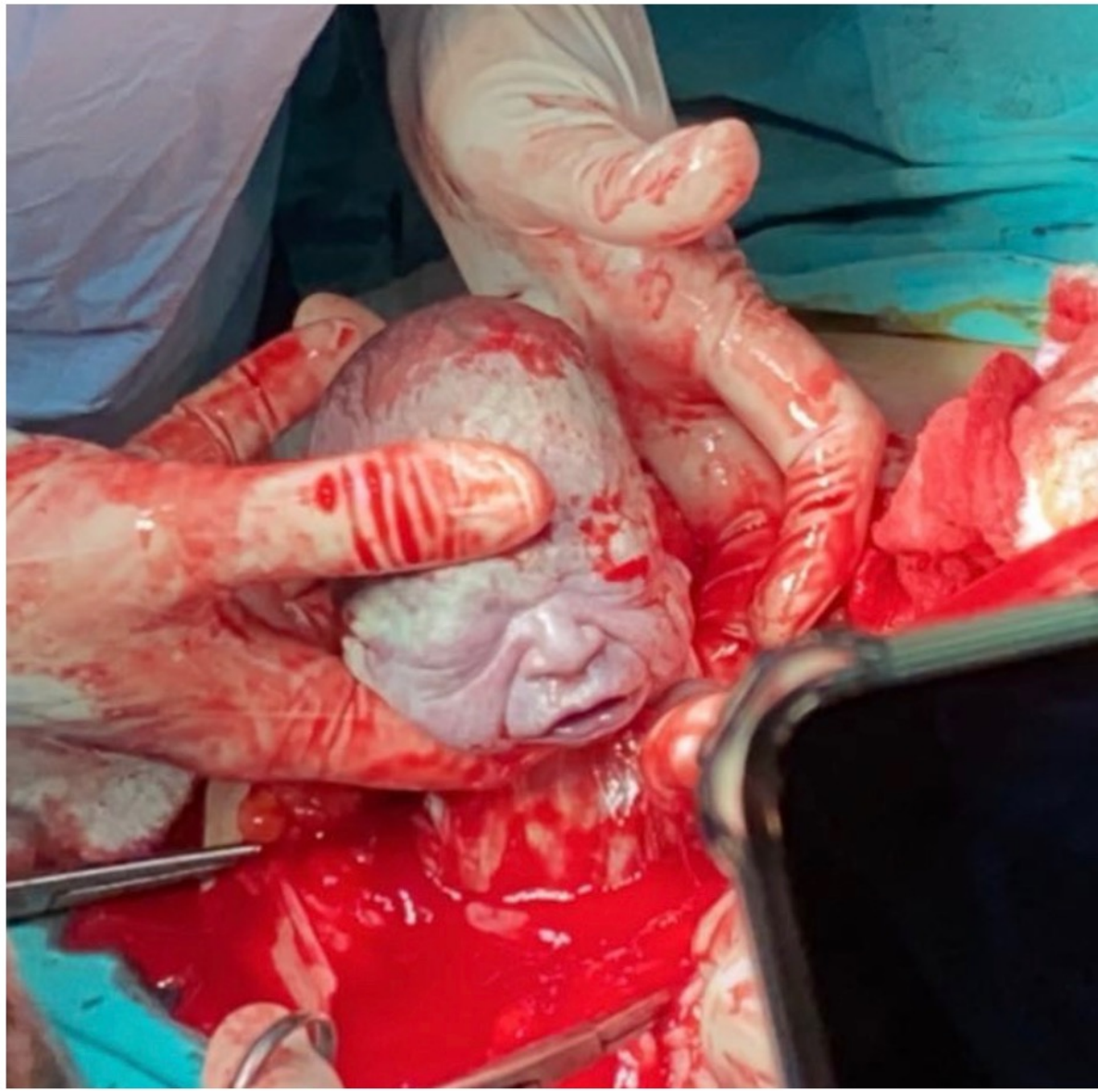




- Delivery at 28 weeks
- IUGR, preeclampsia?
- PPROM



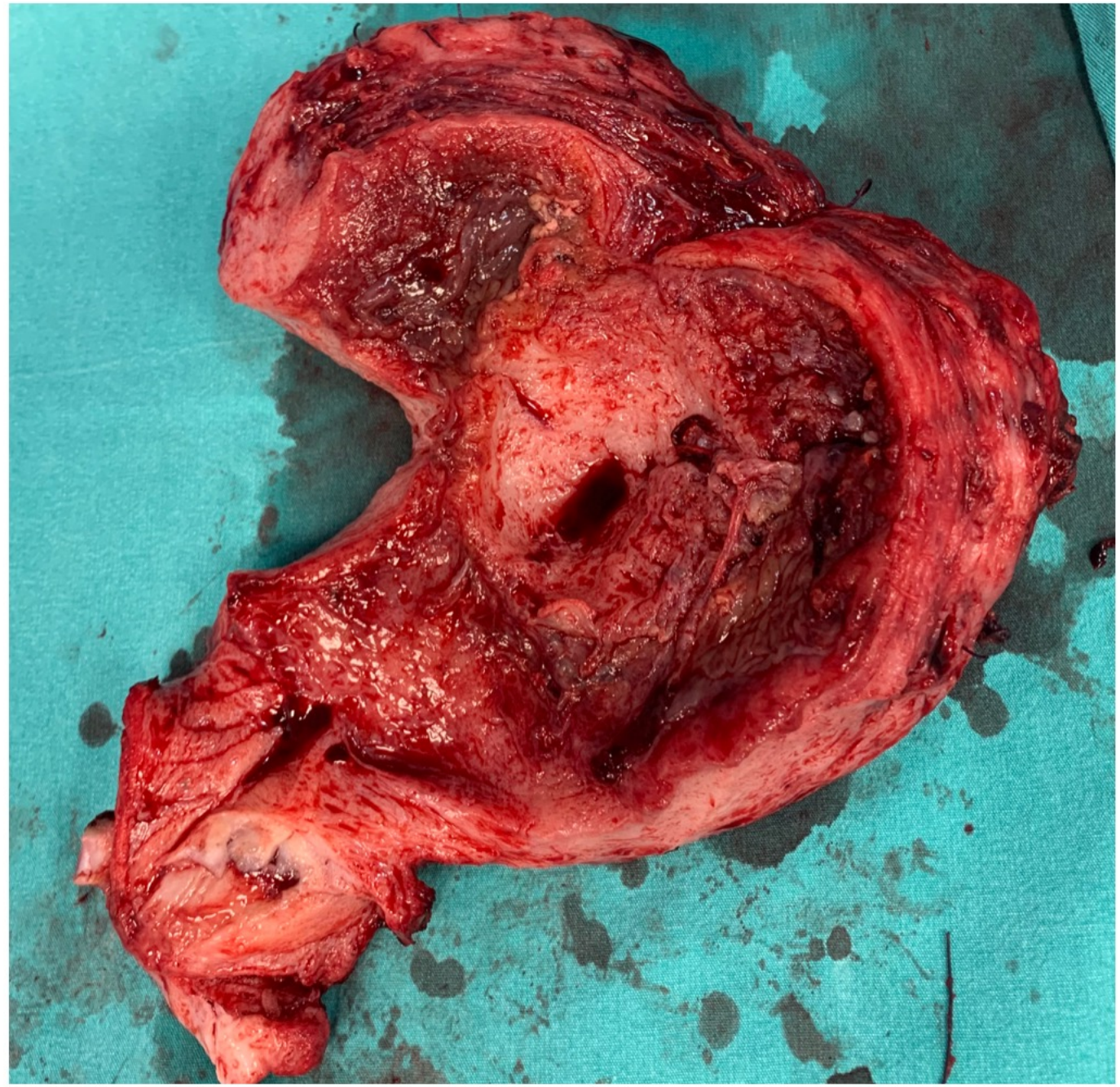




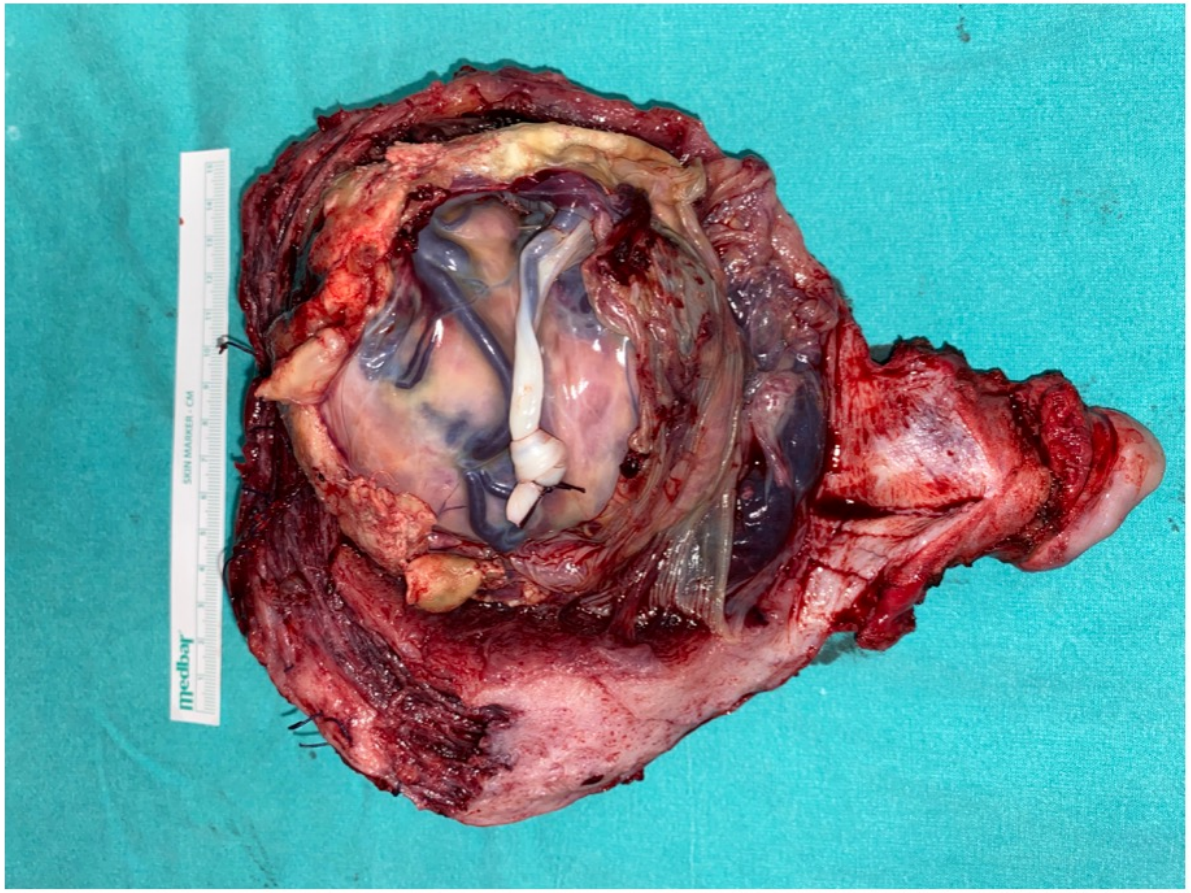
Newborn

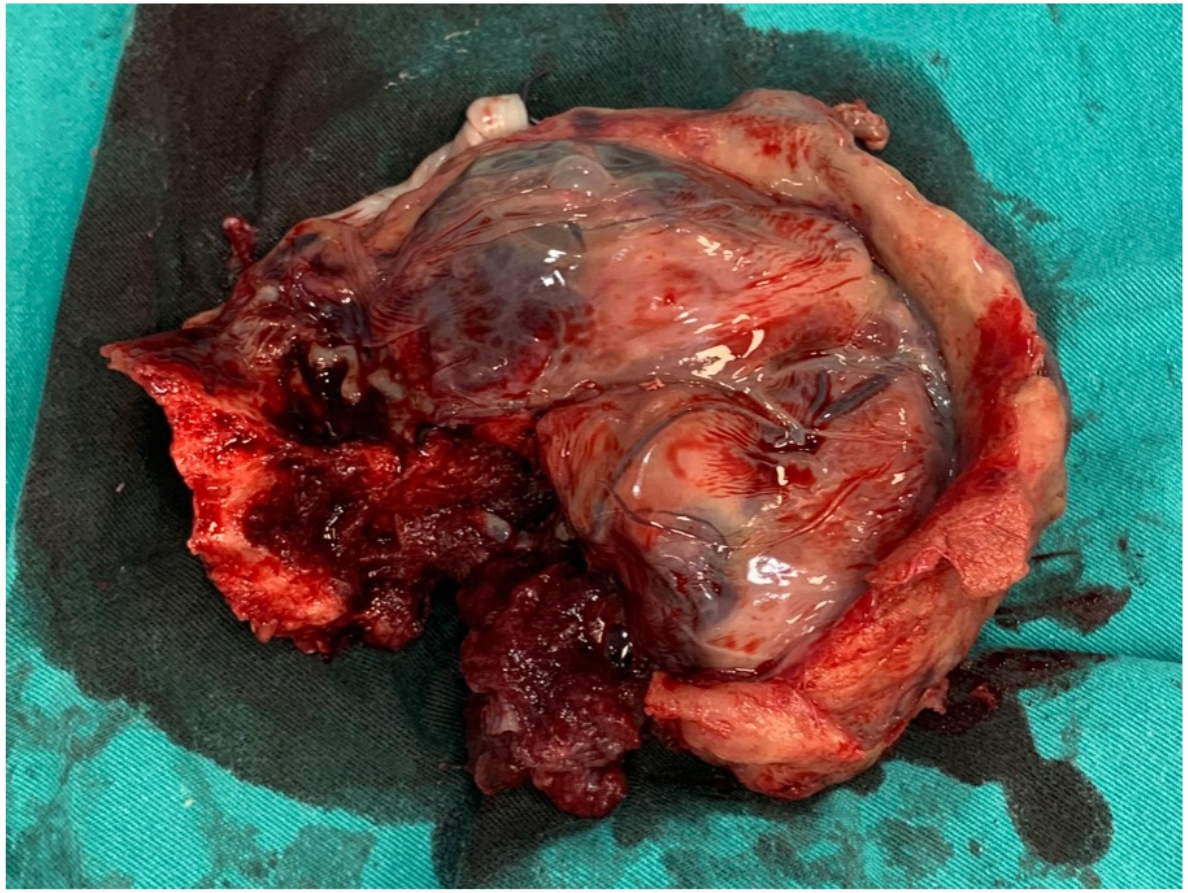
- 760. gr (5 percentil)
- APGAR 5-7-8
- pH: 7.27
- NICU → discharge at 79th day
- 35 months old with normal development milestones


