Uterus transplantation: a rescue technique to save the viability and functionality of the graft after intra-operative outflow thrombosis

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Objective: To study a surgical approach to venous vascular thrombosis after uterus transplantation (UTx). Uterus transplantation is the only treatment for uterine factor infertility when conventional therapies are not possible. One of the major limitations of UTx is the high incidence of vascular thrombosis, which in most series reaches approximately 20%.
Design: A case report.
Setting: Hospital.
Patients: We report here a technique used in a 30-year-old woman with congenital absence of the uterus who developed intraoperative thrombosis after a UTx from a brain-dead donor.
Intervention: The UTx was performed by revascularizing the graft through bilateral donor internal iliac vessels (artery and vein) anastomosed end-to-side to the external iliac vessels of the recipient. The superior uterine veins were not anastomosed and were left unreconstructed. An end-to-end graft to the recipient's vaginal anastomosis was performed. After uterus reperfusion, congestion of the organ was noted, and bilateral venous thrombosis of the internal iliac veins of the graft was found. A "Y-shaped" venous jump graft was used to restore venous outflow of the left superior uterine vein and the internal iliac vein of the graft after thrombectomy.
Main Outcome Measures: Viability and functionality of the uterus graft after intraoperative bilateral venous thrombosis.
Results: The postoperative course was uneventful, and this UTx resulted in the delivery of a healthy infant.
Conclusion: To our knowledge, this is the first successful rescue technique used to restore venous outflow and save the viability and functionality of a transplanted uterus. We demonstrated that a transplanted uterus from a deceased donor with a monolateral outflow could succeed in pregnancy and the delivery of a healthy infant. (F S Rep® 2024;5:223–7. ©2024 by American Society for Reproductive Medicine.)
Key Words: Infertility, thrombosis, reconstruction, pressure, clot

Uterus transplantation (UTx) is the only cure for uterine factor infertility when conventional therapies are not possible. The first successful UTx was performed in 2011 in Turkey by a deceased donor (1). Two years later, a Swedish team reported the first case series of nine UTxs from living donors (2). Currently, there have been approximately 80 UTxs performed worldwide from deceased or living donors, with >40 live births reported. One of the major barriers to the widespread adoption of UTx is the high incidence of vascular thrombosis, causing graft failure in approximately 20% of the cases (3, 4).

Although an overview of the technical aspects of UTx has been previously reported (5, 6), the specific approach to intraoperative vascular

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Data can be shared on request to investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose.
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thrombosis has not been described. We report here a unique rescue technique used intraoperatively to re-establish venous outflow in a transplanted uterus that developed bilateral venous thrombosis. This approach could be used in both living and deceased donor UTx.

CASE REPORT

From February 2016 to January 2022, eight UTx from deceased donors were performed at Cleveland Clinic, and five of the transplants resulted in the delivery of a healthy infant. All patients underwent UTx because of uterine infertility secondary to Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome. The main characteristics of donors and recipients are reported in Table 1. The vascular nomenclature was used according to the published guidelines on UTx (7). Here we present a case of a 30-year-old woman with uterine infertility secondary to MRKH syndrome, who underwent UTx using a compatible 27-year-old parous deceased brain-dead donor. The patient gave full permission for the publication. Table 2 shows donor and recipient data. The procurement surgery, the graft implantation, and the postoperative management were performed according to our previously described protocol (5, 6, 8). Briefly, the graft included both right and left internal iliac arteries and veins, which represent, respectively, the inflow and outflow vessels for the inferior uterine arteries and veins. The superior uterine vein was ligated bilaterally, as per our practice. A bolus of 5,000 units of intravenous heparin was given before starting the vascular anastomosis. Inflow and outflow of the graft were established by a bilateral end-to-side anastomosis between the internal iliac arteries and veins of the donor and the external iliac vessels of the recipient. The graft was revascularized sequentially after completing the right-side vessels first, followed by the contralateral venous and arterial anastomosis. Graft perfusion appeared optimal, and an intraoperative vascular ultrasound showed excellent intraparenchymal perfusion throughout the organ. The vaginal cuff of the donor was therefore anastomosed to the vaginal cuff of the recipient (9). After completing the vaginal anastomosis, the graft appeared to be severely congested, with elevated arterial resistance and poor venous flow at intraoperative ultrasound (Fig. 1A and B). Inspection of the vessels revealed the presence of bilateral thrombosis of the inferior uterine vein and internal iliac veins of the uterine graft (Fig. 2A). A thrombectomy of the left inferior uterine vein and the internal iliac vein of the graft was performed. The decision was also made to use the left superior uterine vein, which at this point appeared to be engorged (approximately 5–6 mm in diameter). The left internal iliac vein of the graft was transected proximal to the anastomosis after ligating the distal end. A "Y-shaped" donor venous graft (from the same deceased donor) including the common, internal, and external iliac veins was used to re-establish the graft outflow. The internal iliac vein of the venous graft was anastomosed in an end-to-end fashion to the superior uterine vein, whereas the external iliac vein of the venous graft was anastomosed in an end-to-end fashion to the internal iliac vein of the uterine graft. The venous graft was then anastomosed to the left common iliac vein of the recipient in an end-to-side fashion (Fig. 2B). After venous revascularization, the graft appeared well-perfused and no longer congested. At the end of the procedure, the uterine graft had left-sided and right-sided arterial inflow and only left-sided venous outflow. The intraoperative vascular ultrasound before abdominal closure revealed excellent intraparenchymal flow. The arterial resistance index (a measure of pulsatile flow that reflects the resistance to the blood flow caused by the microvascular bed distal to the site of the measurement) that was high at the time of the thrombosis (Fig. 1A) normalized after the revascularization (Fig. 1C). Moreover, the venous flow within the uterus graft was insufficient at the time of thrombosis (Fig. 1B) and improved after revascularization (Fig. 1D).

