Original Research Article

Hysterectomy after uterus transplantation and detailed analyses of graft failures

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Abstract

Introduction: The first live birth after uterus transplantation occurred in Sweden in 2014. Uterus transplantation has repeatedly, and at many centers worldwide, proven to be a feasible treatment for absolute uterine factor infertility. Hysterectomy in live donors and transplantation are well described in numerous reports. However, there are no reports of hysterectomy in the recipient after uterus transplantation, which will occur at either graft failure, after childbirth, or after numerous failed pregnancy attempts. We present the first report of hysterectomy in recipients after uterus transplantation with detailed analyses of findings in conjunction with graft failures.

Material and Methods: An analysis of recipient hysterectomies (n = 10), performed in 2012–2020, was conducted. Data from the international uterus transplantation registry (ISUTx registry) were extracted, and medical records were systematically reviewed, to collect and compile characteristics of recipients and donors, as well as pre-, per-, and postoperative data, including clinical course of graft failures.

Results: Hysterectomy in recipients was performed in conjunction with cesarean section (n = 3), 3–6 months after cesarean section (n = 3), or after failed pregnancy attempts (n = 1) or graft failure (n = 3). The durations of anesthesia (2 h 36 min to 7 h 35 min) and hysterectomy surgery (1 h 42 min to 5 h 52 min) ranged widely, with long perioperative interruptions for insertion of ureteral catheters in two cases. Adhesions to the uterus were abundant, the majority being mild. Three uteri that subsequently showed graft failure (hysterectomy at 1, 3, and 8 months post transplantation) showed histological signs of ischemia in biopsies taken 1-week post-transplant and early signs of central hypoperfusion by Doppler ultrasound. In these graft failure explants, there were no epithelial linings in the uterine cavity or in the cervix. The inner uterine wall was severely ischemic and/or necrotic, whereas outer parts were partly viable. There were signs of moderate atherosclerosis of uterine arteries but no rejection. Mild postoperative complications were frequent (6/10), with one supravaginal hematoma requiring surgical drainage.

Abbreviations: GF, failed uterine graft; UTx, uterus transplantation.


1 | INTRODUCTION

The first clinical trial of uterus transplantation (UTx) was initiated in Gothenburg, Sweden, with surgeries performed in 2012–2013.1 Within the framework of this trial, the first live birth occurred in September 2014, representing a proof of concept for UTx as an infertility treatment for what used to be called absolute uterine factor infertility.2 The second birth after UTx took place in Gothenburg, after a mother-to-daughter UTx procedure,3 and seven more births followed from the initial UTx trial,1 which was a live donor trial. The first live birth after deceased donor UTx occurred in Brazil in 2017.4 As such, UTx is emerging as a valuable option for women with absolute uterine factor infertility seeking biological and gestational motherhood, and the research field has been rapidly expanding globally, with more than 80 cases of UTx performed.5

The vast majority of UTx cases are based on live donation. Donor hysterectomy is a complicated procedure, with surgical durations ranging from 6 to 12 h.1,6 The complexity and associated long surgical durations are because of the need for total ureteral dissection to the bladder and the meticulous and no-touch dissection of vessels, including the deep uterine veins down to the internal iliac veins. Deceased donor hysterectomy is much less complicated, with shorter surgical duration, since ureter management does not have to be taken into account.7

Transplanting the graft into the recipient is regarded as a more facile procedure with surgical durations of 4–5 h.1,6 It involves surgery through a sub-umbilical midline incision and preparations to expose the vaginal vault and the external iliac arteries and veins for anastomoses. At transplantation, two arterial and two to four venous anastomoses are performed end-to-side to the external iliacs as well as vaginal–vaginal anastomosis and uterine fixation in the pelvis. Ovaries and fallopian tubes are not transplanted.