medbar
SKIN MARKER - CM



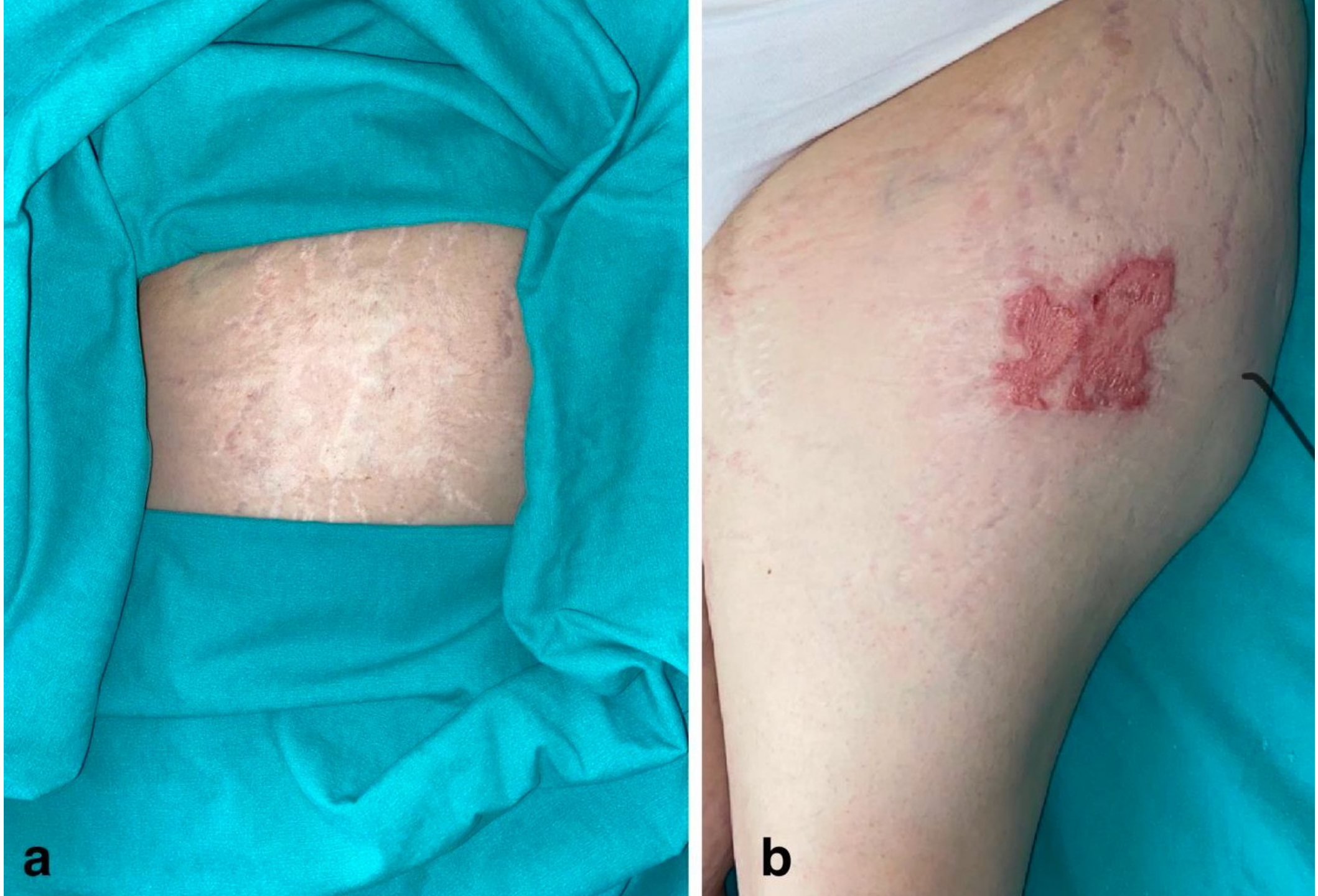
Plasenta





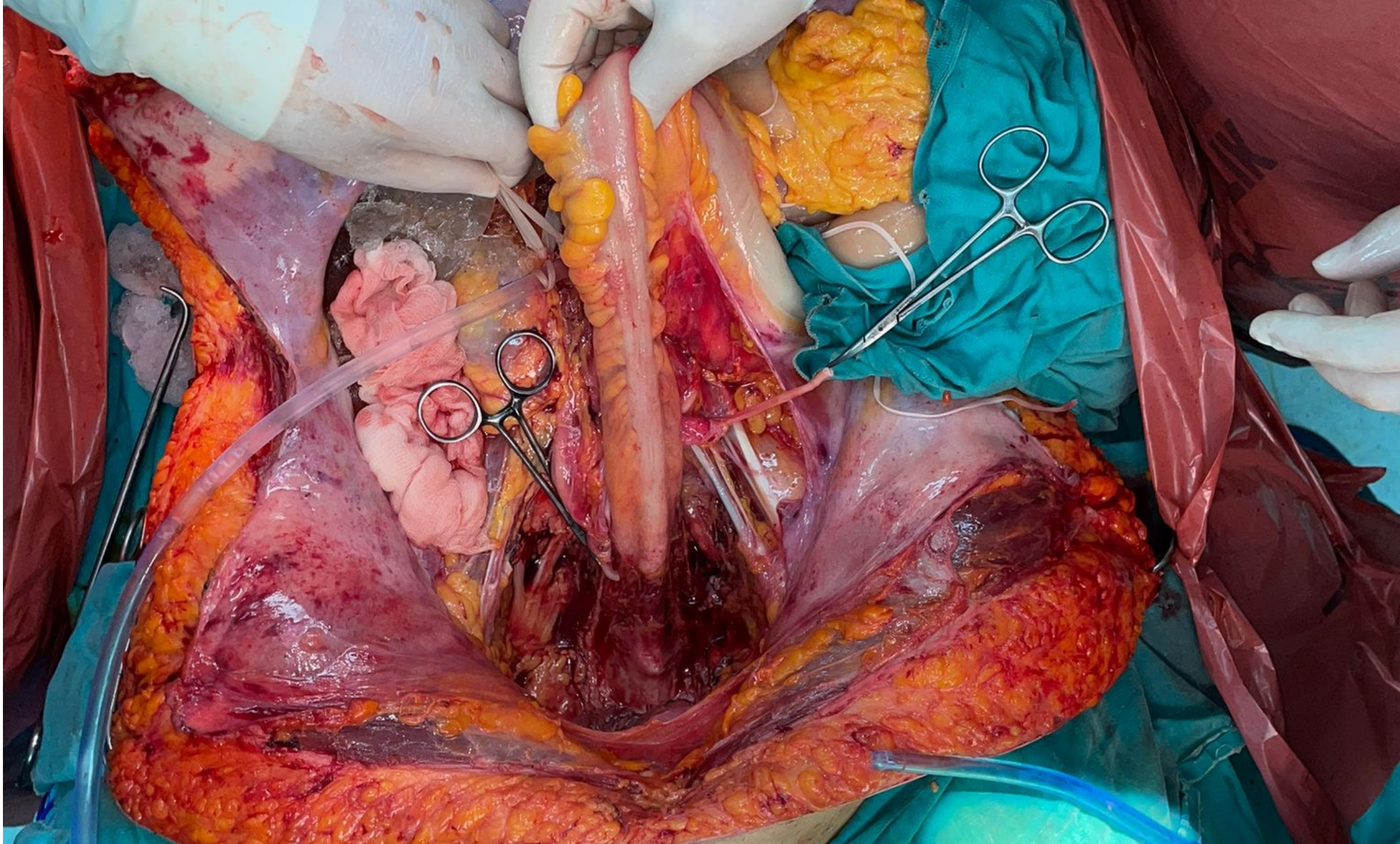
Plasenta 273 gr, **3 vessels +, eccentiric cord insertion**