TABLE 1

Summary of our experience with uterus transplantation at Cleveland Clinic.

Donor's data (n = 8)	Average	Median
Donor's age (y)	30 ± 8	30 (21–45)
Donor's BMI (kg/m^2)	29.4 ± 3.5	30.5 (22.7–32.7)
Procurement time (min)	228 ± 76	194 (158–358)
Recipient's data (n = 8)		
Recipient's age (y)	33 ± 3.6	33 (26–39)
Recipient BMI (kg/m^2)	25.3 ± 3.5	24.3 (20.8–32.4)
Transplant duration (min)	537 ± 172.2	498 (334–748)
Length of stay (d)	11.5 ± 7.8	8.5 (5–30)

Note: BMI = body mass index.

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TABLE 2

Donor and recipient data.

Characteristics	Donor	Recipient
Age (y)	27	30
BMI (kg/m^2)	29.7	32.4
Blood type	0^-	A^-
CMV IgG serostatus	+	+
Fertility history	One full-term pregnancy	—
CT angiography preoperative	Normal	Normal
Ultrasound and/or hysteroscopy	Normal	Absence of native uterus
Tobacco use	Never	Never
Vaginal length before transplant (mm)	15 (procured graft)	63
Recipient-only data		
Etiology of uterine infertility		MRKH
No. of IVF treatment cycles after transplant		1
No. of frozen blastocysts		6
Hospital length of stay (d)		16
Transplant operative data		
Cold ischemia time (min)		216
Warm ischemia time (min)		35
Operative time (min)		748
Blood loss (mL)		2,000
Packed red cells (U)		0

Note: BMI = body mass index; CMV = cytomegalovirus; CT = Computed tomography; IgG = immunoglobulin G; IVF = in vitro fertilization; MRKH = Mayer-Rokitansky-Küster-Hauser syndrome.

