Early Uterine Transplant Graft Loss Due to Thrombosis: Single-Center Experience With Causes, Prevention, Diagnosis, and Treatment

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Received July 20, 2022
Accepted August 3, 2022

Summary

Uterus transplantation (UTx) is a promising treatment option for women who wish to give birth but suffer from absolute uterine factor infertility. This paper presents an interim analysis of a trial focusing on the causes, prevention, diagnosis, and management of graft thrombosis. Our team analyzed 10 cases of UTx (recipients numbered 1 to 10). Early thrombosis developed in 2 of 10 (20 %) recipients, and thrombectomy and temporary viability preservation were achieved in both cases. However, re-thrombosis developed in both cases, and a graft hysterectomy was carried out. In recipient number 2, vascular changes might have contributed to graft thrombosis. The histopathological finding of the explant revealed subintimal excentric fibrosis with focal sclerotic changes. In recipient number 8, thrombosis was facilitated by external compression of the vascular pedicles by the hematoma as well as production of *de novo* donor-specific antibodies. Thrombosis led to graft loss in both cases despite an attempt at a thrombectomy. Therefore, the focus must be on the prevention including a thorough evaluation of the donor candidate. In the postoperative course, perfusion is closely followed-up with an ultrasound, Doppler flow monitoring, and macroscopic evaluation of the cervix. In the case that findings are unclear, a relaparotomy should be promptly indicated. If thrombosis is revealed, a thrombectomy and an attempt to salvage of the graft are indicated; however, the role of this strategy is questionable due to the low chance of long-term success. The indication of upfront graft removal and early re-transplantation in the treatment of uterine graft remains debatable.

Key words

Assisted Reproductive Technique • Female Infertility • Mullerian aplasia • Organ Transplantation • Uterine factor infertility

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Introduction

Uterine transplantation (UTx) is an experimental method of fertility restoration for women suffering from absolute uterine factor infertility. By restoring reproductive anatomy, UTx enables affected women to meet their reproductive aspirations and give birth [1]. The first UTx was performed in Saudi Arabia in 2000 [2]. From 2012 to 2013, a Swedish team from Gothenburg performed nine living-donor (LD) UTx procedures [3]. The first live birth from a uterine transplant patient occurred in

September 2014 [4]. This historic event ignited enormous interest, rapidly spreading throughout the international transplant community [5-9]. The number of centers performing UTx has risen rapidly, as has the number of cases of UTx performed. Both LD and deceased-donor (DD) grafts are suitable sources of uteri [4,8].

There is an ongoing discussion on the number of veins used for vascular anastomoses. The technical aspect of the procedure is based on the establishment of steady inflow and outflow of the uterine graft. The inflow is provided by two anastomoses from the anterior portion of the internal iliac artery (IIA) graft to the external iliac artery (EIA) in an end-to-side (E-S) fashion. Establishing outflow rather than inflow is more variable, depending on the quality and caliber of individual graft veins. Up to 4 veins can provide the outflow: two uterine veins (UV) and/or two utero-ovarian veins (UOV; the portion of the ovarian vein between the ovaries and the uterus) [10]; however, a minimum of 2 venous anastomoses must always be established.

In this article, we analyze the causes of early graft loss and vascular complications in a cohort. Equally, as in other organ transplants, thrombosis is a severe complication, often resulting in graft loss. Two types of thromboses are distinguished: (i) early (≤ 1 month); and (ii) late (> 1 month). Generally, early thrombosis is frequently caused by an erroneous surgical technique. However, the etiology of UTx thrombosis is often complex and multifactorial. Possible reasons for graft thrombosis are listed in Table 1. We wish to suggest prevention, diagnosis, and treatment strategies for this rare entity.

Table 1. Possible reasons and risk factors for early graft thrombosis

Poor quality of graft vessels
Damage to the vessels during procurement or *ex vivo* perfusion (e.g., intimal dissection caused by cannulation of the uterine artery)
Poor quality perfusion, *ex vivo* perfusion
Long cold or warm ischemia time
A technical error in construction of the anastomosis
Long vascular pedicles, kinking of vessels
Insufficient prophylaxis by low-molecular-weight heparin
Coagulation disorder following reperfusion
Compression of vessels by hematoma
Microvascular obstruction caused by fibrinogen accumulation
The use of arterial conduits
Performance of transplantation in a low-volume center

Material and Methods

Study design, ethical approval

This prospective clinical trial studies the feasibility of UTx with grafts retrieved both from LDs and DDs. Donor and recipient evaluation, organ retrieval, transplantation, and early follow-ups after transplantation were performed at the Institute for Clinical and Experimental Medicine, Prague, Czech Republic. The trial was performed according to a revised version of the Declaration of Helsinki from 2013 [11]. An institutional review board approval number was obtained (identifier 2044/15 [NM-15-01]) on November 11, 2015, *i.e.,* prior to commencement of the trial. The Czech Ministry of Health granted the trial approval to perform up to 10 cases of LD and 10 cases of DD UTx (trial registration number MZDR 32776/2015). The trial is registered in the ClinicalTrials.gov database (identifier NCT03277430). Dr. Jiri Fronek, the principal investigator, adequately and repeatedly explained the details of the study to all of the participants, who later provided informed consent. All of the participants each provided informed consent.