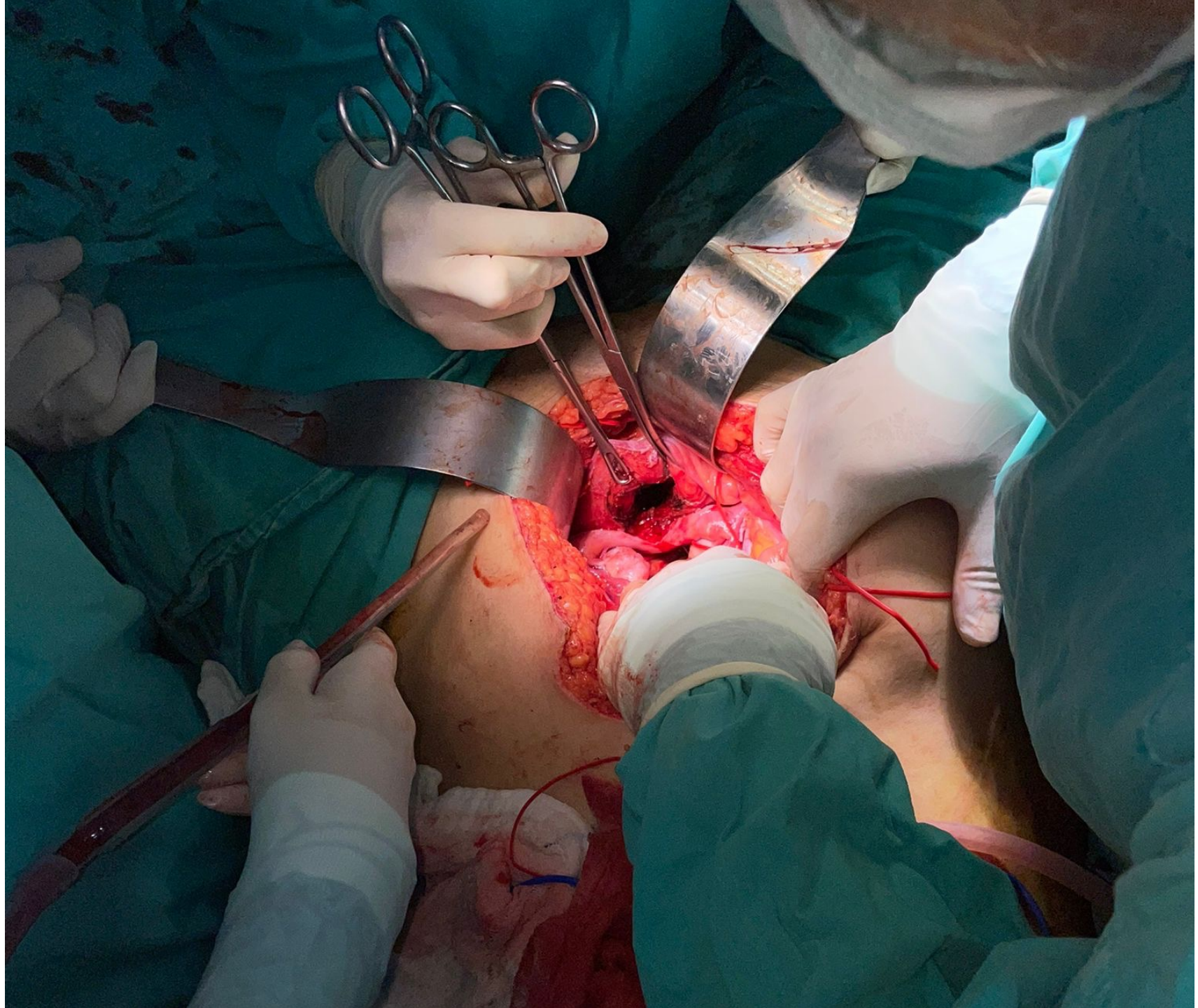

d

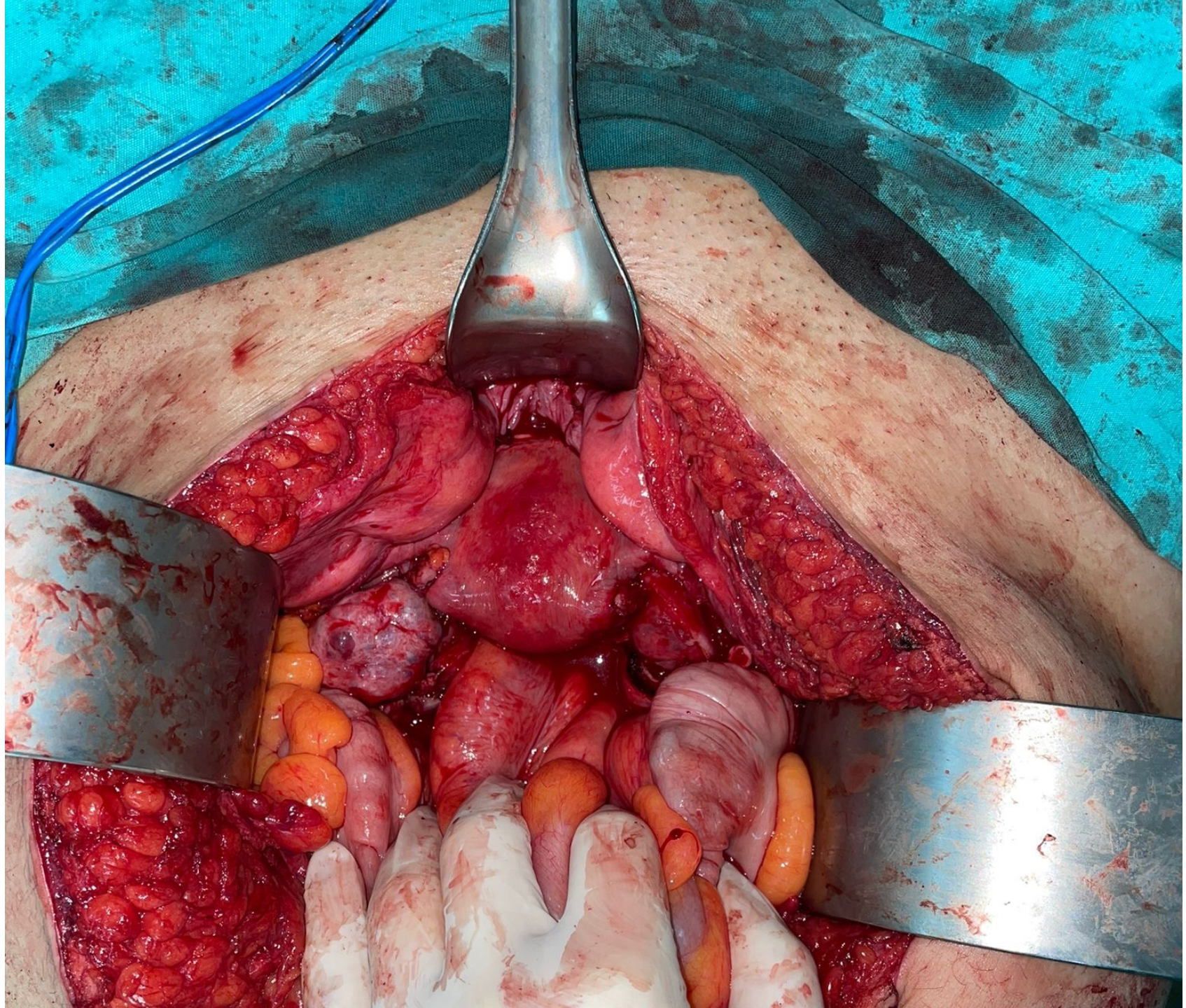

a
b

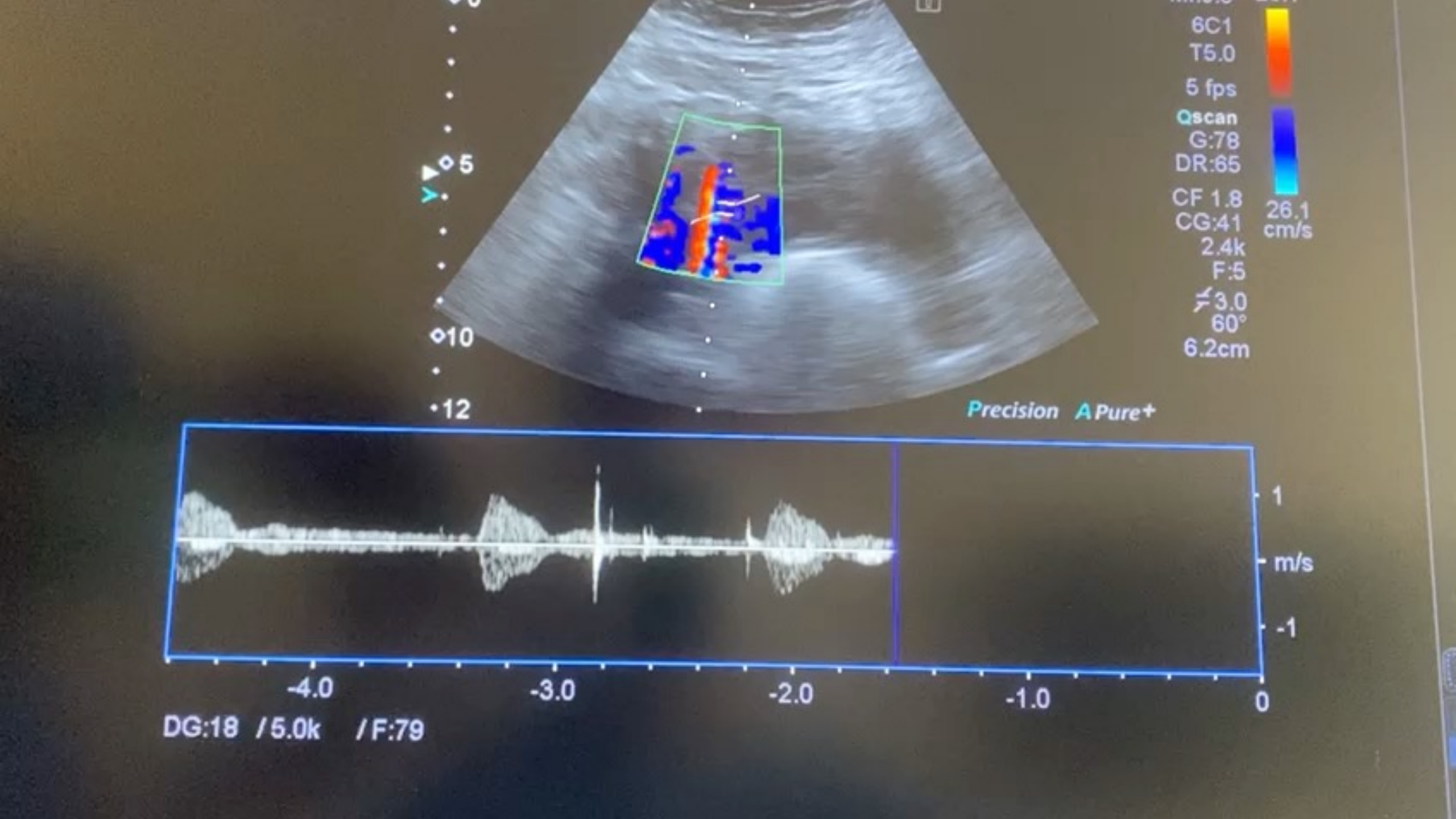
2nd Uterus Transplant in Turkey

- 27 July 2021
- Donor, 37 y, G4P4, brain death, SAH (multiorgan donor)
- Recipient , 32y, RKMH
- Operation technique
  - Addition of ovarian veins



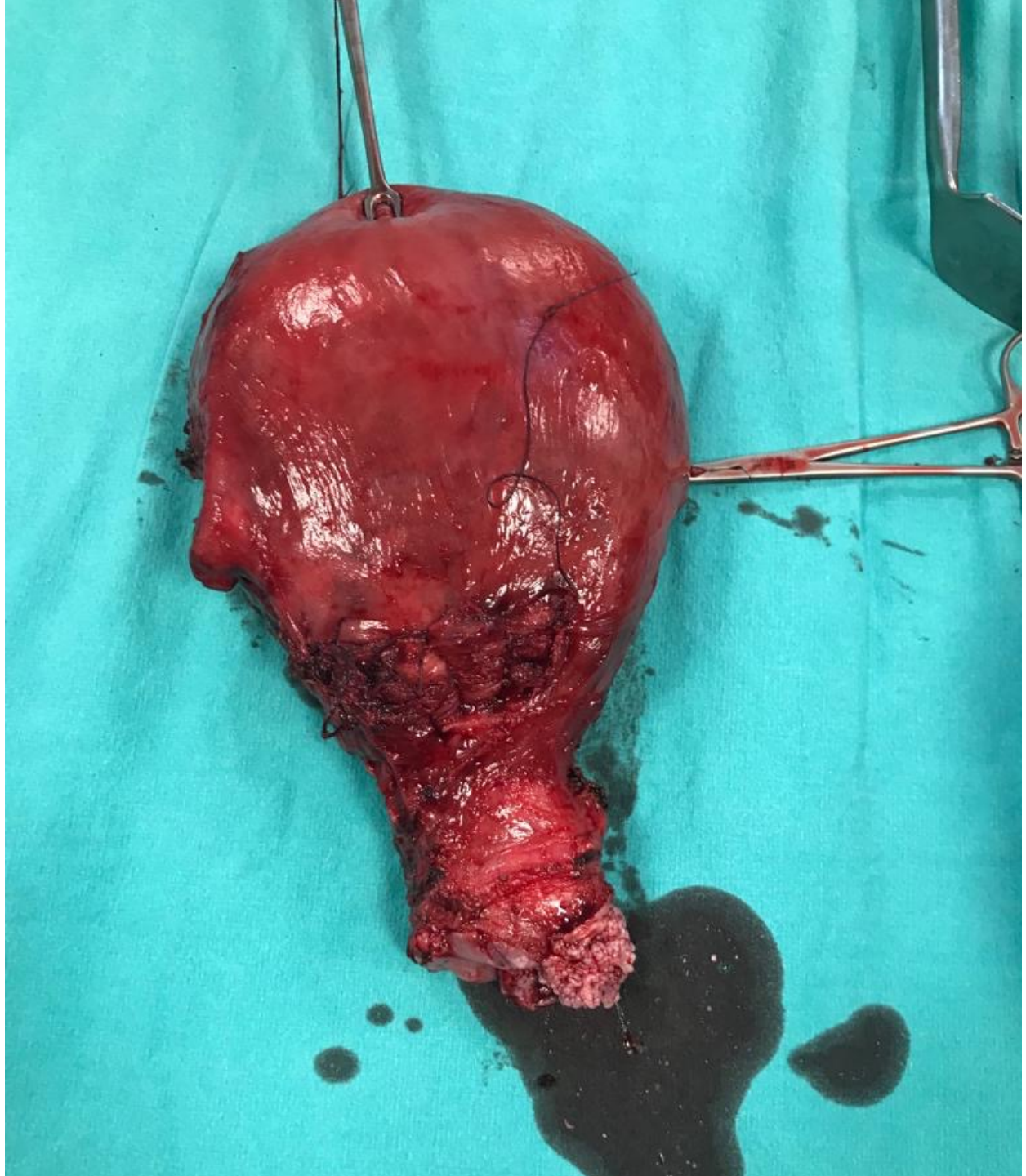





6C1
T5.0
5 fps
Qscan
G:78
DR:65
CF 1.8
CG:41
2.4k
F:5
3.0
60°
6.2cm
26.1
cm/s
5
10
12
Precision A Pure+
1
m/s
-1
-4.0
-3.0
-2.0
-1.0
0
DG:18 / 5.0k / F:79

- Post operative bleeding → re-operation
- Mild rejection third month (pulse steroid)
- 6 months after Utx –> ET

- Pregnancy + at first attempt
- At 28 w PPROM
- Regular contractions, vaginal bleeding
- Genital warts
- c/s birth 29 weeks
- 1720 g female fetus
- NICU → discharge at 47th day
- 11 months old with normal development milestones



ANNALS OF SURGERY

ORIGINAL ARTICLE: PDF ONLY

Birth of a Healthy Baby 9 years after a Surgically Successful Deceased Donor Uterus Transplant

Ozkan, Omer*; Ozkan, Ozlenen*; Dogan, Nasuh Utku†; Bahceci, Mustafa‡; Mendilcioglu, Inanc†; Boynukalin, Kubra‡; Ongun, Hakan§; Kantarci, Abdul Mecit¶; Yaprak, Muhittin||; Cengiz, Melike**; Hadimioglu, Necmiye**; Kafadar, Yusuf Taner††; Celik, Kiymet§

Author Information

ORIGINAL ARTICLE

Birth of a Healthy Baby 9 Years After a Surgically Successful Deceased Donor Uterus Transplant

Omer Ozkan,✉ Ozlenen Ozkan,* Nasuh Utku Dogan,† Mustafa Bahceci,‡ Inane Mendilcioglu,† Kubra Boynukalin,‡ Hakan Ongun,§ Abdul Mecit Kantarci,¶ Muhittin Yaprak,|| Melike Cengiz,** Necmiye Hadimioglu,** Yusuf Taner Kafadar,†† and Kiymet Celik§*

Objective: To describe surgical procedures, previous failed pregnancies, methods for overcoming pregnancy failure and, most importantly, birth of a healthy infant, in a uterus transplantation from a deceased donor.

Background: Majority of uterus transplants have involved live donors, but several advantages make deceased donor transplantation a practicable option, principally by eliminating surgical risks to the live donor.