In comparison with other solid organ transplants intended for lifesaving and life-long purposes, a transplanted uterus is ephemeral. Hysterectomy is predetermined as an elective procedure to be performed after live birth or multiple failed pregnancy attempts to limit the duration of immunosuppressive treatment and thereby the risk of long-term side effects, such as nephrotoxicity. Several possible scenarios exist for the performance of post-UTx hysterectomy. In the event of live birth(s), the hysterectomy can be performed in conjunction with cesarean section or as an elective procedure some months after parturition, when the uterus is back to normal size and the baby has been observed for some months to assure good health. Hysterectomy can also be performed in the event of primary graft failure or irreversible rejection. In a restricted number of cases, the uterus may show functionality in terms of regular menstruation and possibly also early pregnancies but be unable to generate a live birth after several years of pregnancy attempts.

Hysterectomy is one of the most common major surgical procedures in women, with great progress made regarding surgical approach and technique. However, hysterectomy secondary to UTx is likely to be different in several aspects. Furthermore, hysterectomy is included in the set of UTx surgeries, which also include transplantation and cesarean section(s).

In the present study, we report on surgical outcomes of post-UTx hysterectomy for the first time, and we also present the first detailed description of graft failures.

2 | MATERIAL AND METHODS

2.1 | Design and setting

The patients were from two observational studies on UTx, registered as clinical trials (NCT01844362, NCT02987023). Informed written consent was obtained from each participant. The data were collected retrospectively.

2.2 | Population and data accumulation

A total of 11 women participating in either of these two studies completed the UTx course with hysterectomies performed in 2012–2020. One graft removal because of vascular thrombosis of uterine vessels occurred only 3 days after UTx. This procedure is merely a transplantectomy before formation of any adhesions and with easily identified anastomosis lines that can readily be opened. Such a uterus removal procedure would not have any resemblance to a hysterectomy. Thus, the final inclusion was ten women, with eight patients from the study

Conclusions: Hysterectomy after uterus transplantation is a complex and time-consuming procedure, and perioperative ureteral catheters may be helpful. Histopathology of early cervical biopsies showing ischemic signs may indicate subsequent irreversible damage, leading to graft failure.

KEYWORDS
graft failure, hysterectomy, infertility, transplantation, uterus

Key message
Hysterectomy post uterus transplantation is a complex surgical procedure that may be aided by insertion of ureteral catheters. Signs of subsequent graft failure due to hypoperfusion can be detected as ischemic changes on cervical biopsies as early as around 1 week after transplantation.
“Prospective case series of human uterus transplantation from live donor,” with UTx surgeries performed in 2012–2013, and two patients from the study “Uterus transplantation from live donors with robotic assisted surgery,” with UTx surgeries performed in 2017–2019. The International Society of Uterus Transplantation registry and all hospital medical records were systematically reviewed to extract and compile recipient and donor characteristics and pre-, per-, and postoperative data. Any data from the registry were verified in patient records. Current smoking was an exclusion criteria, and the extent of previous smoking habits was expressed as pack years (= number of packs of cigarettes smoked per day multiplied by number of years of smoking). All data were de-identified when extracted, and the participants were subgrouped and categorized based on cause of hysterectomy, being either electively planned after live birth, in conjunction with cesarean section, after multiple failed pregnancy attempts, or due to graft failure.

2.3 | Transplantation surgery

The surgery of the recipient at transplantation was essentially as follows and similar in all study patients. Detailed descriptions have previously been published.1,8 Through a sub-umbilical midline incision, the rudimentary uterine tissue was divided in the midline to expose the vaginal vault. The external iliac vein and artery were separated and dissected bilaterally for a distance of around 5 cm. Sutures for later fixation of the uterus were placed bilaterally in the round ligaments, the sacrouterine ligaments, and the divided uterine rudiment. The uterine graft was then placed in the pelvis, and end-to-side anastomoses were performed on the external iliac veins and arteries. The vaginal vault was then opened, and the vaginal rim of the uterine graft was anastomosed end-to-end to the vaginal top of the recipient. The uterus was fixed in its position by the six sutures, and the abdomen was closed.

2.4 | Graft failure and histopathology of failed grafts

A graft failure was defined as a uterine graft showing evidence of continued partial necrosis and with no signs of proliferation of endometrium and/or menstruation. Detailed histopathological assessments were carried out on protocol of cervical biopsies and taken for rejection diagnosis, and included occasional transabdominal biopsies from the uterine corpus. The evaluations were performed by two expert pathologists (JM, VB) with >5 years of experience in diagnosis of uterine rejection.9,9 All slides were stained with hematoxylin-eosin.