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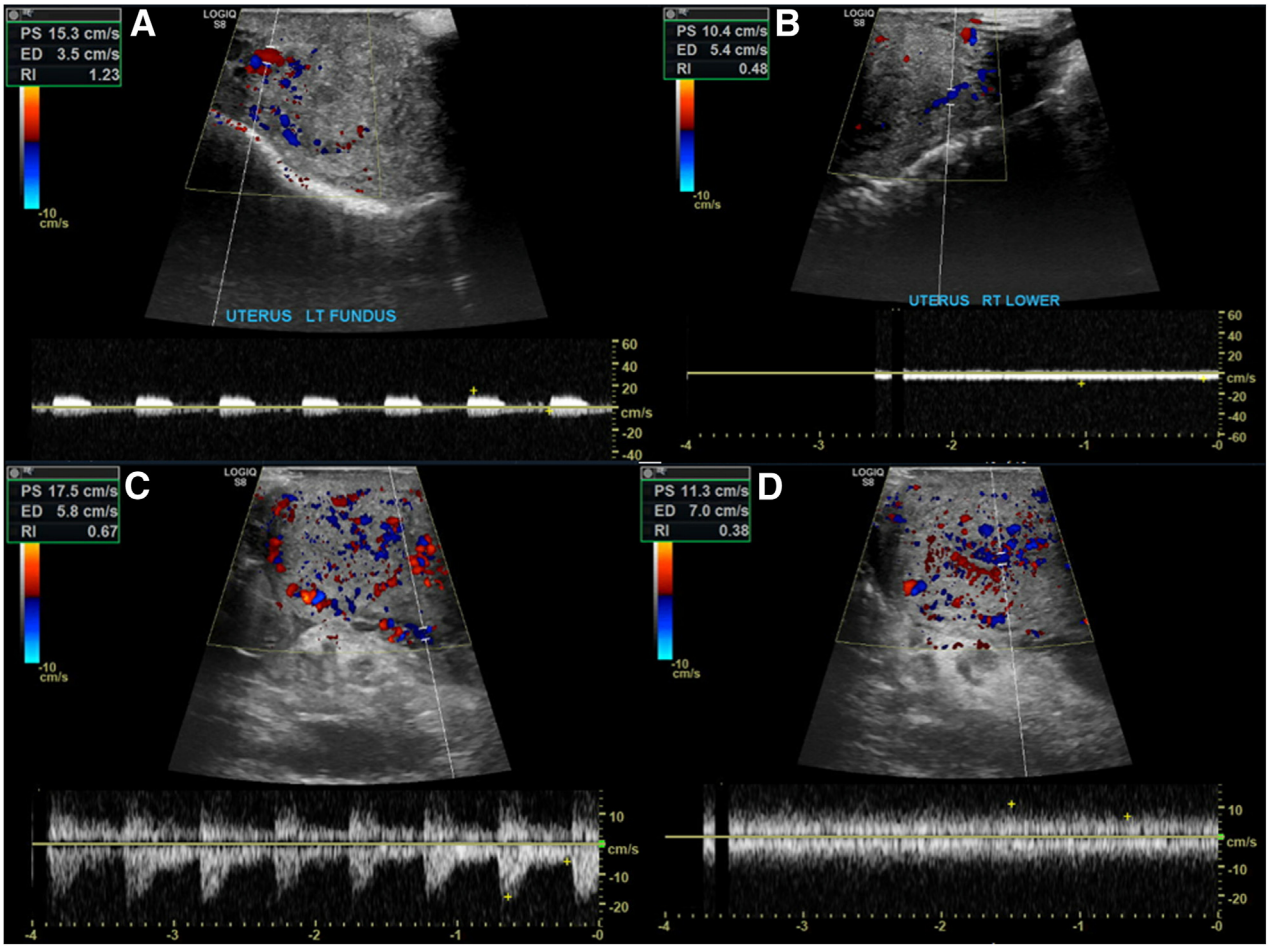
FIGURE 1



Intraoperative Doppler ultrasound of the uterus graft with (**A**) high arterial resistive index and (**B**) poor venous flow because of outflow obstruction. (**C**) Arterial resistive index normalized and (**D**) venous flow improved after left-side venous revascularization using a "Y-shaped" venous graft.

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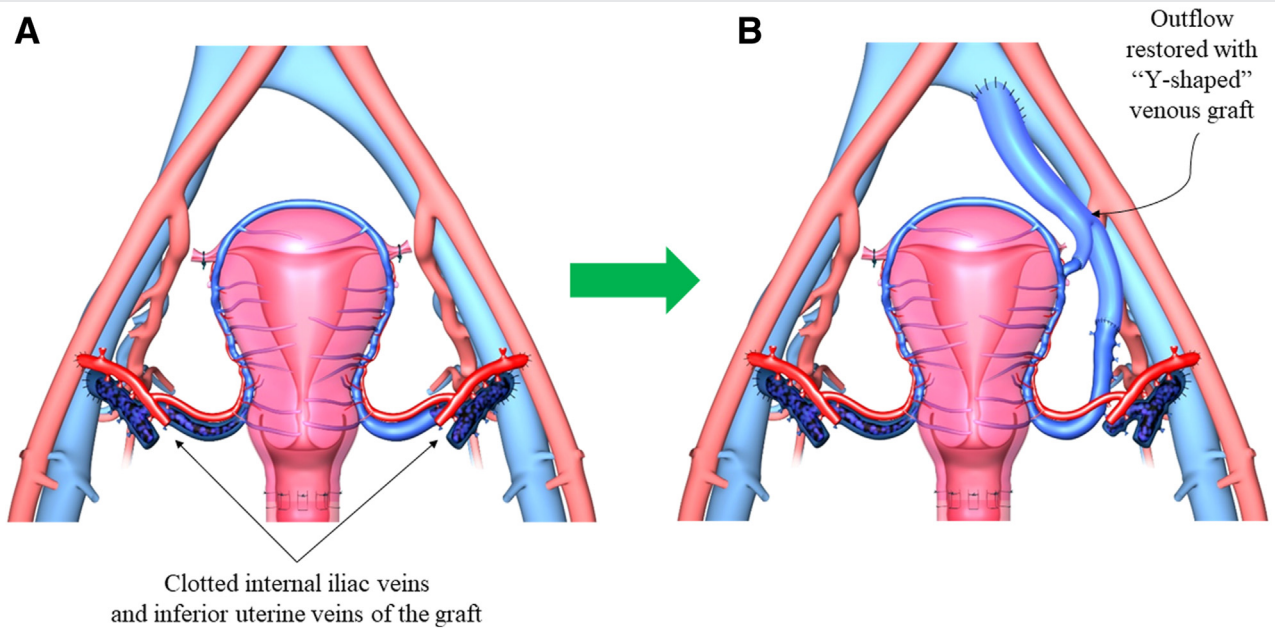
The estimated blood loss was 2,000 mL. During the transplant, the cell saver (intraoperative blood salvage) was used to maintain the hematocrit level approximately 30%; the patient did not require any heterologous transfusion. The postoperative course was unremarkable, and the patient was discharged home on postoperative day 15. Aspirin and enoxaparin were used after the transplant and maintained until the delivery. Her first spontaneous menses occurred 20 days after transplantation. Routine cervical biopsies revealed normal histology without evidence of graft rejection for 7 months, at which time preparations for embryo transfer were initiated. A single high-quality blastocyst was transferred on July 31, 2019. Pregnancy was confirmed, and serial ultrasounds demonstrated appropriate growth. A healthy neonate was delivered at 34 weeks of gestation using cesarean section. No predisposition or cause for the thrombosis has yet been identified, considering donor and recipient data.