(*Ann Surg* 2022;275:825–832)

Absolute uterine factor infertility affects 3% to 5% of all reproductive women, and no treatment for this condition has been available until recently.[1] Surrogacy and adoption are alternative methods for overcoming uterine-related infertility, although surrogacy is not legal in many countries, and adoption does not establish a

ANNALS OF SURGERY

EDITORIAL

The History of Uterus Transplantation, Rewritten

Giuliano Testa, MD, MBA,✉ Greg J. McKenna, MD, and Liza Johannesson, MD, PhD

Uterus transplantation is a fertility treatment that allows women affected by absolute uterine infertility to experience pregnancy and give birth. Until the report by Dr. Ozkan and his group, the first live birth following uterus transplant had been announced in 2014 by Brännström et al,[1] and the first birth after a deceased donor uterus transplant by Ejzenberg et al[2] in 2018. However, the 23-year-old woman who in 2011 underwent a technically successful deceased donor uterus transplant is now also to be considered the first woman to deliver a child after a uterus transplant.[3]

ULTRASOUND in Obstetrics & Gynecology

isuog

State-of-the-Art Review

Pregnancy management and outcome after uterus transplantation

I. Mendilcioglu, N. U. Dogan, O. Ozkan, M. Bahceci, K. Boynukalin, S. Dogan, O. Ozkan

First published: 05 December 2022 | https://doi.org/10.1002/uog.26134

Review

Women's Health

Women's Health
2016, Vol. 12(4) 442–449

DOI: 10.1177/1745505716653849
whe.sagepub.com
SAGE

Uterus transplantation: From animal models through the first heart beating pregnancy to the first human live birth

Omer Ozkan[1], Nasuh Utku Dogan[2], Ozlenen Ozkan[1], Inanc Mendilcioglu[2], Selen Dogan[2], Batu Aydinuraz[3] and Mehmet Simsek[2]

Journal of
Clinical Medicine

MDPI

Review

The Ozkan Technique in Current Use in Uterus Transplantation: From the First Ever Successful Attempt to Clinical Reality

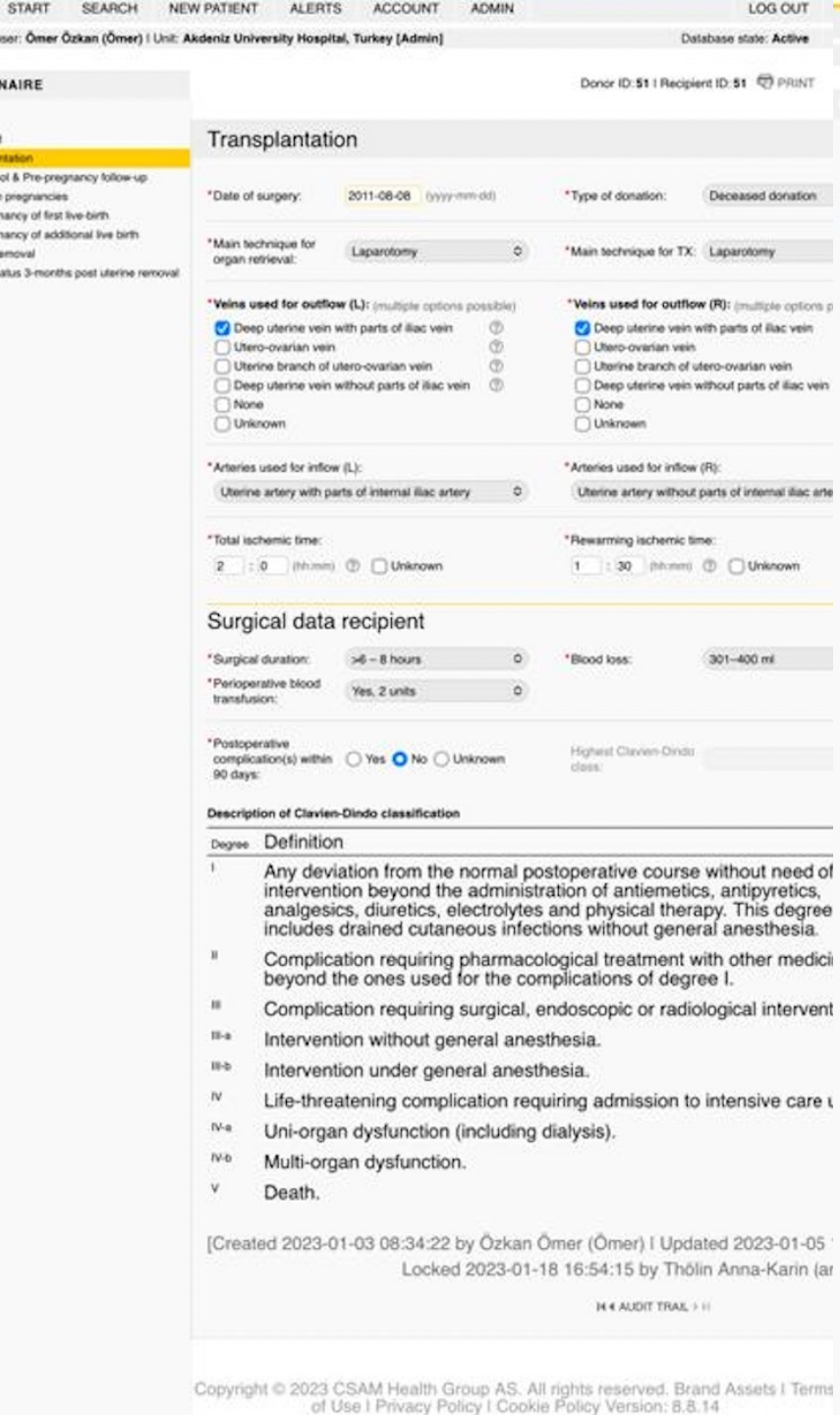
Omer Ozkan [1,*], Ozlenen Ozkan [1] and Nasuh Utku Dogan [2]

[1] Department of Plastic Surgery, Faculty of Medicine, Akdeniz University, 07070 Antalya, Turkey
[2] Department of Gynecology, Faculty of Medicine, Akdeniz University, 07070 Antalya, Turkey
* Correspondence: omozkan@hotmail.com

Abstract: Uterus-related infertility affects 3–5% of all young women, including Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, hysterectomy, or severe Asherman syndrome. For these women with uterus-related infertility, uterus transplantation is now a viable option. We performed the first surgically successful uterus transplant in September 2011. The Donor was a 22-year-old nulliparous woman. After five failed pregnancy attempts (pregnancy losses), ET attempts were discontinued in the first case, and a search for underlying etiology was performed, including static and dynamic imaging studies. Perfusion computed tomography revealed an obstructed blood outflow, particularly in the left anterolateral part of the uterus. In order to correct blood flow obstruction, a revision surgery was planned. By laparotomy, a saphenous vein graft was anastomosed between the left

- 230 candidates evaluated
- 16 women on the waiting list

Welcome to ISUTx



START SEARCH NEW PATIENT ALERTS ACCOUNT ADMIN LOG OUT

ser: Ömer Özkan (Ömer) | Unit: Akdeniz University Hospital, Turkey [Admin] Database state: Active

NAIRE

Donor ID: 51 | Recipient ID: 51 PRINT

Transplantation

*Date of surgery: 2011-08-08 (yyyy-mm-dd)

*Type of donation: Deceased donation

*Main technique for organ retrieval: Laparotomy

*Main technique for TX: Laparotomy

*Veins used for outflow (L): (multiple options possible)
- [x] Deep uterine vein with parts of iliac vein
- [ ] Utero-ovarian vein
- [ ] Uterine branch of utero-ovarian vein
- [ ] Deep uterine vein without parts of iliac vein
- [ ] None
- [ ] Unknown

*Veins used for outflow (R): (multiple options p
- [x] Deep uterine vein with parts of iliac vein
- [ ] Utero-ovarian vein
- [ ] Uterine branch of utero-ovarian vein
- [ ] Deep uterine vein without parts of iliac vein
- [ ] None
- [ ] Unknown

*Arteries used for inflow (L): Uterine artery with parts of internal iliac artery

*Arteries used for inflow (R): Uterine artery without parts of internal iliac arte

*Total ischemic time: 2 : 0 (hh:mm) Unknown

*Rewarming ischemic time: 1 : 30 (hh:mm) Unknown

Surgical data recipient

*Surgical duration: >6 – 8 hours

*Blood loss: 301–400 ml

*Perioperative blood transfusion: Yes, 2 units

*Postoperative complication(s) within 90 days: Yes No Unknown

Highest Clavien-Dindo class:

Description of Clavien-Dindo classification

Degree	Definition
I	Any deviation from the normal postoperative course without need of intervention beyond the administration of antiemetics, antipyretics, analgesics, diuretics, electrolytes and physical therapy. This degree includes drained cutaneous infections without general anesthesia.
II	Complication requiring pharmacological treatment with other medici beyond the ones used for the complications of degree I.
III	Complication requiring surgical, endoscopic or radiological intervent
III-a	Intervention without general anesthesia.
III-b	Intervention under general anesthesia.
IV	Life-threatening complication requiring admission to intensive care u
IV-a	Uni-organ dysfunction (including dialysis).
IV-b	Multi-organ dysfunction.
V	Death.

[Created 2023-01-03 08:34:22 by Özkan Ömer (Ömer) | Updated 2023-01-05
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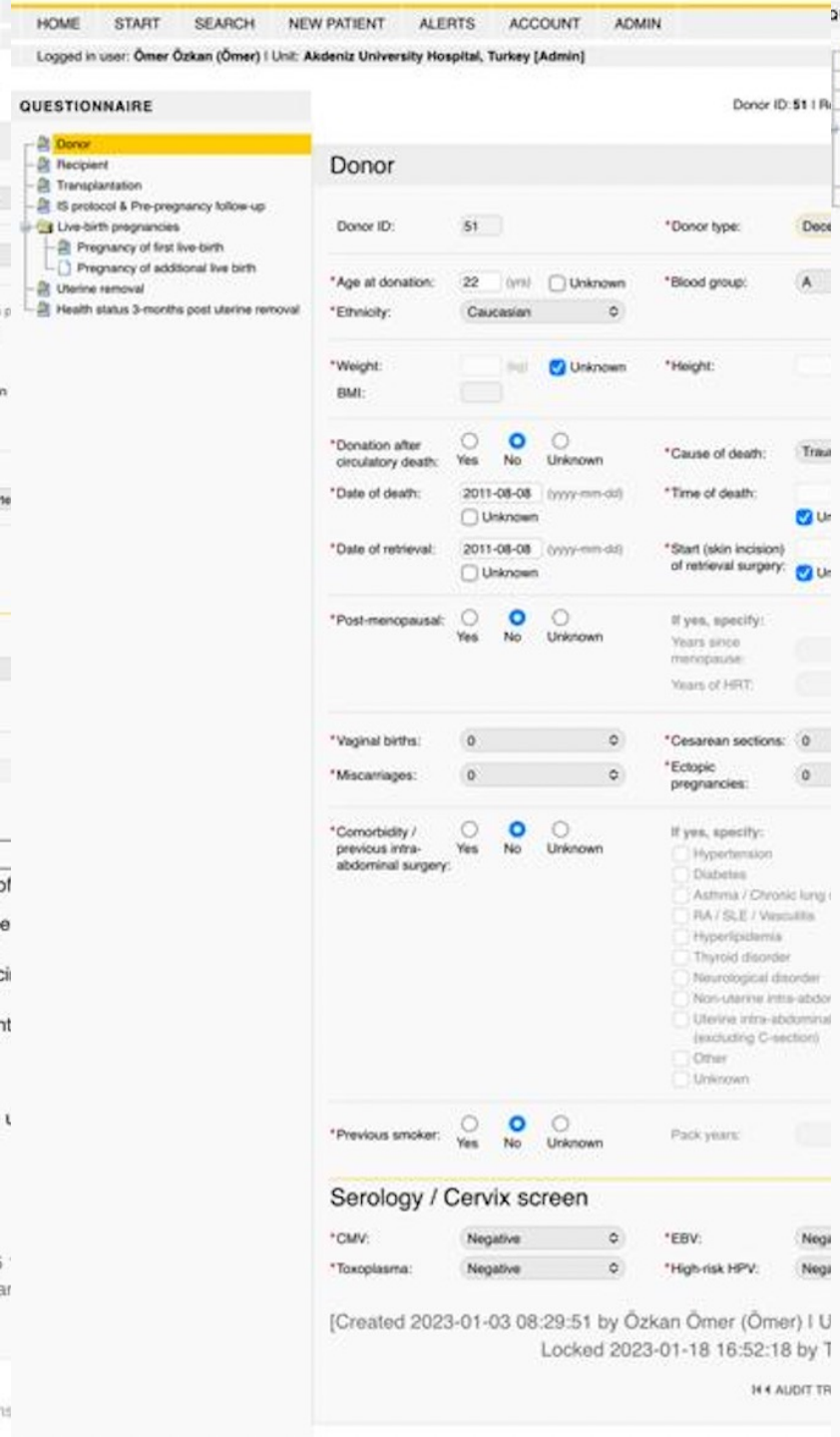
AUDIT TRAIL



HOME START SEARCH NEW PATIENT ALERTS ACCOUNT ADMIN

Logged in user: Ömer Özkan (Ömer) | Unit: Akdeniz University Hospital, Turkey [Admin]

QUESTIONNAIRE
- Donor
- Recipient
- Transplantation
- IS protocol & Pre-pregnancy follow-up
- Live-birth pregnancies
  - Pregnancy of first live-birth
  - Pregnancy of additional live birth
- Uterine removal
- Health status 3-months post uterine removal

Donor ID: 51 | Re

Donor

Donor ID: 51

*Donor type: Dece

*Age at donation: 22 (yrs) Unknown

*Blood group: A

*Ethnicity: Caucasian

*Weight: (kg) Unknown

*Height:

BMI:

*Donation after circulatory death: Yes No Unknown

*Cause of death: Trau

*Date of death: 2011-08-08 (yyyy-mm-dd) Unknown

*Time of death:

*Date of retrieval: 2011-08-08 (yyyy-mm-dd) Unknown

*Start (skin incision) of retrieval surgery:

*Post-menopausal: Yes No Unknown

If yes, specify:
Years since menopause:
Years of HRT:

*Vaginal births: 0

*Cesarean sections: 0

*Miscarriages: 0

*Ectopic pregnancies: 0

*Comorbidity / previous intra-abdominal surgery: Yes No Unknown

If yes, specify:
- Hypertension
- Diabetes
- Asthma / Chronic lung
- RA / SLE / Vasculitis
- Hyperlipidemia
- Thyroid disorder
- Neurological disorder
- Non-uterine intra-abdo
- Uterine intra-abdominal (excluding C-section)
- Other
- Unknown

*Previous smoker: Yes No Unknown

Pack years:

Serology / Cervix screen

*CMV: Negative

*EBV: Nega

*Toxoplasma: Negative

*High-risk HPV: Nega

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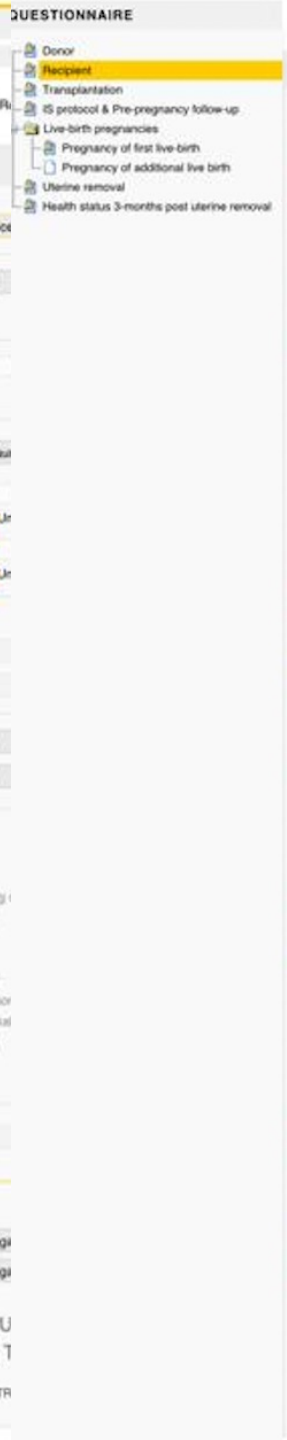
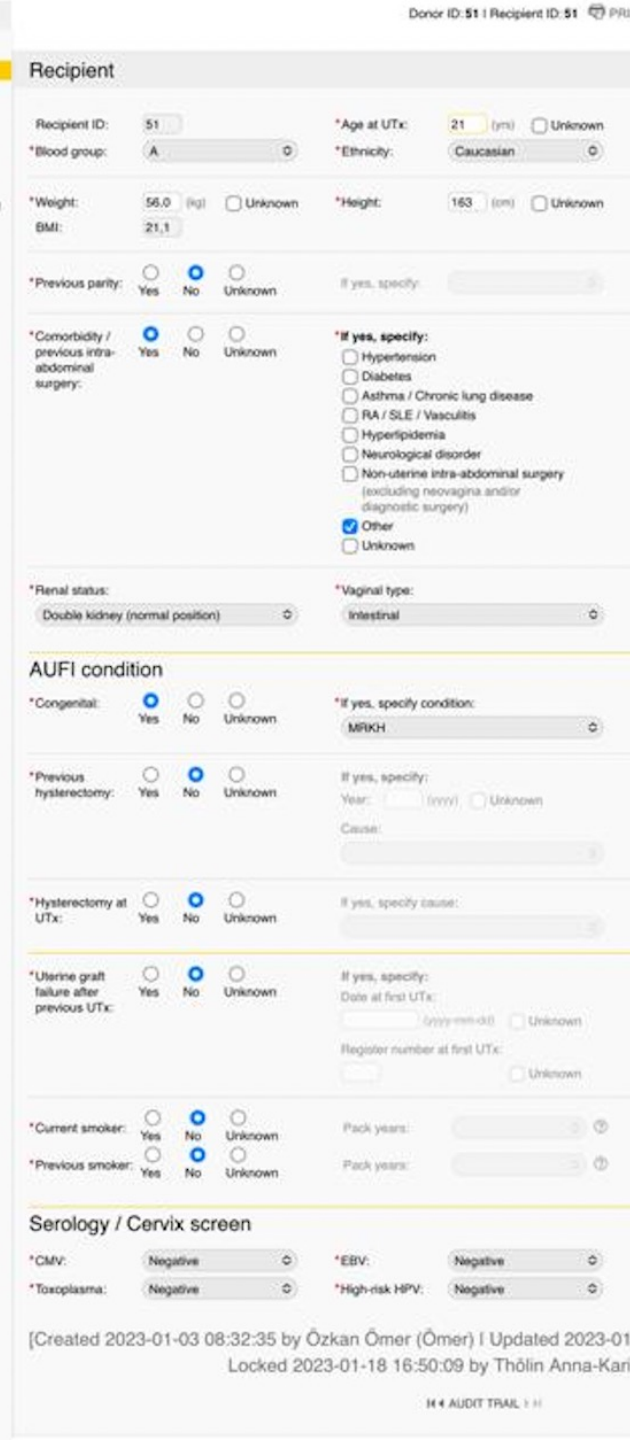
AUDIT TR



QUESTIONNAIRE
- Donor
- Recipient
- Transplantation
- IS protocol & Pre-pregnancy follow-up
- Live-birth pregnancies
  - Pregnancy of first live-birth
  - Pregnancy of additional live birth
- Uterine removal
- Health status 3-months post uterine removal



Donor ID: 51 | Recipient ID: 51 PRI

Recipient

Recipient ID: 51

*Age at UTx: 21 (yrs) Unknown

*Blood group: A

*Ethnicity: Caucasian

*Weight: 56.0 (kg) Unknown

*Height: 163 (cm) Unknown

BMI: 21.1

*Previous parity: Yes No Unknown

If yes, specify:

*Comorbidity / previous intra-abdominal surgery: Yes No Unknown

*If yes, specify:
- [ ] Hypertension
- [ ] Diabetes
- [ ] Asthma / Chronic lung disease
- [ ] RA / SLE / Vasculitis
- [ ] Hyperlipidemia
- [ ] Neurological disorder
- [ ] Non-uterine intra-abdominal surgery (excluding neovagina and/or diagnostic surgery)
- [x] Other
- [ ] Unknown

*Renal status: Double kidney (normal position)

*Vaginal type: Intestinal

AUFI condition

*Congenital: Yes No Unknown

*If yes, specify condition: MRKH

*Previous hysterectomy: Yes No Unknown

If yes, specify:
Year: (yyyy) Unknown
Cause:

*Hysterectomy at UTx: Yes No Unknown

If yes, specify cause:

*Uterine graft failure after previous UTx: Yes No Unknown

If yes, specify:
Date at first UTx: (yyyy-mm-dd) Unknown
Register number at first UTx: Unknown

*Current smoker: Yes No Unknown

Pack years:

*Previous smoker: Yes No Unknown

Pack years:

Serology / Cervix screen

*CMV: Negative

*EBV: Negative

*Toxoplasma: Negative

*High-risk HPV: Negative

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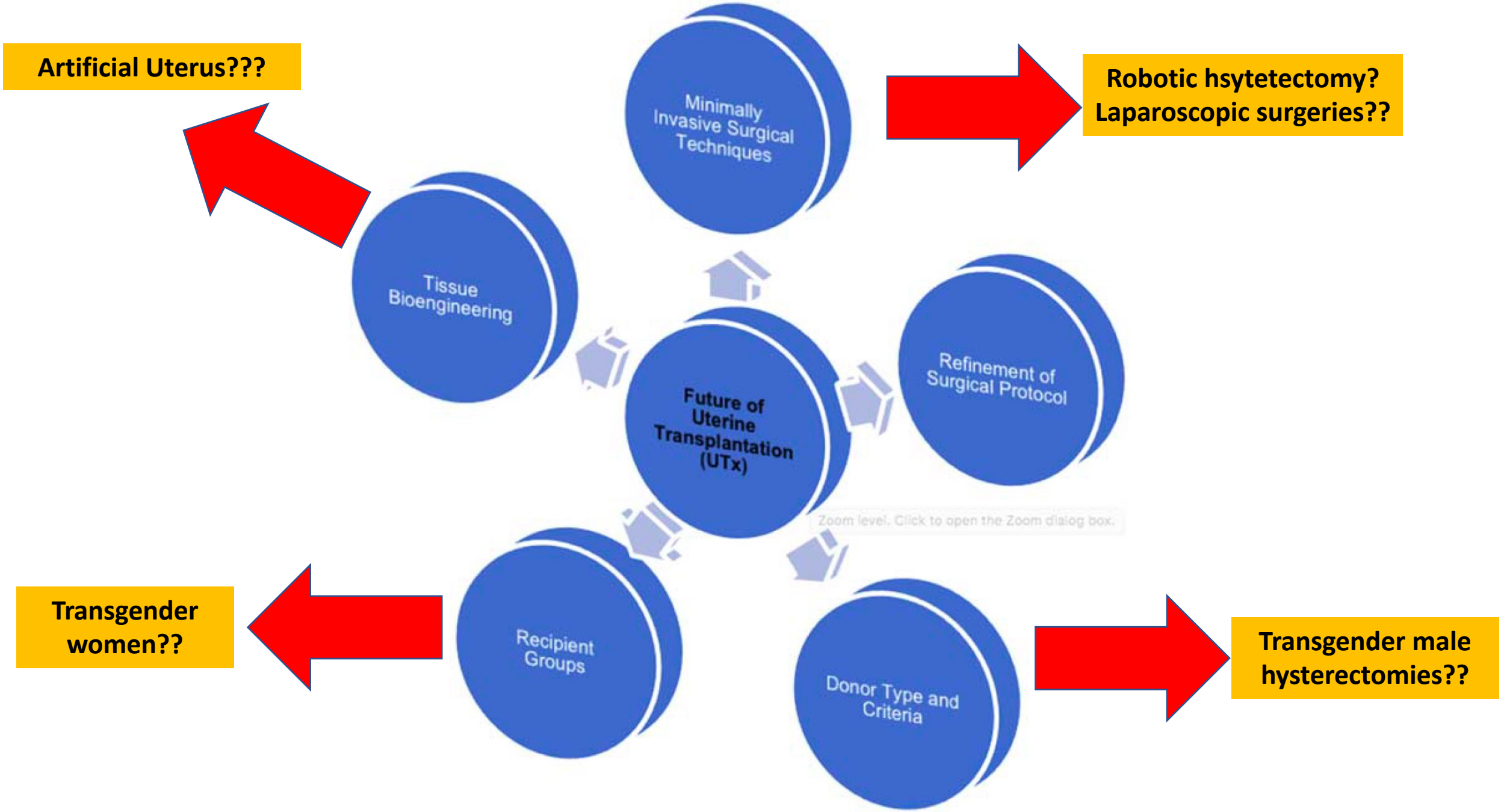
AUDIT TRAIL

Future Perspectives

- Deceased donor use
- Alternative venous outflow-use (esp Ovarian vein)
- Minimal invasive surgery
- Bioengineered Uterus


Artificial Uterus???
Minimally Invasive Surgical Techniques
Robotic hsytetectomy?
Laparoscopic surgeries??
Tissue Bioengineering
Future of Uterine Transplantation (UTx)
Refinement of Surgical Protocol
Transgender women??
Recipient Groups
Donor Type and Criteria
Transgender male hysterectomies??