Cohort of patients

This article is an interim analysis of early graft loss that occurred in the first half of the trial. This paper

analyzes 10 cases of UTx, *i.e.,* 5 cases of LD and 5 cases of DD UTx. The transplantation procedures were performed from April 2016 to April 2018 at the Institute of Experimental Medicine, Prague, Czech Republic.

Donor candidate evaluation

Uterine donor candidates are required to meet inclusion and exclusion criteria discussed elsewhere [12]. Part of uterine donor candidate evaluation involves assessing uterine vessel quality. At our institution, computed tomography (CT) angiography is used to evaluate arteries and veins. We evaluate arteries for their diameter, course, degree of atherosclerosis, variant anatomy, *etc.* Veins are evaluated for their number and caliber.

Uterine retrieval, back table, transplantation procedure

Uterine procurement, as a part of multiorgan procurement from DDs, has been described elsewhere [13]. The uterus is the last organ to be procured since it is a non-vital organ. Longer vascular pedicles can be procured from a DD than from a LD (ovarian rather than utero-ovarian veins, UV with segments of internal iliac veins [IIV], uterine arteries [UA] with segments of IIA). In LD retrievals, only short vascular pedicles can be retrieved due to the risk posed to the donor (ureteric injury, premenopausal ovarian insufficiency, bleeding, neural injury, *etc.*). Once heparin is administered, perfusion is carried out with a preservation solution, the uterus is excised, and the graft is examined and adjusted on a "back table."

The "back table" procedure involves assessment of the organ, including the quality of perfusion (homogeneity, color) and uterine vessels (length, diameter, patency, degree of atherosclerosis, *etc.*), and evaluates the endometrium through a hysteroscopy. A Pap smear (a screening method to detect potentially precancerous/cancerous processes of the cervix) is also carried out as part of the procedure. The number of veins used for anastomoses varies from 2 to 4, depending on their quality. All vessels of sufficient quality are adjusted for implantation; the remaining vessels are ligated.

Transplantation is performed via infraumbilical laparotomy. External iliac vessels are dissected bilaterally. Arterial and venous anastomoses are constructed E-S with polypropylene 6-0 to 8-0 sutures, depending on the vessel caliber. The rim of the graft's vagina is anastomosed to the recipient vagina/neovagina. The graft is retained in its position by sutures in order to prevent dislocation and consequent vessel torsion/kinking, which could lead to thrombosis. A Cook-Swartz Doppler blood flow probe (Cook Medical, Bloomington, IN, USA) is placed on one supplying UA and exteriorized to enable postoperative perfusion monitoring. Technical details of the vessels used for anastomosis are provided in Table 2.

Follow-up of perfusion, prophylaxis of thrombosis

Graft perfusion is closely monitored in the postoperative period with the help of both a transabdominal ultrasound (US) and the Doppler blood flow probe. The transabdominal US is performed twice a day for 6 days and consequently once a day until the patient is discharged. Furthermore, arterial patency is checked with the Doppler probe every 4 hours for the first 3 days and every 6 hours on days 4 through 7. On day 7, the probe is extracted. In case of uncertainty, cervix color is inspected, and a transvaginal US is performed to verify perfusion. Once released from hospital care, the recipients are checked twice a week in the first month, once every two weeks in months 2 to 6, and once every 3 weeks in the further course [9].

To prevent graft thrombosis, we treat all recipients with low-molecular-weight heparin at a prophylactic dose for one month according to protocol. They also receive 100 mg of acetylsalicylic acid daily for the entire time the graft remains *in situ* [9].

Histopathology of explanted grafts

All removed grafts, either urgently or electively, underwent a histopathological examination. A detailed examination was performed on parametrial tissue with vascular structures as well as on tissue obtained from the exocervix (the ectocervical part of the uterine cervix lined with squamous epithelium), the endocervix, and the uterine body (endometrium, myometrium, perimetrium). Formalin-fixed tissue sections were cut and routinely stained with hematoxylin and eosin (H&E, Merck & Co., Inc., NJ, USA). Additionally, connective tissue was highlighted using the Verhoeff–Van Gieson stain (proprietary technique). For immunohistochemical analysis, 4 µm thick paraffin sections were incubated with anti-C4d (Biomedica Medizinprodukte GmbH, Wien, Austria), anti-CD31, and anti-D2-40 primary antibodies (Dako North America Inc., Carpinteria, California, USA; secondary antibody: Ventana Medical Systems, Inc., Tucson, Arizona, USA). Two pathologists (E.S. and J.M.) carried out the evaluation. The specimens were assessed for signs of rejection, infection, and vascular pathology.