2.5 | Follow-up and postoperative complications

The patients were followed weekly for the initial months with cervical biopsies, laboratory investigations, ultrasound, and clinical control.1,9 During months 2 and 3, patients were seen biweekly and then every month. Occurrence of any postoperative complication was retrieved from the hospital records and graded according to the Clavien–Dindo (CD) classifications score system.10 Grade I includes any complication deviating from the expected postoperative course, with no other than standard postoperative treatment needed. Grade II includes complications requiring non-standard treatment such as antibiotics, blood transfusion, and total parenteral nutrition. Grade III includes complications requiring radiological, endoscopic, or surgical intervention, with a distinction between IIIa (without general anesthesia) and IIIb (with general anesthesia). Single organ dysfunction is graded as IVa and multiorgan dysfunction as IVb. Grade V is a complication leading to the death of a patient.

2.6 | Ethical approval

The two observational studies on UTx were registered as clinical trials (NCT01844362, NCT02987023). Ethical permission was obtained from the regional ethics committee: no. 088-12 on May 9, 2012, and no. 362-16 on July 13, 2016. Informed written consent was obtained from each participant.

3 | RESULTS

3.1 | Patients and uteri

Characteristics of the recipients concerning diagnosis, kidney status, type of vagina, age, smoking, and body mass index are given in Table 1, as are donor characteristics relating to age, body mass index, smoking, menopausal state, and relation to the recipient. Nine of the recipients who underwent hysterectomy after UTx had no uterus from birth (Mayer–Rokitansky–Küster–Hauser), and one had previously undergone radical hysterectomy with pelvic lymph node sampling because of cervical cancer. There were three types of kidney positioning and vaginal types among patients (Table 1). Median ages and ranges of the recipients at hysterectomy and their uteri at the time of UTxwere 34 (23–38) and 53 (36–62) years, respectively. Five donors and two recipients were previous smokers, with one donor with profound smoking (>20 pack years).

Data regarding obstetric history of the uteri before and after UTx and the reason for hysterectomy are given in Table 2. The median number of pregnancies before and after UTx was 3 (range 1–5) and 1 (range 0–2), respectively. The corresponding figures for live births before and after UTx were 3 (range 1–5) and 1 (range 0–2), respectively.

3.2 | Hysterectomies

In the study cohort, ten hysterectomies were performed after UTx, divided into three categories (Table 2). Elective hysterectomies...
### TABLE 1 Characteristics of recipients and donors

| Pair | Ref. ID | AUFI cause | Kidneys | Vagina | Relation | Age/BMI | Smoking |
|------|---------|------------|---------|--------|----------|---------|---------|
| E1   | #5a    | MRKH       | single NP | Dilated | friend   | 36/20.6 | 60/20.4 |
| E2   | #7a    | MRKH       | double NP | Dilated | mother   | 29/25.8 | 50/25.1 |
| E3   | #8a    | MRKH       | single NP | McIndoe | sister   | 35/28.2 | 36/28.5 |
| E4   | #3a    | MRKH       | double NP+PP | McIndoe  | aunt     | 34/23.9 | 54/20.0 |
| C1   | #1a    | Cervical cancer | double NP | Normal | mother | 37/27.7 | 52/15.1 |
| C2   | #4a    | MRKH       | single NP | Dilated | mother   | 31/32.4 | 50/27.5 |
| C3   | #6a    | MRKH       | double NP | Vechietti | mother  | 34/23.2 | 54/29.8 |
| GF1  | #2a    | MRKH       | double NP | Dilated | mother   | 38/23.2 | 62/32.4 |
| GF2  | #3a    | MRKH       | double NP | Dilated | mother   | 34/25.2 | 55/24.4 |
| GF3  | #8a    | MRKH       | double NP | Dilated | mother   | 23/25.7 | 46/22.8 |

Abbreviations: AUFI, absolute uterine factor infertility; BMI, body mass index; C, cesarean section; D, donor; E, elective procedure; GF, graft failure; MRKH, Mayer–Rokitansky–Küster–Hauser; NP, normal position, PP, pelvic position; py, pack years (pack year = number of packs of cigarettes smoked per day multiplied by number of years of smoking); R, recipient.

a First clinical trial 2012–2013.
b Second trial 2017–2019.
c Postmenopausal, age expressed in full years, BMI expressed in kg/m².