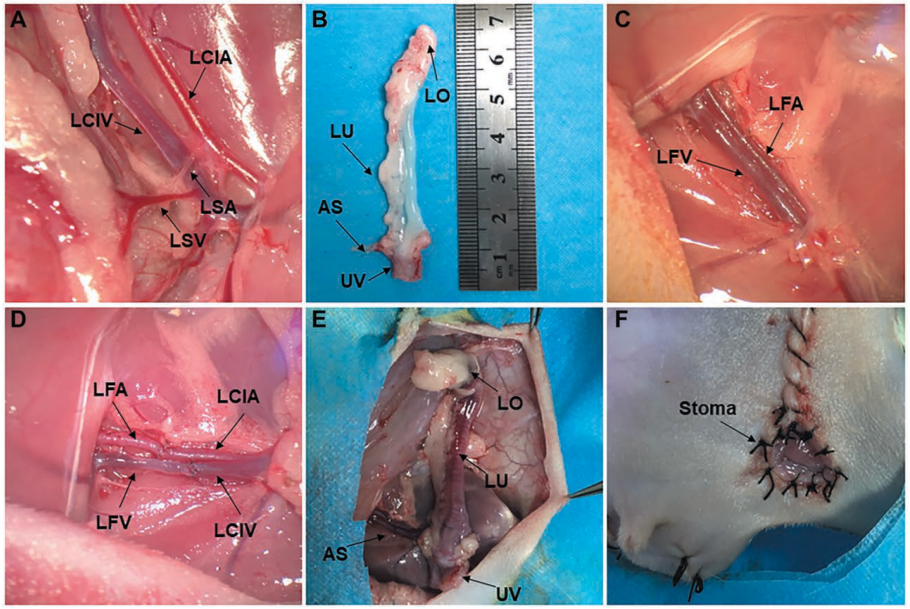
OPEN

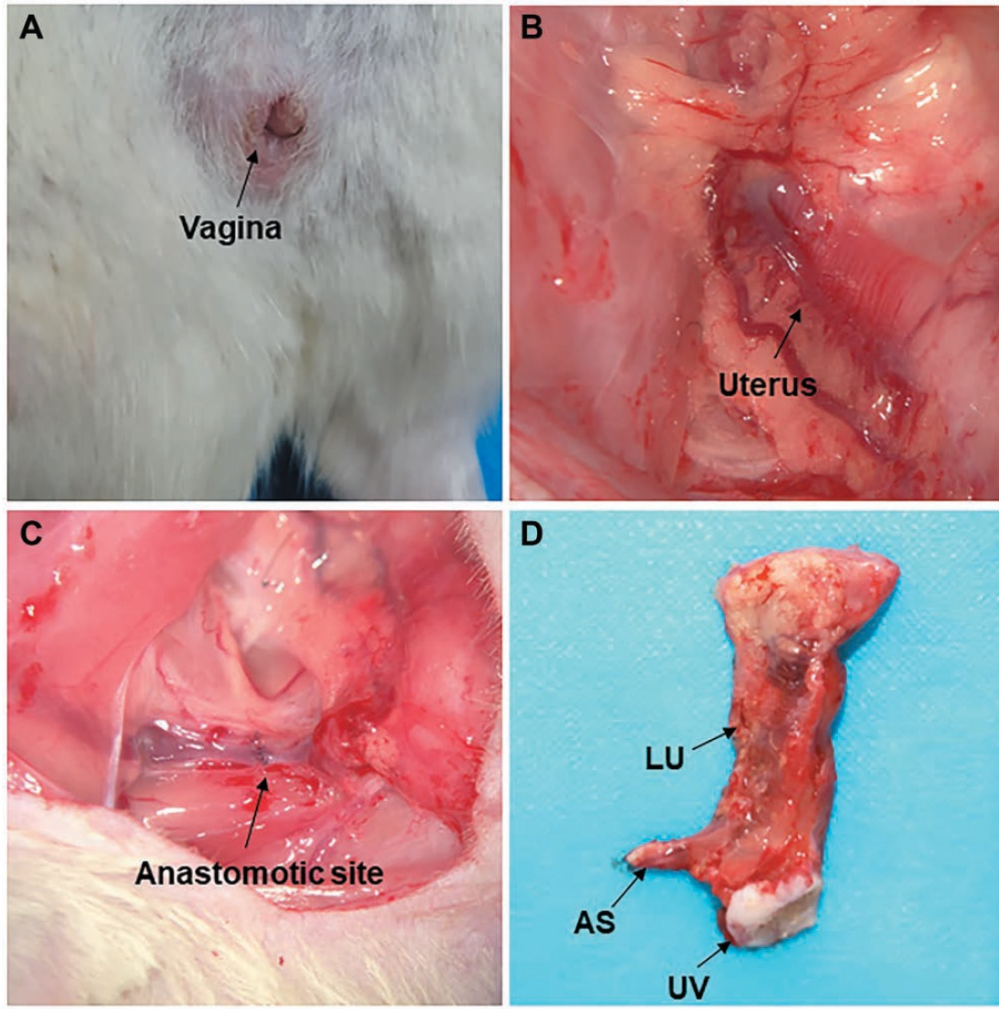
Transplantation of the Uterus in the Male Rat

Liu Yang, MD,[1] Tong Wang, MD,[1] Lin Chen, MD,[1] Xia Li, PhD,[2] Yajuan Song, MD,[1] Zhou Yu, MD, PhD,[1] and Baoqiang Song, MD, PhD[1]

Background. Uterus transplantation (UTx) is one of the potential methods to cure absolute uterine factor infertility of transgender. However, this mostly comes with many technological challenges. **Methods.** Left inguinal UTx was performed in 13 castrated male rats. End-to-end anastomosis of donor common iliac vessels to recipient femoral vessels was used for transsexual UTx. Sampling was performed on day 30 after transplantation. Grafts were used to analyze the histological changes. TUNEL assay was applied to stain the apoptotic cells. Immunological rejection was judged by flow cytometry. **Results.** Six uteri, 4 ovaries, and 4 upper vaginas were found at day 30 posttransplantation. Similar histological changes to proestrus, estrus, and diestrus of female rats were examined in the transplanted uteri. The histological changes of transplanted vaginas showed similarity to proestrus, estrus, and metestrus of the female rats. Follicles of different stages and corpus luteum with distinct morphological appearances were also observed. The TUNEL assay revealed a higher apoptosis of granulosa cells in transplanted ovaries compared with normal ovaries. **Conclusions.** A rat model of transsexual unilateral inguinal uterine transplantation in castrated rats was established, which will provide a reference for bilateral transsexual UTx in animals and genetically 46 XY individuals who wish to become real women through transsexual UTx.

(*Transplantation* 2023;00: 00–00).





- 14 robotic-assisted UTx retrievals
- 4 laparoscopic assisted
- Sweeden, China, India, Spain
- China oophorectomy in the premenopausal donor to retriev ovarian vein

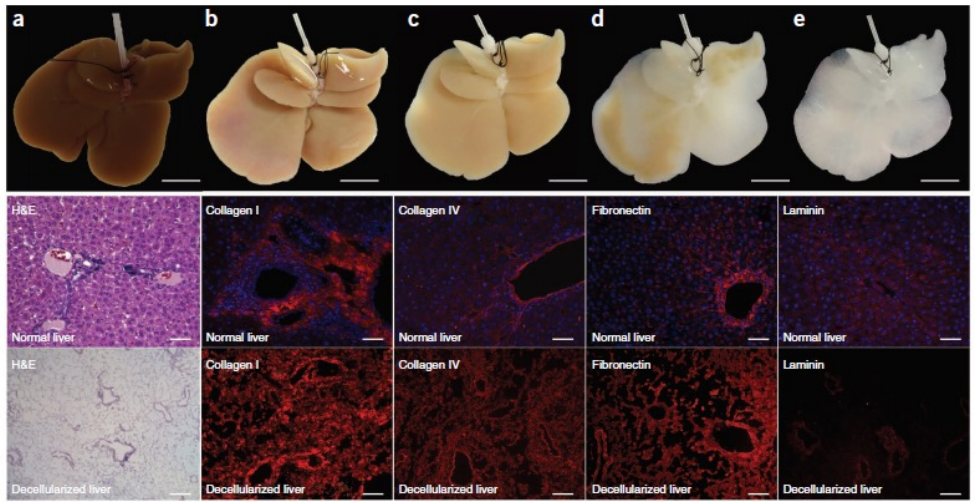
tissue engineered rat livers

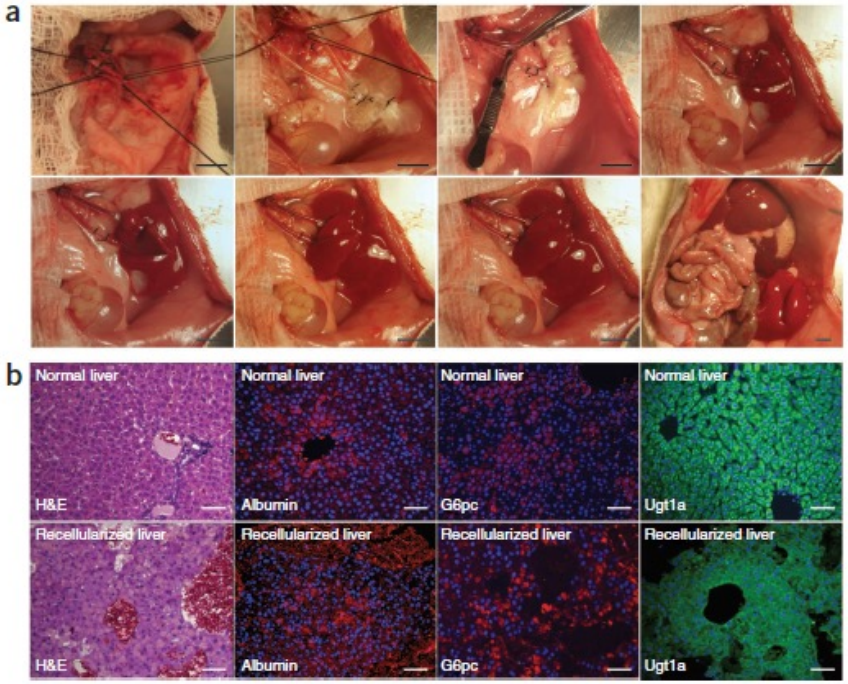
TECHNICAL REPORTS

nature medicine

Organ reengineering through development of a transplantable recellularized liver graft using decellularized liver matrix

Basak E Uygun[1], Alejandro Soto-Gutierrez[1,6], Hiroshi Yagi[1,6], Maria-Louisa Izamis[1], Maria A Guz
Carley Shulman[1], Jack Milwid[1], Naoya Kobayashi[3], Arno Tilles[1], Francois Berthiaume[1,4], Martin
Yaakov Nahmias[1,6], Martin L Yarmush[1,4] & Korkut Uygun[1]



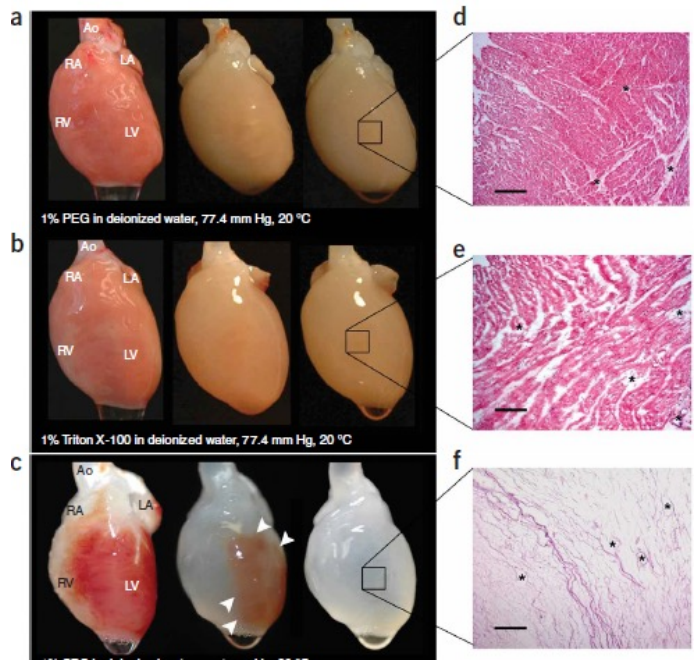


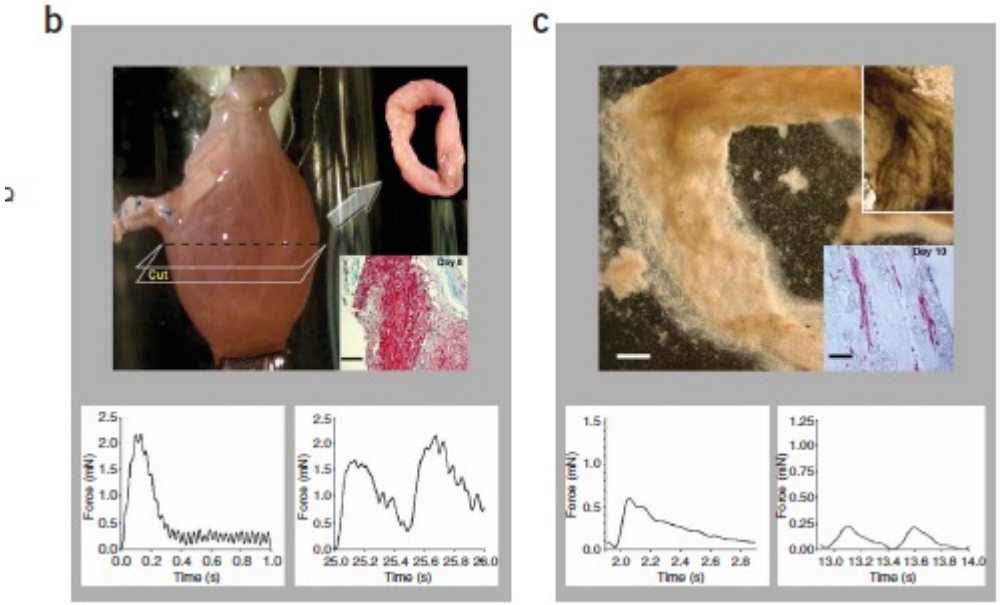
nature medicine

n/naturemedicine

Perfusion-decellularized matrix: using nature's platform to engineer a bioartificial heart

Harald C Ott[1], Thomas S Matthiesen[2], Saik-Kia Goh[2], Lauren D Black[3], Stefan M Kren[2], Theoden I Netoff[3] & Doris A Taylor[2,4]