Table 2. Details of vascular anastomoses of uterine grafts

	Donor type	Arterial anastomosis				Venous anastomosis				Number of venous anastomoses
		Right		Left		Right		Left		
		Donor	Recipient	Donor	Recipient	Donor	Recipient	Donor	Recipient	
Recipient 1	LD	UA	IIA	UA	EIA	OV	IIV	OV	EIV	2
Recipient 2	DD	IIA segment	EIA	IIA segment	EIA	UV, 2xUOV*	EIV	UV, OV	EIV	4
Recipient 3	DD	IIA segment	EIA	IIA segment	EIA	UV	EIV	UV	EIV	2
Recipient 4	LD	UA	EIA	UA with a patch of the IIA	EIA	UOV	EIV	UOV	EIV	2
Recipient 5	DD	IIA segment	EIA	IIA segment	EIA	UV, OV	EIV	UV, OV	EIV	4
Recipient 6	LD	UA	EIA	UA	EIA	OV***	EIV	OV***	EIV	2
Recipient 7	DD	IIA segment	EIA	IIA segment	EIA	UV, OV	EIV	UV, OV	EIV	4
Recipient 8	LD	UA	EIA	UA	EIA	UV, UOV**	EIV	UV	EIV	2**
Recipient 9	LD	UA	EIA	UA	EIA	UV, OV***	EIV	UV, OV***	EIV	4
Recipient 10	DD	IIA segment	EIA	IIA segment	EIA	UV, OV	EIV	UV, OV	EIV	4

Abbreviations: DD, deceased donor; EIA, external iliac artery; EIV, external iliac vein; IIA, internal iliac artery; IIV, internal iliac vein; LD, living donor; OV, ovarian vein; UA, uterine artery; UOV, utero-ovarian vein; UV, uterine vein. * Two right UOVs were reconstructed into a single orifice, ** Due to an unsuccessful thrombectomy of the right UV, a new anastomosis of the right UOV to the EIV was performed during re-operation on postoperative day 5, *** A bilateral oophorectomy was performed along with retrieval of the uterus.

Table 3. Characteristics of recipients and donors

	Donor type	Cause AUFI	Kidneys number/ position	Vagina	Relation donor-recipient	Age (y)		BMI (kg/m^2)		Smoking	Menopausal state	Parity of donor (vaginal/ C-section)	HLA mismatch class I/II	PRA	Length of procurement (min)	Length of transplantation (min)
Recipient 1		MRKH	2/normal	normal		30		22		yes			2/1	0 %		209
Donor 1	LD				mother		53		30	yes	yes, 5 y	2/0			321	
Recipient 2		MRKH	2/normal	Lap. Vecchietti		29		20		no			4/2	0 %		245
Donor 2	DD						57		20	no	yes	1/0			427*	
Recipient 3		MRKH	2/normal	Lap. Vecchietti		26		20		no			4/1	3 %		250
Donor 3	DD						24		33	yes	no	0/0			459*	
Recipient 4		MRKH	2/normal	Lap. Vecchietti		26		18		no				0 %		229
Donor 4	LD				mother's sister		58		34	no	yes, 5 y	2/0	1/1		369	
Recipient 5		MRKH	2/normal	dilation		24		21		no				0 %		299
Donor 5	DD						19		24	yes	no	0/0	3/1		420*	
Recipient 6		MRKH	2/normal	Lap. Vecchietti		23		26		no				0 %		296
Donor 6	LD				mother		47		36	no	yes, 6 mo	0/1	1/1		431	
Recipient 7		MRKH	1(right kidney agenesis)/normal	normal		32		17		no			3/2	7 %		233
Donor 7	DD						56		22	yes	yes	1/0			293*	
Recipient 8		MRKH	2/normal	Lap. Vecchietti		25		19		no			2/1	10 %		216
Donor 8	LD				mother		49		19	no	no	3/0			326	
Recipient 9		MRKH	2/normal	Lap. Vecchietti		26		21		no			1/1	0 %		216
Donor 9	LD				mother		48		22	no	no	2/0			332	
Recipient 10		MRKH	2/normal	normal		29		31		yes				7 %		319
Donor 10	DD						45		32	no	no	1/0	2/2		432*	
mean ± SD						28±3	46±14	22±4	27±6						351±46 (LD) 396±65*(DD)	249±39

Abbreviations: AUFI, Absolute uterine factor infertility; BMI, body mass index; C-section, cesarean section; DD, deceased donor; HLA, human leukocyte antigen; Lap., laparoscopic; LD, living donor; mo, month(s); MRKH, Mayer-Rokitansky-Küster-Hauser syndrome; PRA, pre-transplant panel reactive antibodies; SD, standard deviation; y, year(s), * total length of multiorgan procurement.