### TABLE 2 Obstetrical history of the uteri and category of hysterectomy including graft duration and graft age at hysterectomy

| Pair | P/M/LB | Hysterectomy cause | Graft duration | Graft age at hysterectomy |
|------|--------|-------------------|----------------|--------------------------|
| E1   | 1/0/1  | elective          | 22             | 62                       |
| E2   | 1/0/1  | elective          | 23             | 52                       |
| E3   | 1/0/1  | elective          | 34             | 39                       |
| E4   | 6/6/0  | elective          | 71             | 60                       |
| C1   | 2/0/2  | C-section         | 52             | 56                       |
| C2   | 2/0/2  | C-section         | 56             | 55                       |
| C3   | 2/0/2  | C-section         | 83             | 61                       |
| GF1  | 0/0/0  | graft failure     | 3              | 62                       |
| GF2  | 0/0/0  | graft failure     | 8              | 56                       |
| GF3  | 0/0/0  | graft failure     | 1              | 46                       |

Abbreviations: C, cesarean section; D, donor; E, elective procedure; GF, graft failure; P/M/LB, pregnancies/miscarriages/live births; graft duration expressed in rounded months, graft age at hysterectomy expressed in full years; R, recipient.
(n = 4) were performed 3–6 months after childbirth or, in one case, due to multiple implantation failures (n = 10) and repeated (n = 6) miscarriages, with a predicted very low chance of obtaining live birth. Hysterectomy in conjunction with cesarean section was performed in three patients after the delivery of their second child. Hysterectomy was conducted in the same session as the cesarean section because the ethics application required a maximum of two children to minimize the time receiving potentially nephrotoxic immunosuppression and because we also wanted to avoid another surgical session for the patient. In three patients, hysterectomy was performed because of graft failure, with no previous pregnancy after UTx. The durations of the different segments of the surgeries are graphically depicted in Figure 1, with interruptions for insertion of ureteral catheters indicated. Table 3 provides detailed surgical data, including information on adhesions and surgical difficulties.

### 3.3 Surgery techniques and lessons learned

Considering the possibility of atypically located ureters and their location in relation to the uterine vessels anastomosed together with the presence of adhesions after UTx, prophylactic ureteral catheters were inserted as planned procedures in most cases (n = 6) of hysterectomy, excluding the graft failures. Ureteric catheters were not applied in hysterectomies of graft failures because of the predicted small uterine size after insufficient perfusion and no need for extensive dissection because anatomical planes could be easily opened manually. In the first elective hysterectomy after childbirth, the patient had a single ureter, and protection by ureteral catheter was performed to minimize the risk of damage to this sole kidney outflow. The second patient undergoing hysterectomy had double ureters, and ureteral catheterization was not planned; however, during the procedure, it was very difficult to identify the exact positions of the ureters by ordinary dissection because of the altered anatomy and adhesions on the pelvic sidewalls. Thus, ureteral catheterization was carried out in this case and in subsequent hysterectomies, excluding those in graft failures (as detailed earlier).

We noted some extent of adhesions between the uterus and surrounding tissues in most cases (Table 1), but these were generally light to moderate adhesions and could be divided using standard techniques. The uterus could then be identified and ordinary hysterectomy dissection conducted, first in the front to reach the level of the vaginal vault. Concerning dissection of uterine graft vessels, the general strategy was to identify them close to the uterus and then with dissection towards the anastomotic sites on the external iliac vessels. The vessels were dissected to leave a minimum of graft vessel pedicle of approximately 0.5–1 cm in most cases, to minimize immune response and at the same time not cause strictures on the external iliacs by excision of anastomotic sites.

### 3.4 Clinical course and histopathology of graft failures

All three failed uterine grafts (GF1–3) showed early ischemic signs and were removed within the first year after transplantation. The clinical courses and histopathological findings in biopsies from the cervix and myometrium were similar, albeit with possible differences in further clinical course and histopathology of hysterectomy specimens depending on the time between transplantation and graft hysterectomy.