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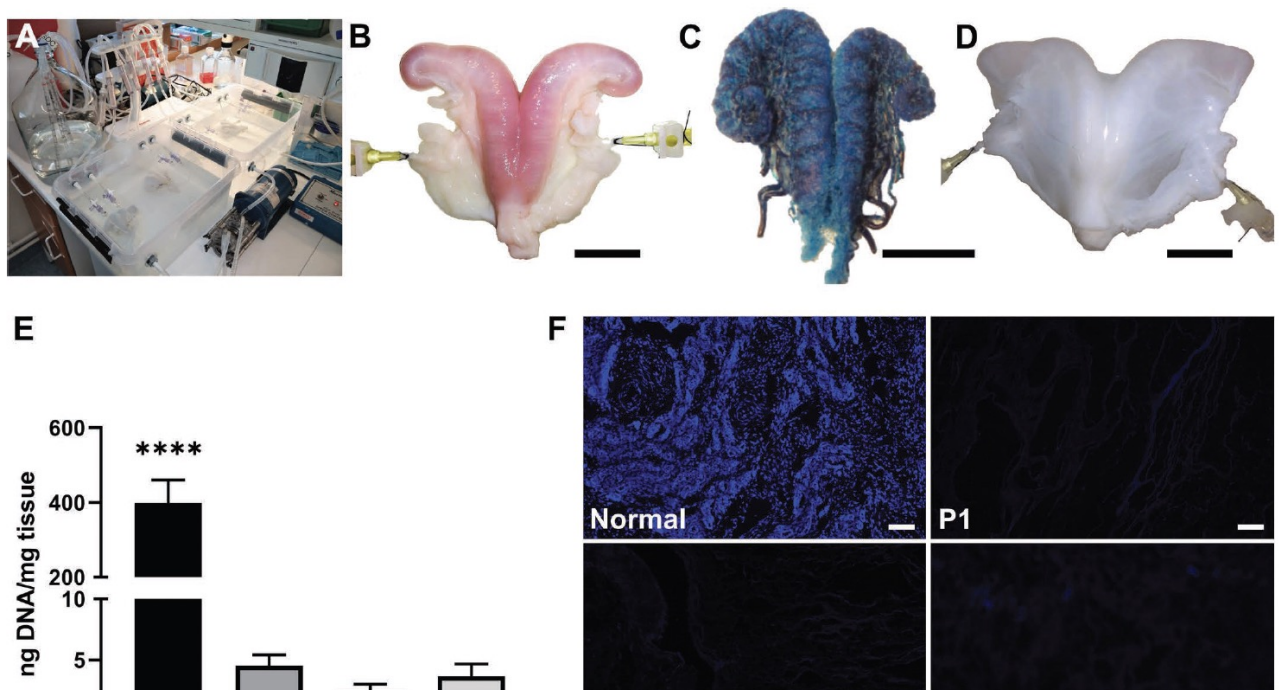
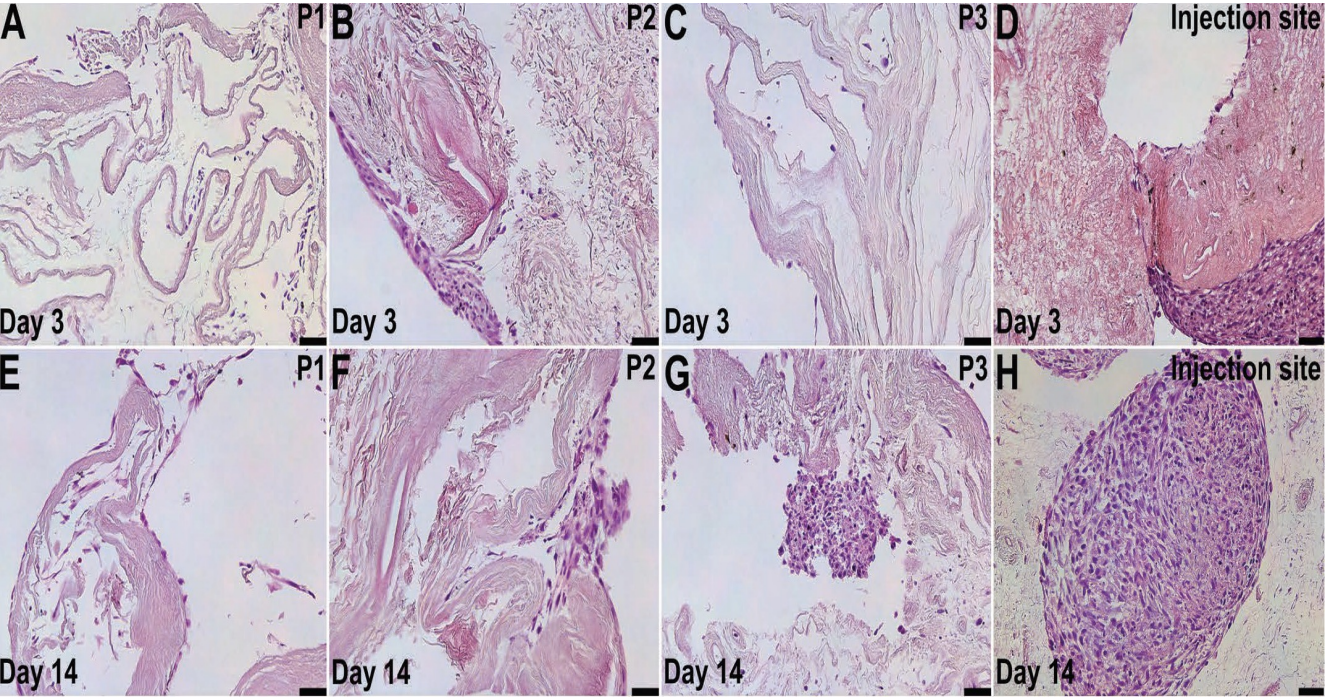
ORIGINAL RESEARCH

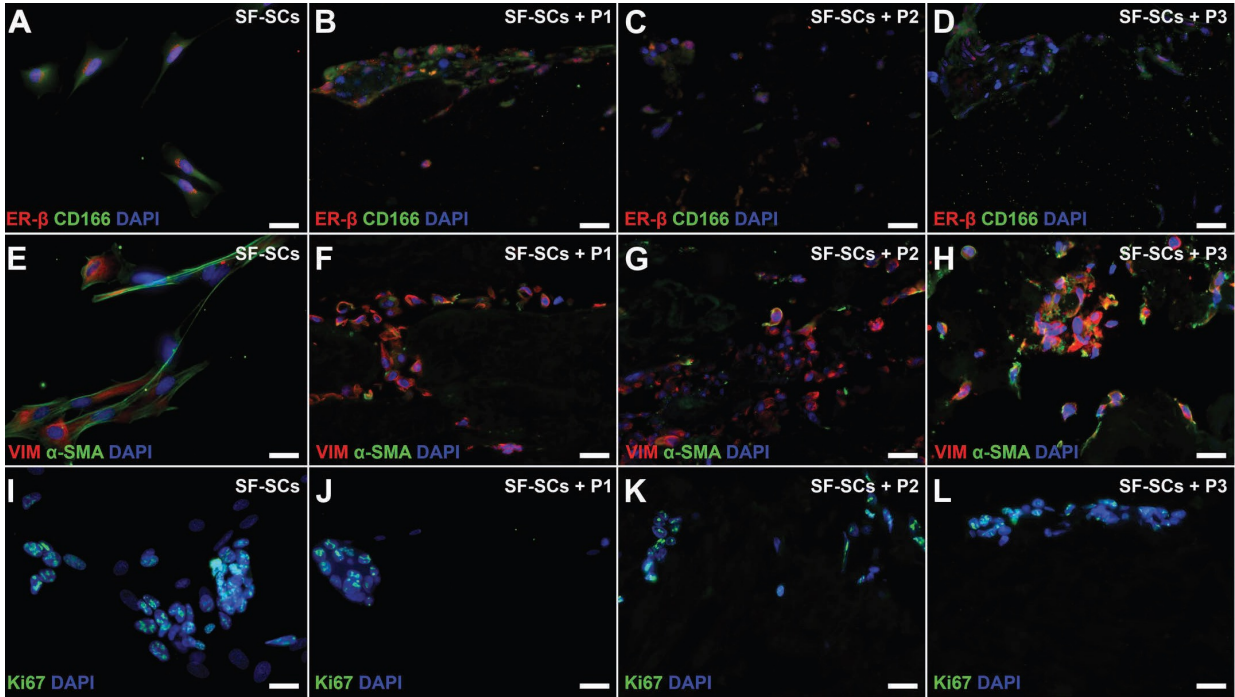
Towards uterus tissue engineering: a comparative study of sheep uterus decellularisation

T.T. Tiemann[1,2,3], A.M. Padma[1,2], E. Sehic[1,2], H. Bäckdahl[4], M. Oltean[1,5], M.J. Song[1,2,6], M. Brännström[1,2,7], and M. Hellström[1,2,*]



Recellularisation

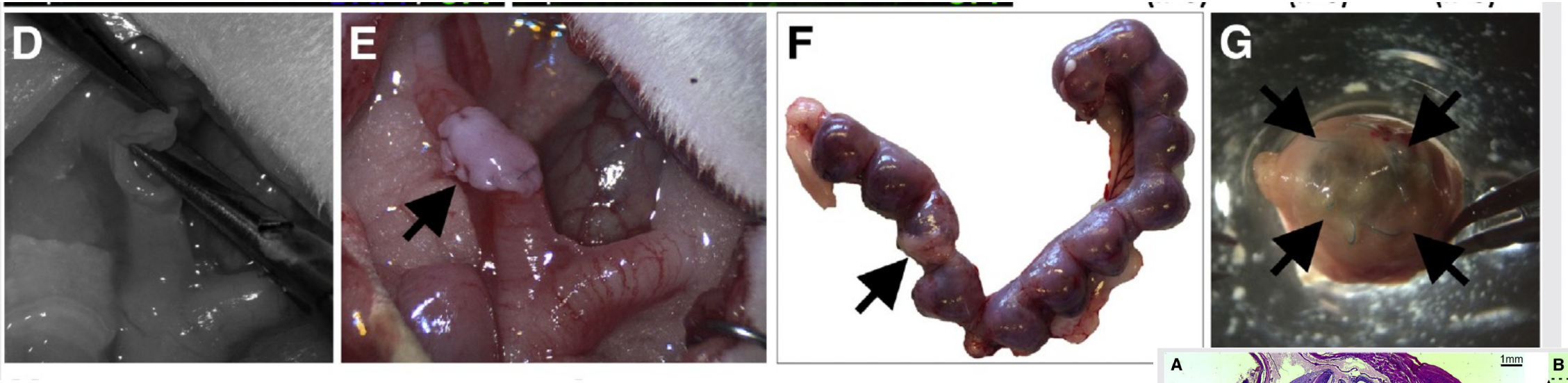


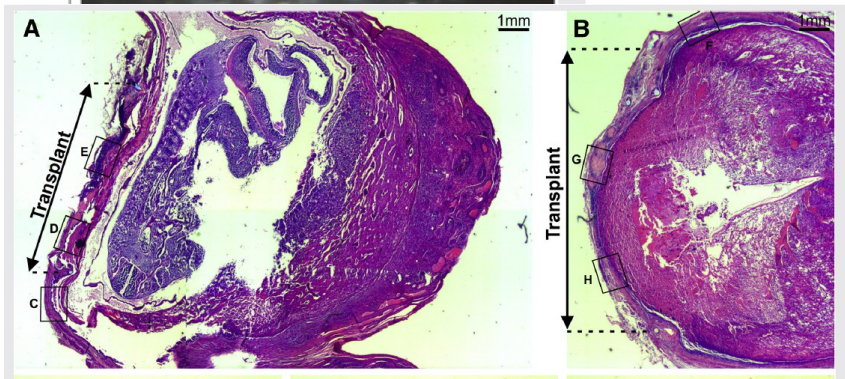


ORIGINAL ARTICLE: REPRODUCTIVE SCIENCE

Bioengineered uterine tissue supports pregnancy in a rat model

Mats Hellström, Ph.D.,[a,b] Juan M. Moreno-Moya, Ph.D.,[a,b] Sara Bandstein, M.Sc.,[a,b] Eva Bom, Ph.D.,[a,c] Randa R. Akouri, M.D., Ph.D.,[a,b] Kaoru Miyazaki, M.D., Ph.D.,[d] Tetsuo Maruyama, M.D., Ph.D.,[d] and Mats Brännström, M.D., Ph.D.[a,b]





ARTICLES
https://doi.org/10.1038/s41587-020-0547-7
nature biotechnology

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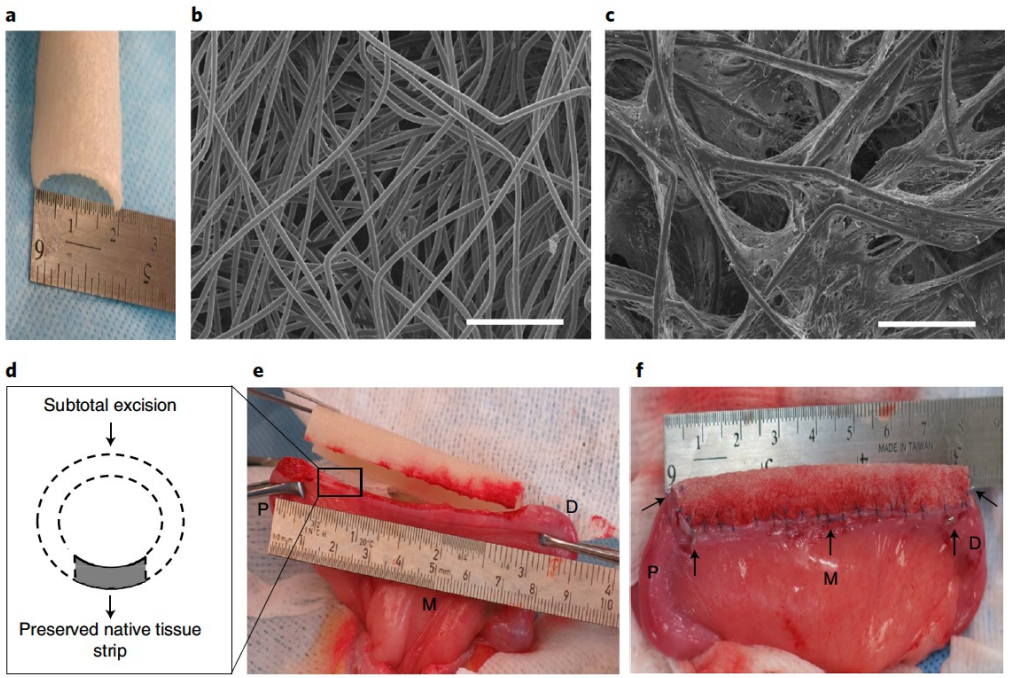
A tissue-engineered uterus supports live births in rabbits

Renata S. Magalhaes, J. Koudy Williams, Kyung W. Yoo, James J. Yoo and Anthony Atala