Table 4. Details of outcomes

	Donor type	Graft outcome	Transfer/ pregnancy/ live birth	Live birth	Hysterectomy	Hysterectomy cause
Recipient 1	LD	viable until hysterectomy	8/1/1	live birth, POD 1713 (4y 8mo 9d)	elective, POD 1830 (5y 0mo 4d)	live birth achieved
Recipient 2	DD	graft loss	0	0	urgent, POD 7	thrombosis (arterial)
Recipient 3	DD	graft currently viable, POD 2054 (5y 7mo 30d)	13/5/0	0	0	0
Recipient 4	LD	viable until hysterectomy	12/2/0	0	elective, POD 1983 (5y 5mo 6d)	renal function impairment, multiple unsuccessful embryo-transfers
Recipient 5	DD	viable until hysterectomy	4/1/1	live birth, POD 950 2y 7mo 8d	elective, POD 1109 (3y 0mo 14d)	live birth achieved, multiple complications in the post-transplantation course (recurrent ACR, leukopenia, *Clostridium difficile* colitis, renal function impairment, vaginal anastomotic stenosis)
Recipient 6	LD	viable until hysterectomy	5/0/0	0	semi-elective, POD 1468 (4y 0mo 7d)	subtotal graft necrosis, chronic rejection
Recipient 7	DD	graft loss	0	0	semi-elective, POD 213 (0y 7mo 1y)	non-functional graft (chronic rejection, partial thrombosis, HSV infection, no growth of endometrium)
Recipient 8	LD	graft loss	0	0	urgent, POD 15	thrombosis (venous)
Recipient 9	LD	live birth	9/1/1	live birth, POD 721 1y 11mo 22d	elective, POD 1621 (4y 5mo 9d)	live birth achieved, multiple unsuccessful embryo transfers, no desire for further pregnancy
Recipient 10	DD	graft currently viable, POD 1480 4y 0mo 19d	9/2/0	0	0	0

Abbreviations: ACR, acute cellular rejection; d, day(s); DD, deceased donor; HSV, herpes simplex virus; LD, living donor; mo, month(s); POD, post-operative day; y, year(s)

Results

Patients and uteri

The most significant demographic characteristics of the donors and recipients, such as age, BMI, history of tobacco abuse, and gynecologic history, are provided in Table 3. All recipients were affected by congenital absence of the uterus, known as Mayer-Rokitansky-Küster-Hauser syndrome (MRKH). The mean age of the LD and DD at the time of transplantation was 50.8 years (range 47-58) and 34.7 years (range 19-57), respectively. One LD, three DDs, and two recipients had a history of cigarette smoking. Three of the 5 LDs (60 %) and 2 of the 5 DDs (40 %) were menopausal. Two donors (both deceased) were nulliparous.

Uterine graft removal

Graft hysterectomy was performed in 8 of the 10 recipients (Table 4). The graft was removed on either an urgent, semi-elective, or elective basis. An urgent hysterectomy was performed in 2 of 10 (20 %) recipients (in both cases due to thrombosis). A semi-elective hysterectomy was performed in recipients number 6 and 7. An elective hysterectomy was performed in 4 of 10 (40 %) recipients; three of these four recipients had previously achieved live birth (recipients number 1, 5, 9). Recipient number 4 suffered from renal function impairment, a side effect of immunosuppression, and decided not to carry on with embryo transfers and to have the graft removed. Two recipients still have grafts *in situ* (recipients number 3 and 10).

Analysis of individual cases of graft thrombosis

Recipient number 2

Recipient number 2 received a DD graft from a 57-year-old donor who had experienced one vaginal delivery and had no history of tobacco abuse. A multiorgan deceased donor retrieval included the following organs: heart, lungs, liver, pancreas, kidneys, the great saphenous vein, and the uterus. Two transplant surgeons performed the procedure with a gynecologist serving as the second assistant. The UTx procedure lasted 245 minutes. Inflow was augmented using segments of the IIA, while four venous anastomoses provided the outflow. There was a total blood loss of approximately 200 ml.