In the case of patient GF1, initial Doppler observations of uterine blood flow showed clear blood flow in the periphery of the uterus but with less blood distribution towards the inner part of the uterine wall. The initial protocol cervical biopsy 1-week post transplantation showed necrotic material, and a follow-up myometrial biopsy 1 day later showed patchy ischemic changes, although with the presence of viable smooth muscle cells. Subsequent cervical biopsies during month 1 and 2 displayed necrotic tissue fragments with variable amounts of inflammatory cells, mainly neutrophils. Color Doppler

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**FIGURE 1** Segmented individual surgical courses of patients with hysterectomy as elective procedure (E), in conjunction with cesarean section (C), or at graft failure (GF). A, general anesthesia; S, spinal anesthesia; UC, insertion of ureteral catheter(s); Hyst, hysterectomy; CS, cesarean section.
still showed a distribution of blood flow in the periphery of the grafts. The patient was admitted 3 months post UTx with infectious symptoms, and a uterine abscess was subsequently found. Drainage via the vaginal route was performed twice, and she was treated with intravenous broad-spectrum antibiotics. Due to initial signs of sepsis and since there had been no signs of menstruation or endometrial growth on repeated transvaginal ultrasound examinations, the decision was made to perform the hysterectomy. This was 3.5 months after UTx. The explanted uterus showed mainly viable myometrium, whereas the inner half was necrotic with focal neutrophil infiltration. Sections from the cervix showed no viable epithelium and some inflammation dominated by neutrophils. Severe atherosclerosis was observed focally in large arteries. There was no evidence of rejection. The total length of hospital stay was 32 days because no signs of rejection (Figure 3). Enterococcus faecium was found in vaginal culture. A cervical biopsy 1-week post transplantation showed severe ischemic changes with loss of surface epithelium, vessel endothelium, and ischemic stroma (Figure 2). Subsequent weekly cervical biopsies during the initial post-UTx months displayed severe ischemia towards the surface with some neutrophil infiltration but partially viable cells in deeper parts of the cervix. The infection was treated with antibiotics, but the patient was readmitted to the hospital because of increasing infectious parameters. Further biopsies showed necrotic material, and the uterus was explanted 1-month post transplantation. Analysis of the hysterectomy specimen showed that the inner part of the uterine wall was ischemic with complete loss of epithelium, and the outer part contained partially viable myometrium with some ischemic changes and focal necrosis. Vessels were congested, and focal interstitial hemorrhage was observed. At least moderate atherosclerosis was seen but no signs of rejection (Figure 3).
3.5 | Postoperative period

Postoperative data for all hysterectomies are presented in Table 4. The median length of hospital stay was 3.5 days (range 1–32). Transitory postoperative hematuria, possibly due to the ureteric stents, was present in two patients, and anemia was present in three patients, with compensatory blood transfusion in two cases. Symptoms indicating peroneal nerve palsy emerged in patient GF3 but with complete remission soon after hospital discharge. Superficial wound infection was noted in patient C3 at a hospital revisit, and this was treated with oral antibiotics. Patient E2 experienced a supravaginal hematoma (3 × 5 cm), discovered after hospital discharge, which required surgical intervention 4 weeks after the hysterectomy surgery. The hematoma was evacuated by transvaginal drainage under anesthesia and graded as CD IIIb. The patient recovered shortly afterwards and had no sequelae.

4 | DISCUSSION

Until less than a decade ago, a portion of patients with uterine factor infertility were considered irreversibly infertile since no treatment existed. Patients with no uterus, from birth or after hysterectomy, belonged to the most obvious group of permanently uterine infertile patients. Additionally, women with an existing uterus, although with no capacity to carry a pregnancy, had no means of achieving a biological child apart from using a gestational surrogate with their embryo placed inside the uterus of another woman. The breakthrough in treatment of absolute uterine factor infertility came with the report of the first live birth after UTx, which occurred in Sweden in 2014. Since then, reports on surgical outcomes of UTx and obstetrical outcomes have been presented by several centers worldwide. However, there are no scientific reports concerning the graft hysterectomy and no detailed analyses of clinical and histopathological courses of graft failures. The present study is the first to address these important aspects of UTx.