DISCUSSION

Vascular thrombosis is one of the most common causes of graft failure after UTx, accounting for 15%–20% of all graft hysterectomies (3, 4, 10). This usually happens during the first 2 weeks after transplantation. This proportion is larger than what has been reported after the transplantation of other abdominal organs such as the liver and kidney (11, 12). Surgical techniques, the site of vascular anastomosis, severe ischemia-reperfusion injury, and a microcirculatory bed characterized by low resting flows are thought to be the most important causes of vascular failure, although too little is known to draw firm conclusions.

The uterus venous system has a rich anastomotic network that connects the left with the right side, as well as the fundus with the most caudal portion of the organ. This network drains into the periuterine venous plexus, which in turn drains into the inferior and superior uterine veins (13).

FIGURE 2



(**A**) Bilateral thrombosis (in purple) involving the inferior uterine vein and the internal iliac veins of the uterine graft. (**B**) A "Y-shaped" donor venous graft, including the common, internal, and external iliac veins, was used to re-establish the left-side graft outflow.

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Optimal tissue perfusion is key to graft viability and ultimately to achieving and maintaining a pregnancy (14). Achieving appropriate venous outflow is the most difficult part of the procedure. The inferior uterine veins are the preferred graft outflow in cadaveric UTx (4, 10). The superior uterine vein is commonly used in combination with the inferior uterine vein in living donor UTx. Very rarely, these are used as the sole venous outflow (4, 10).

To our knowledge, this is the first case of successful UT using only one side of the venous system as the main outflow from the graft. Our surgical approach permitted salvage of the graft; after bilateral thrombosis of both graft internal iliac veins was discovered intraoperatively. Importantly, this unilateral outflow was able to maintain the viability of both the uterine graft and gestation, leading to the delivery of a healthy infant.

CONCLUSION

This case shows that salvage venous revascularization is possible in UTx using a venous conduit after primary anastomotic failure and that unilateral venous drainage can support a healthy pregnancy and delivery.

CRediT Authorship Contribution Statement

Giuseppe D'Amico: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Writing - review & editing. **Koji Hashimoto:** Writing - review & editing. **Luca Del Prete:** Resources, Data curation, Conceptualization, Writing - review & editing. **Elliott Richards:** Data curation, Writing - review & editing. **Stephanie Ricci:** Writing - review & editing. **Rebecca Flyck:** Writing - review & editing. **Bijan Eghtesad:** Writing - review & editing. **Teresa Diago:** Writing - review & editing. **Tommaso Falcone:** Resources, Writing - review & editing. **Charles Miller:** Conceptualization, Writing - review & editing. **Andreas Tzakis:** Conceptualization, Writing - review & editing. **Cristiano Quintini:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, writing - review & editing.

Declaration of Interests

G.D.A. has nothing to disclose. K.H. has nothing to disclose. L.D.P. has nothing to disclose. E.R. has nothing to disclose. S.R. has nothing to disclose. R.F. has nothing to disclose. B.E. has nothing to disclose. T.D. has nothing to disclose. T.F. has nothing to disclose. C.M. has nothing to disclose. A.T. has nothing to disclose. C.Q. has nothing to disclose.

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