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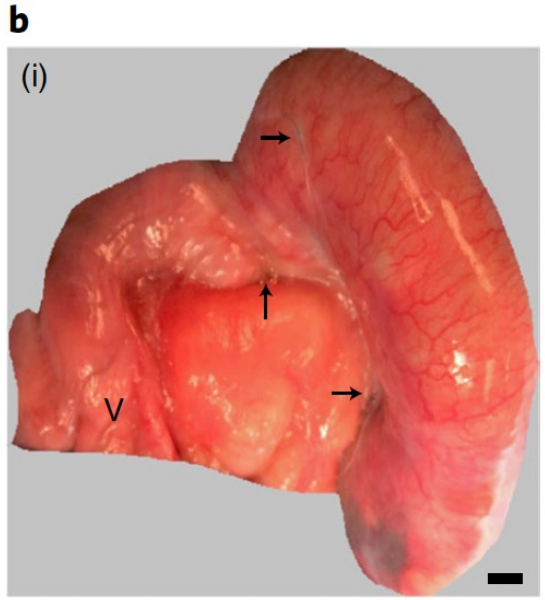
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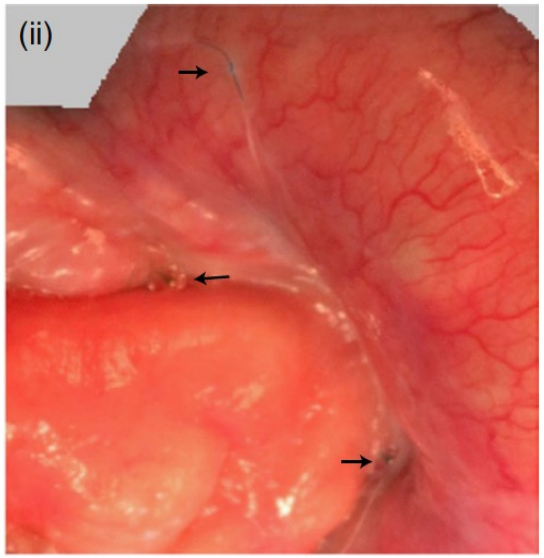
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Multivisceral transplantation of pelvic organs in rats

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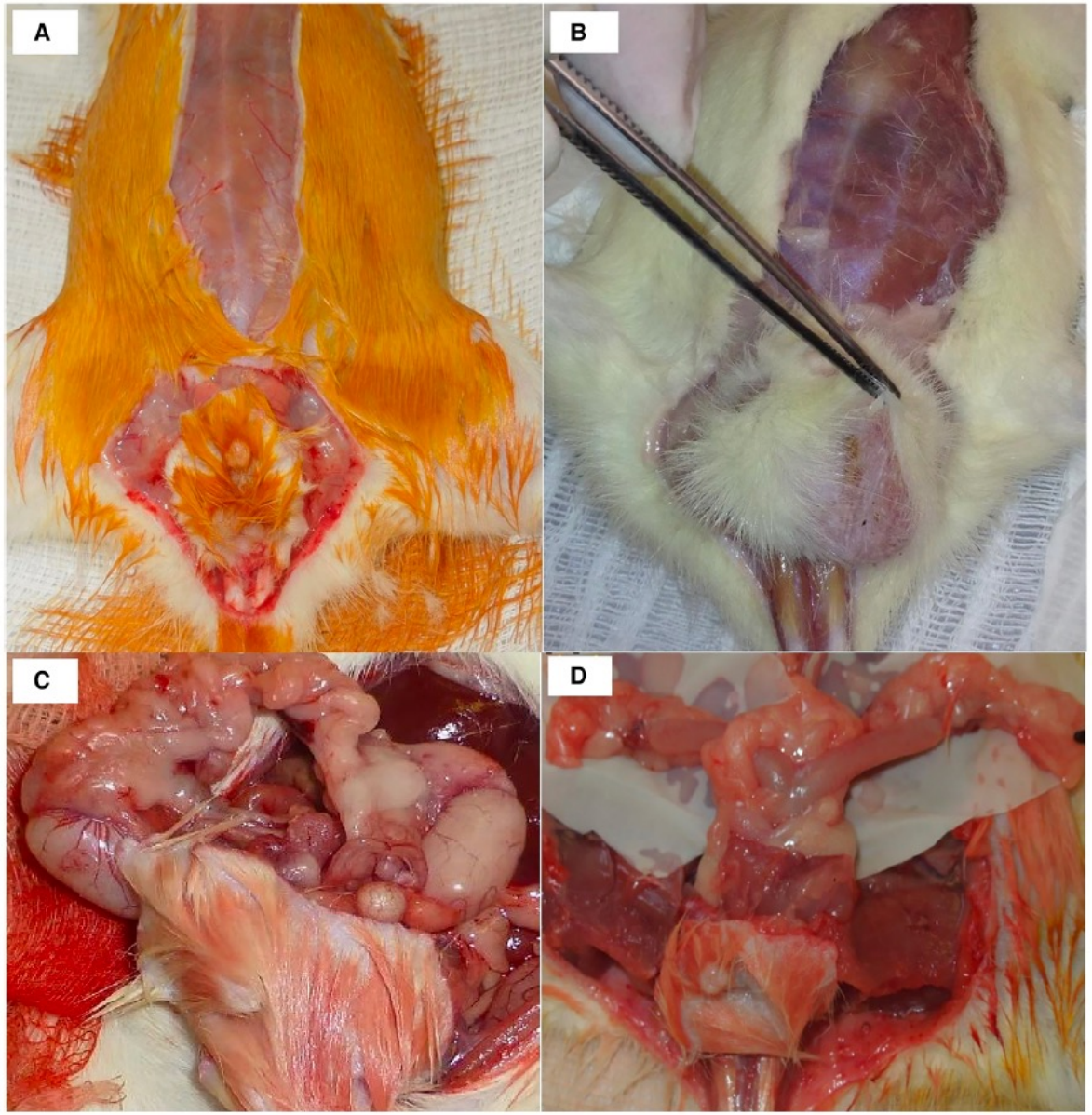
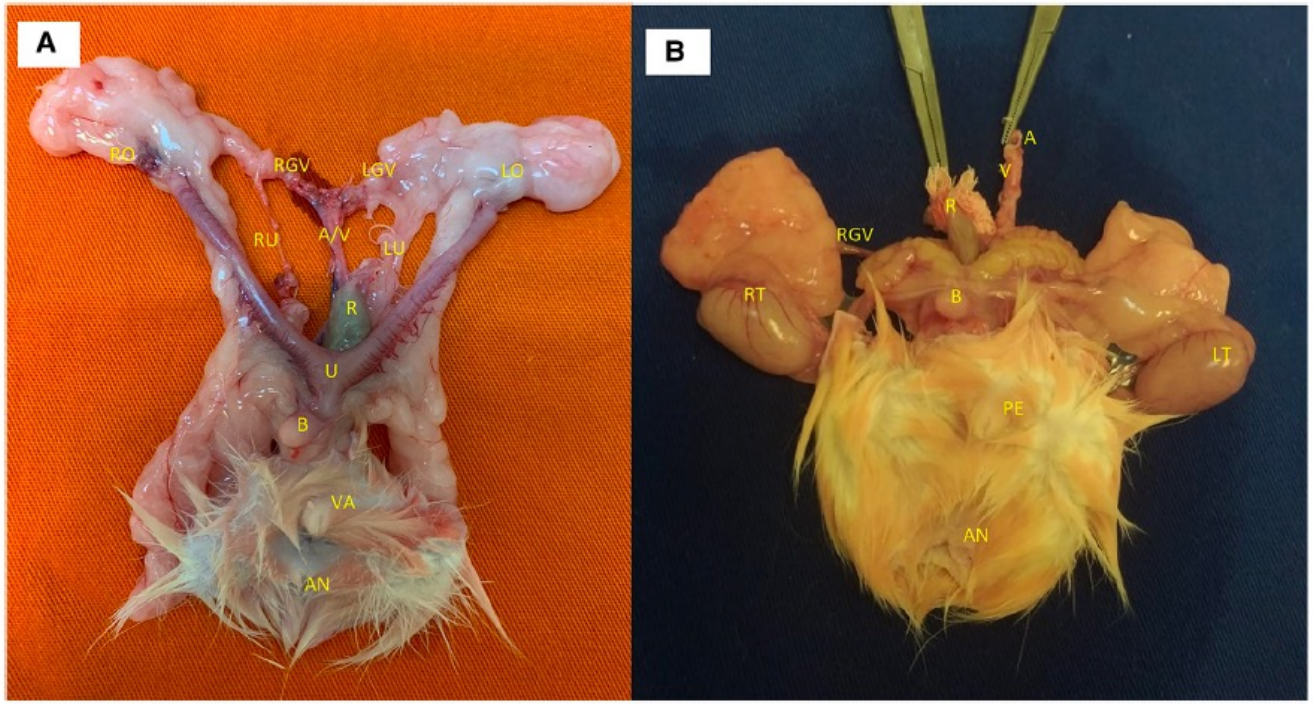


FIGURE 1
Incision details in male (A) and female (B) donors. Graft dissection in male (C) and female (D) rats.



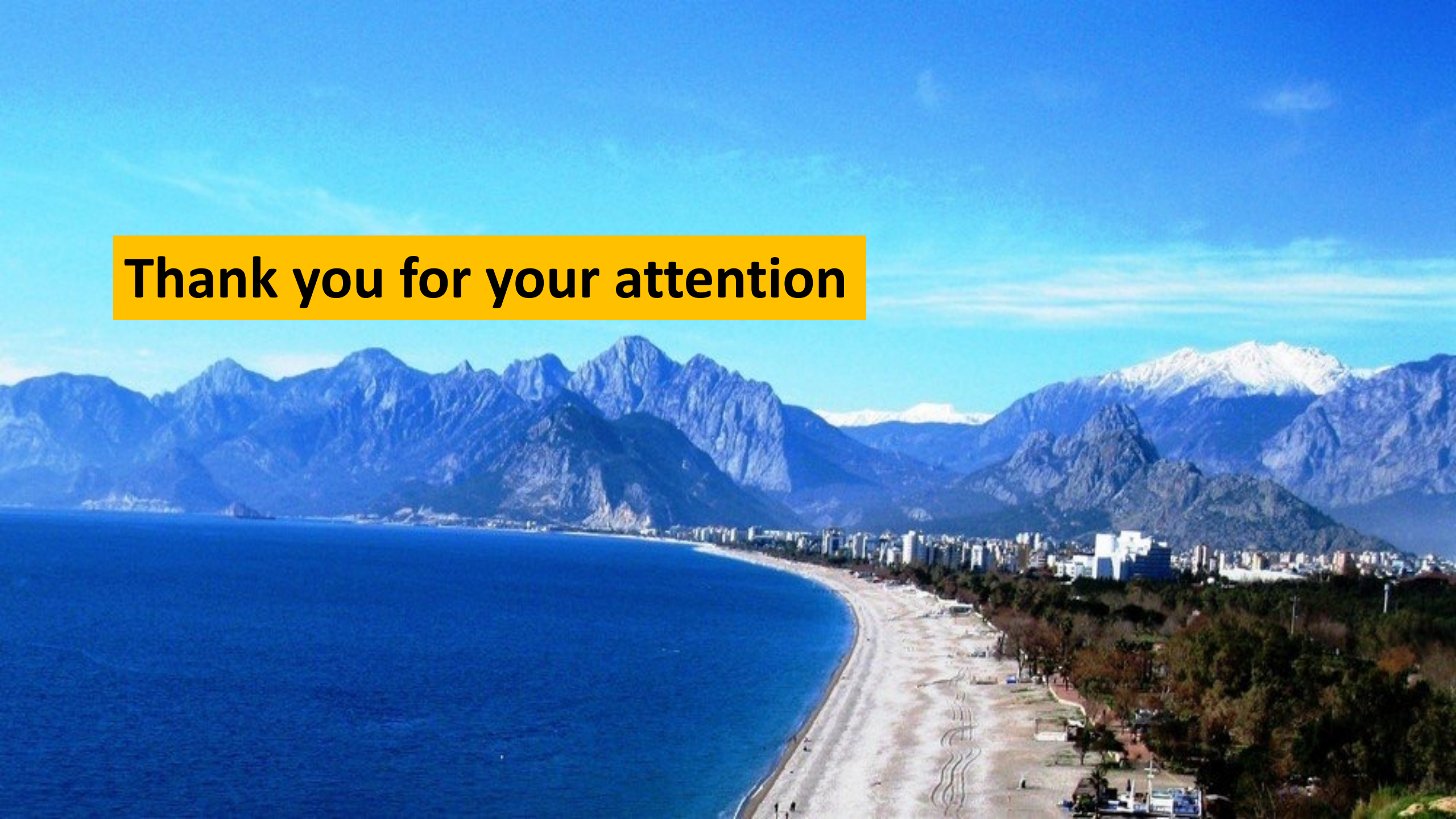
RE 3
emale graft: RO, right ovary; LO, left ovary; RGV, right gonadal vessels; LGV, left gonadal vessels; A/V, aorta and vena Cava; RU, right ureter; LU, left er; R, rectum; U, uterus; B, bladder; VA, vagina; AN, anus. (**B**) Male graft: RT, right testicle; LT, left testicle; RGV, right gonadal vessels; R, rectum; A, a; V, vena cava; B, bladder; PE, penis; AN, anus.

FIGURE 4
The final appearance of pelvic floor transplantation in a male subject.

Conclusion

-Utx transplantation still risky and experimental

- Risks from immunosuppression
- at least three surgical procedures
  - initial allotransplantation
  - Caesarian section to deliver the child (and a second section if a second child is desired)
  - graft hysterectomy after the delivery.
- a high-risk pregnancy
- Utx recipients (Transgender women??)
- Tissue bioengineering (Artificial Uterus)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