Hysterectomy after allogeneic UTx is necessary to end the need for immunosuppressive treatment in the recipient, as it carries substantial risks for negative side effects such as nephrotoxicity, susceptibility to serious viral and fungal infections, and malignancies. This time period, with the uterus as a graft in the recipient, should be minimized because of side effects from the immunosuppression but at the same time allow time for success and achievement of the goal of the entire UTx procedure: healthy babies. Thus, our initial recommendation was that hysterectomy should be performed before a graft time up to 7 years or before that after transplantation success in terms of live birth(s).
but around 5 h in two cases. These hysterectomy surgery durations and inserted perioperatively, with extra time to call in the urologist. Of ureteral catheters, since these were not initially planned in all cases lying cause of long anesthesia durations was time taken for insertion ratios ranging between 1 h 42 min and 5 h 52 min. The major under
Swedish registry study of more than 27 000 hysterectomies.

| TABLE 4 | Data of postoperative period after hysterectomy |
|---------|-----------------------------------------------|
| ID      | LOS (days) | Postoperative complications | Clavien–Dindo classification |
| E1      | 2          | —                             | Grade I                      |
| E2      | 4          | Hematuria                      | Grade I                      |
|         |            | Anemiaa                       | Grade II                     |
|         |            | Vaginal hematomb                | Grade IIIb                   |
| E3      | 3          | Hematuria                      | Grade I                      |
| E4      | 2          | —                             | —                             |
| C1      | 4          | Anemia                         | Grade I                      |
| C2      | 5          | —                             | —                             |
| C3      | 3          | Wound infectionc               | Grade II                     |
| GF1     | 32         | —                             | —                             |
| GF2     | 1          | —                             | —                             |
| GF3     | 5          | Peroneal nerve palsy           | Grade I                      |
|         |            | (transitory)                  | Grade II                     |
|         |            | Anemiaa                       | Grade II                     |

Abbreviation: GF, failed uterine graft; LOS, length of hospital stay.
aBlood transfusion.
bSurgical intervention.
cOral antibiotics.

Naturally, hysterectomy is also indicated in cases of obvious graft failure, but with some observation time between the initial signs of failure and the decision for hysterectomy to rule out the possibility of the graft recovering.

The distribution of causes of hysterectomy was a predicted mix. Three hysterectomies were performed because of graft failures before any pregnancy was attempted. The clinical courses and associated histopathological findings followed similar patterns in all cases, although the time until hysterectomy was performed ranged from 1 to 8 months. Primarily, this was because we accumulated clinical experience in the typical early signs of graft failures, such as low or non-visible blood flow in central parts of the uterus and necrosis on cervical biopsies. Thus, an early decision for hysterectomy was taken in the last case of graft failure to avoid a prolonged period of anxiety for the patient and possible infection, with associated symptoms. In the first case of graft failure, an untreatable intrauterine infection occurred, and this developed into initial septicemia.

Times of anesthesia and surgery varied widely, with anesthesia durations ranging between 2 h 36 min and 7 h 35 min and surgery durations ranging between 1 h 42 min and 5 h 52 min. The major underlying cause of long anesthesia durations was time taken for insertion of ureteral catheters, since these were not initially planned in all cases and inserted perioperatively, with extra time to call in the urologist. The typical duration of hysterectomy surgery was between 2 and 3 h, but around 5 h in two cases. These hysterectomy surgery durations can be compared with the surgical duration of 100 (±41) min for total abdominal hysterectomy on benign indications reported in a recent Swedish registry study of more than 27 000 hysterectomies.11 The reasons for the longer durations are most likely related to the presence of adhesions in conjunction with the uterus and the complex dissection of the uterine vessels, with their altered anatomical locations in relation to the ureters and external iliac vessels.