A relaparotomy was performed in the first 24 hours due to hemoperitoneum in the pelvis surrounding the uterine graft. Surprisingly, there was a thrombosis in the right UA. The entire graft was pink, a bit swollen, and the outflow showed no signs of thrombosis. The team felt that the graft could be salvaged with a thrombectomy, which is the standard procedure in the case of a kidney or liver graft thrombosis. The Doppler probe showed no disturbance since the thrombosis was located on the contralateral supplying artery. Interestingly, a part of the graft's right IIA was patent; the thrombus was located more distally in the UA, which was fragile (≈ 1 mm). A thrombectomy re-established patency. Rotational thromboelastometry revealed no pathology in the coagulation cascade. On day 7, suspicion of blood flow disturbance was raised due to the lividity of the ectocervix as well as the following disturbing findings on the US: (i) absence of perfusion and (ii) enlargement of the graft. During a relaparotomy, the graft, which was necrotic with no perfusion, was removed (Fig. 1a,b).

A pathological examination revealed extensive hemorrhagic necrosis of the uterine graft. The arterial walls were thickened due to fibrointimal proliferation. Notably, there was a narrowing of the lumen of the right UA due to eccentric subintimal fibrosis with a superimposed thrombus (Fig. 1c,d).

Recipient number 8

Recipient number 8 received a graft from her 49-year-old mother (BMI 19, no smoking history, three vaginal births). Two transplant surgeons performed the transplantation procedure with a gynecologist as a second assistant. The UTx procedure lasted 216 minutes. Inflow was established with anterior divisions of the IIA to the EIA. Outflow was established with 2 UVs only. Ovarian veins (OVs) were not anastomosed since they were varicose, and there were no signs of graft congestion.

On day 5, a relaparotomy was performed due to hematoma progression surrounding the graft, which was congested but viable. Both arteries were patent, but venous anastomoses were thrombosed, probably due to external compression from the hematoma. A thrombectomy was successful only in the case of the left UV, so we had to perform a thrombectomy along with an anastomosis on the originally ligated right OV. The graft was able to be preserved since it was pink and outflow had been reestablished. Rotational thromboelastometry revealed no pathology. The patient received seven packed red blood cells perioperatively. On day 15, the ectocervix became livid once again, and there were no signs of perfusion in the US. The graft was removed since it was ischemic with no signs of perfusion.

A histopathological examination confirmed extensive hemorrhagic necrosis of the graft. Shortly after graft removal, an additional Luminex© examination revealed a positive T-FACS cross-match and *de novo* production of donor-specific antibodies against human leukocyte antigens class I (B44, 6700 median fluorescence intensity). This may suggest that the graft thrombosis had an immunological background [9].

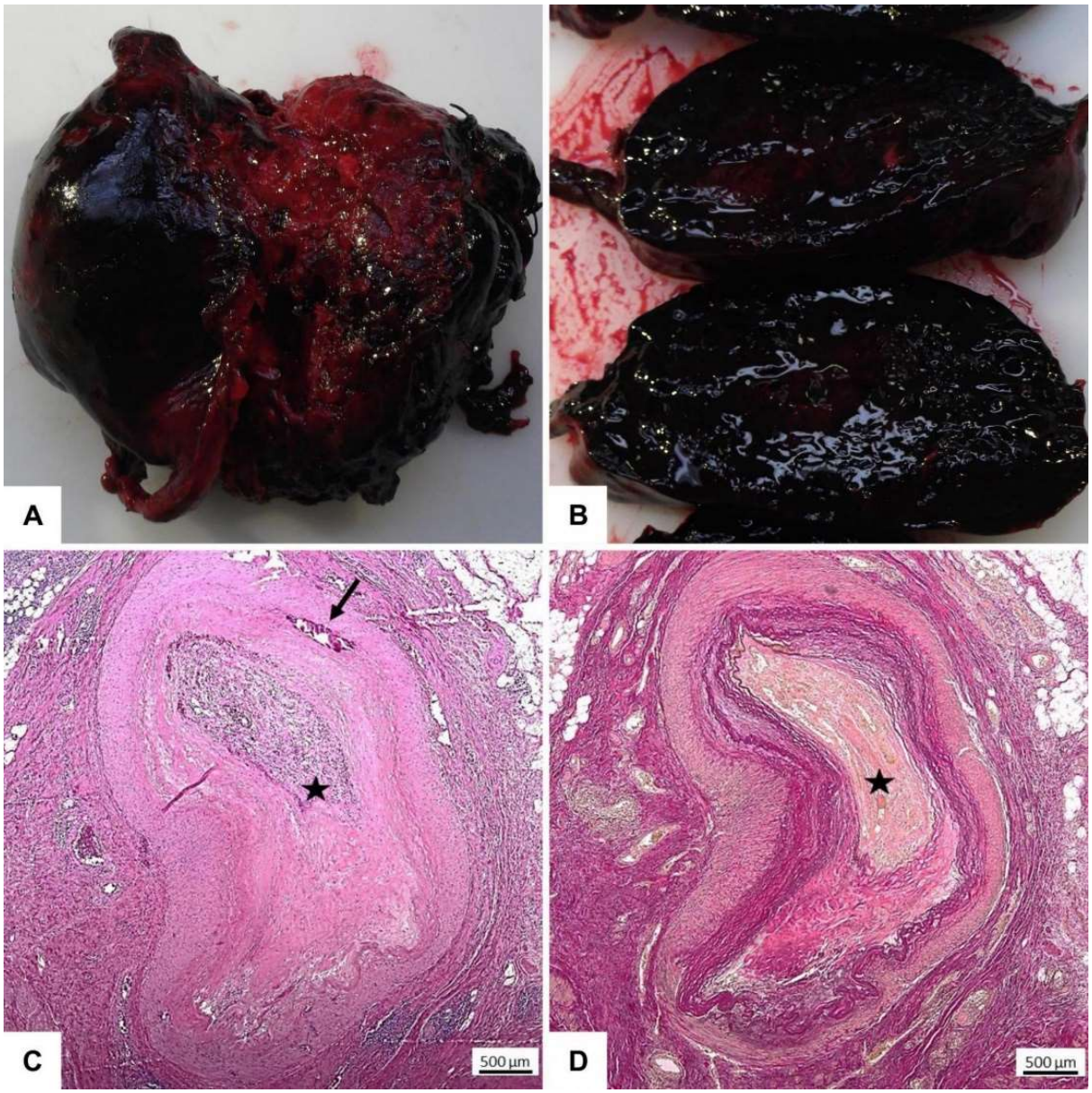

Fig. 1. Macroscopic appearance of hemorrhagic necrosis of the explanted uterus. The explanted graft as a whole (**A**), in cross section (**B**). Uterine artery – histopathology. Excentric fibrointimal proliferation with calcification (arrow) within the arterial wall. The arterial lumen is obliterated by an organized thrombus (asterisks). H&E stain (**C**), elastin-van Gieson's stain (**D**); original magnification x40.

Discussion

Assessment of graft quality

The cornerstone of a successful UTx is a proper evaluation of overall graft quality, which includes its vasculature. In our opinion, US and CT are obligatory modalities when evaluating a donor candidate. CT angiography is suitable for assessing the course and diameter of the UA as well as for evaluating the atherosclerosis burden. CT is very sensitive to calcium; calcified plaques are visible as hyperdensities. However, CT does have limitations for this indication. If the plaque is non-calcified, the characteristic hyperdensity might be absent. Computed tomography angiography can be used for non-calcified plaque assessment, which has been proven by the evaluation of coronary arteries [14]. Generally, CT provides spatial resolution of up to 0,5 mm. Magnetic resonance imaging (MRI) seems more appropriate for evaluating veins than does CT [15]. The roles of CT and MRI in uterine donor candidate evaluation seem to be more complementary than competitive [15].

Which methods should be used to evaluate the quality of a graft more precisely remains a matter of debate. It is unclear if an intraoperative biopsy of the UA to determine the extent of mediocalcinosis and fibrointimal proliferation would be beneficial. The

distribution of vascular changes throughout the graft is non-homogenous. The presence/absence of vascular changes in one part of the vessel does not rule out a completely different finding elsewhere. It is also possible to use a lipid profile to estimate the risk for atherosclerosis in the donor, but its clinical impact seems to be even less defined.

In any case, we suggest that genetic screening for coagulation defects should be part of a preoperative workup. This could help with tailoring thromboembolism prophylaxis to the individual patient in the postoperative course. When faced with a fragile uterine vasculature with an increased risk of bleeding, a surgical team must delicately balance the necessity of thrombosis prophylaxis with the risk of bleeding. In our two cases, both recipients received antithymocyte globulin and both developed bleeding. The recipients received 7 and 11 packed red blood cells. Neither recipient suffered from genetic thrombophilia. We kept anti-Xa activity at levels ranging from 0.2 to 0.5 kIU/l, *i.e.,* the prophylactic level.

Vascular pathology relevant for UTx

Many vascular diseases may affect the UA and limit its function by narrowing its lumina or limiting its elasticity. The spectrum includes intimal hyperplasia, arteriolosclerosis, mediocalcinosis, and atherosclerosis. Intimal hyperplasia and arteriolosclerosis present themselves by thickening the arteriolar wall and narrowing the lumina. Mediocalcinosis differs from other vascular diseases. It is characterized by non-stenosing calcific deposits in the internal elastic lamina (Fig. 2). The lumen of the vessel is not reduced, but the arterial wall becomes rigid, decreasing its elasticity. Physiologically, the diameter of the UA increases substantially during pregnancy. It is questionable whether the mediocalcinotic arteries can sustain the higher demand for blood supply of uterus during pregnancy (an increase from approximately 45 ml/min up to 750 ml/min at term of delivery [16]). Atherosclerosis, on the other hand, does lead to reduction of the vascular lumen. Notably, the distribution of atherosclerotic plaques may be non-homogenous, making it challenging to evaluate graft quality correctly. It is generally known that cholesterol accumulation is progressive over a woman's life and accelerates during the last few years leading up to menopause [17-19]. The thrombosed grafts in our cohort (graft ages 57 and 49) exhibited significant degenerative changes in the UA and its branches. We speculate that young grafts might be superior to perimenopausal grafts due to their less developed vascular changes.

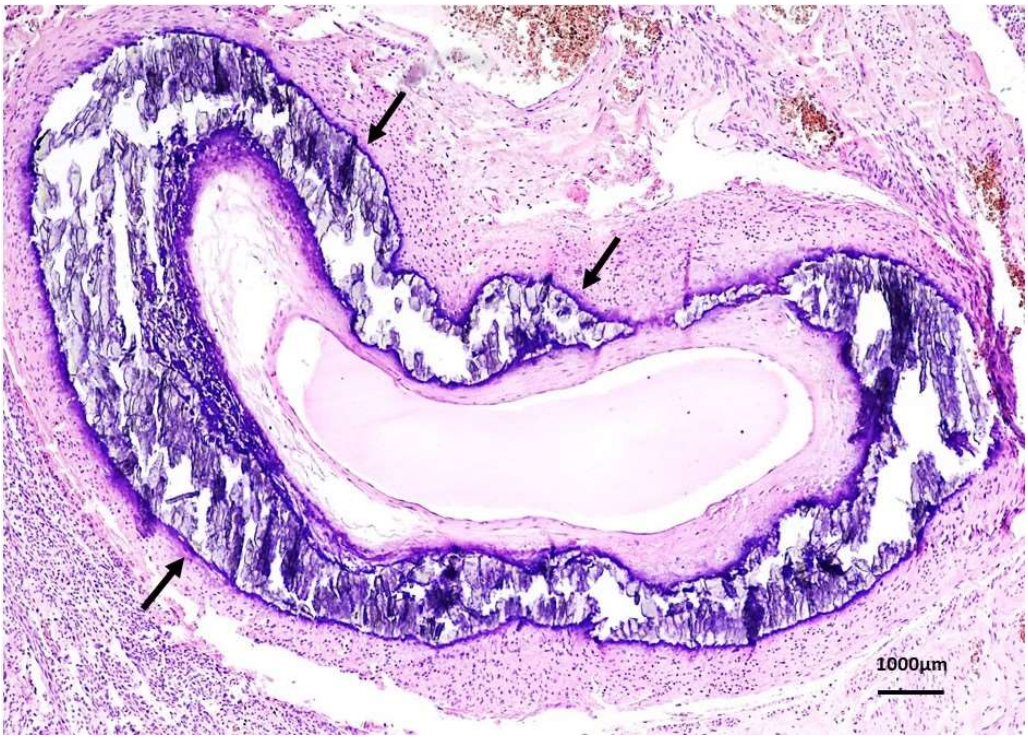

Fig. 2. Mediocalcinosis. A ring-like dystrophic calcification (arrows) within the media of the uterine artery. H&E stain; original magnification x40.

The technical aspect of UTx

Several points need to be addressed in order to optimize the patency rate of vascular anastomoses. One principal course of action is to produce reliable large-caliber anastomoses. This can be facilitated by procuring uterine vessels with a patch or a segment of the IIA or IIV. However, the downside of anastomosing longer and more robust vascular pedicles is that there is a danger of kinking and consequent thrombosis. Hence, the location for the anastomosis and length of the vessel has to be selected with care. We strongly advocate avoiding cannulation of the arteries due to the risk of intimal dissection, which could prove fatal for the graft. The vascular anastomoses should be performed under optical magnification. One pediatric liver transplantation study that compared loupe magnification and operating microscope-assisted anastomoses revealed lower rates of hepatic artery thrombosis in the cohort that underwent microscope-assisted procedures [20]. The question remains as to how many veins should be anastomosed. In reconstructive surgery, meta-analyses have shown that two venous anastomoses reduce vascular compromise of the flap to a much more significant extent than a single venous anastomosis [21,22]. We feel that all uterine veins should be anastomosed if the vessel diameter is appropriate.

Follow-up

The perfusion follow-up is performed with the following: (i) a transabdominal US; (ii) a transvaginal US (with the exception of the first post-operative days); (iii) a Doppler blood flow probe; and (iv) a macroscopic examination of the cervix. In our experience, B-mode sensitivity is considerably limited in the first post-operative days for a variety of reasons: the location of uterus deep in the pelvis, edema of the surrounding tissues, small size of the vessels, bowel gas, artifacts from drains, and skin staples. Assessing the morphology of veins using B-mode imaging is virtually impossible due to their small caliber; they can be better visualized using color Doppler flow mapping. The Cook-Schwartz Probe on one of the UA provides extra perfusion data in the first days after transplantation when the role of the US is limited. In our experience, an enlargement of the anterior-posterior diameter is a more accurate indicator of thrombosis than are pathological findings in B-mode imaging. The craniocaudal diameter is not a reliable parameter. Visual inspection of the cervix did, however, prove extremely valuable in diagnosing perfusion issues.

Treatment of thrombosis

In case of hesitation when determining perfusion, we strongly advocate a low threshold policy for early relaparotomy. A thrombectomy and revascularization is indicated if the thrombosis is diagnosed early. Only early diagnosis can lead to graft salvage. In our cohort, we performed two thrombectomies. In recipient number 2, a thrombectomy of the UA was carried out, and the viability of the graft was preserved. The patency of both arteries was repeatedly confirmed by US. In recipient number 8, we performed a thrombectomy of both UVs (successfully only on one side), and a new anastomosis of an originally ligated OV was established. This led to decongestion and temporary salvaging of the graft. However, both grafts were eventually lost due to rethrombosis (recipient number 2 on day 7; recipient 8 on day 15). The reasons for the rethrombosis and graft loss are unknown. The issues outlined in previous sections (vascular disease, compression by hematoma, and immunological issues) definitely caused or contributed to primary thrombosis and graft injury. However, we assume that pathophysiological mechanisms are so complex that thrombosis due solely to a mechanical factor is a rarity. We speculate that thrombosis is a multifactorial problem, and therefore, we feel it is questionable whether a graft should be preserved despite the fact that thrombectomy is successful and graft viable. We recommend a repeated evaluation of the viability of the graft during a relaparotomy. In case of uncertainty regarding graft viability, we believe graft removal and placing the patient on a list for re-transplantation are in order.

Comparison with other trials

Our outcomes regarding graft loss are roughly in line with those of other trials. A recent review of published UTx experiences reported surgical success rates (defined by a technically successful transplant procedure, established blood flow, and regular menses) of 78 % and 64 % in LD UTx and DD UTx, respectively [23]. In our trial, the rate of early graft survival was 80 % (4/5 cases) in both LD UTx and DD UTx cohorts. A review of 45 UTx procedures (including our nine cases) documented the requirement for an emergency hysterectomy in 13/45 (28.6 %) cases; of those, 53.8 % (7/13) were due to thrombosis, 23.1 % (3/13) to infection, and 15.4 % (2/13) to graft ischemia [24].

Conclusions

Thrombosis is a serious complication of uterine transplantation that often leads to graft loss. Maximum effort must be made towards preventing vascular complications. It is imperative to evaluate uterine donor candidates thoroughly while placing an emphasis on uterine vasculature quality. In the postoperative course, graft perfusion is closely followed-up with ultrasound, a Doppler flow monitoring probe, and a macroscopic evaluation of the cervix. In the event findings are inconclusive, a relaparotomy should be indicated promptly. A thrombectomy to salvage of the graft is in order if a thrombosis is revealed. However, the indication for thrombectomy is questionable due to the low probability of its long-term success. In our trial, we lost two of ten grafts due to thrombosis despite an attempt to salvage them with a thrombectomy. The role of upfront graft removal and early re-transplantation remains debatable.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

This study was supported by the project National Institute for Research of Metabolic and Cardiovascular Diseases (Programme EXCELES, Project No. LX22NPO5104) - Funded by the European Union - Next Generation EU. The authors appreciate contributions by Alena Langerova (Gennet, Prague), Jaromir Masata (Department of Obstetrics and Gynecology, General University Hospital, Prague), Stepan Machac (IVF Clinic, Olomouc), and Radovan Pilka (Department of Obstetrics and Gynaecology, Olomouc University Hospital). They provided essential gynecological and obstetrical expertise. We also wish to thank Brian Kavalir for his proofreading services.

Abbreviations

ACR, acute cellular rejection; AUFI, absolute uterine factor infertility; BMI, body mass index; CT, computed tomography; d, day(s); DD, deceased donor; EIA, external iliac artery; EIV, external iliac vein; E-S, end-to-side; HLA, human leukocyte antigen; HSV, herpes simplex virus; IIA, internal iliac artery; IIV, internal iliac vein; Lap, laparoscopic; LD, living donor; Mo, month(s); MRI, magnetic resonance imaging; MRKH, Mayer-Rokitansky-Küster-Hauser syndrome; OV, ovarian vein; POD, postoperative day; PRA, pre-transplant panel reactive antibodies; SD, standard deviation; UA, uterine artery; US, ultrasound; UOV, utero-ovarian vein; UTx, uterus transplantation; UV, uterine vein;

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