In the present study, we used prophylactic ureteral stenting in several cases to easily identify the ureters and to avoid surgical trauma to the ureters. Prophylactic ureteral stenting is not infrequently used in advanced laparoscopic gynecological surgery for endometriosis, especially in cases with obliterated cul de sac,12 which would be a similar situation as in post-UTx hysterectomy, where the ureters may be hidden in adhesions and be anatomically displaced. Inserting ureteral catheters is a simple procedure to aid in identification of the course of the ureters, thereby avoiding injury, while operating in the narrow pelvis. Although laparoscopic hysterectomy may be associated with a higher risk of ureteral injury than abdominal hysterectomy,13,14 this intervention should still be seen as valuable, as ureters are atypically located after UTx and adhesions may be frequent.

The histopathological findings of uteri with graft failures were loss of surface epithelium of the ectocervix as early as 1-week post transplantation. Subsequent biopsies showed no surface epithelium, ischemic changes in the cervical stroma, and infiltration of neutrophils. In explants, there were no epithelial linings in the uterine cavity or on the cervix. The inner third to half of the uterine wall was severely ischemic and/or necrotic. The outer part was partly viable, with patent vessels close to the serosal surface. There was evidence of at least moderate atherosclerosis of uterine arteries but no rejection. Current observations indicate that ischemia in cervical biopsies are representative of the entity of the uterine graft. Similar statements have recently been made in a report of histological findings in explants at elective hysterectomy on benign indication, where inflammation in the cervix represented inflammation in the organ parenchyma.9 Interestingly, the myometrium showed viable parts in histopathology of all the three hysterectomy specimens at graft failure, which may indicate that deeper myometrial biopsies may not be as representative. Moreover, all graft failures showed moderate atherosclerosis, indicating that uterine perfusion may have been suboptimal prior to transplantation.

In our second, robotics-assisted trial,15 patients #3 and #8, referred to in this study as GF2 and GF3, showed the lowest perioperative mean arterial blood flow of 15 and 24.5 ml/min, respectively, compared with the six subsequently viable grafts where perfusion ranged between 39 and 112 ml/min. Regarding patient #2 in the first trial,1 herein referred to as GF1, uterine infection was discussed as the factor attributable to subsequent graft loss. While this was the clinical manifestation, the infection was most likely due to ischemia and necrosis, as thoroughly described in the results section.

In none of the observed graft failures was early ischemia reversed, indicating that such ischemic changes are signs of irreversible damage and that the organ will subsequently fail. In relation to this, transplantation was aborted during a UTx procedure in Germany16 because of an inability to flush the retrieved organ and to therefore avoid transplanting a uterus with diminished blood flow and with a high risk of graft failure. It may well be that signs
of atherosclerosis or difficulty properly flushing the organ at back-
table preparation indicates that the explanted organ should not be
transplanted.

Postoperative complications in the present study were generally
ordinary complications as expected after hysterectomy, such as ane-
mia and supravaginal hematoma. In a large study of over 16,000 hys-
terectomies, the overall complication rate was 6.8% and the major
postoperative complications rate was 2.3%. Therefore, the rate of six
patients in ten hysterectomies in our study experiencing a complica-
tion is high, even though hysterectomy after UTx is a complex pro-
cedure. Notably, all our study patients were thoroughly monitored, and
all side effects and complications were registered, which may not
be the case in many large retrospective studies, and complications
may be more common than reported. The episodic hematuria seen in
two patients were probably secondary to the ureteric stents. Taken
together, post-hysterectomy complications in recipients were re-
versed, and no sequelae were reported in any patient. Nevertheless,
the complication rate after hysterectomy after UTx must be min-
imized in future trials and when the UTx procedure is adopted in
general health care.

5 | CONCLUSION

Hysterectomy secondary to UTx is a novel aspect to a well-known
surgical procedure in women. Our observations indicate that the
procedure is more complex and time consuming than ordinary total
abdominal hysterectomy on benign indications. Abdominal adhe-
sions are frequently observed, and perioperative ureteral catheter(s)
may aid in surgery and shorten surgery time. Histopathological find-
ings in cervical biopsies appear to be representative for the entire
organ. Early signs of ischemia in cervical biopsies and Doppler as-
sessments that indicate mostly peripheral blood flow may indicate
irreversible perfusion damage and subsequent graft failure. Such as-
sessments should be carefully considered in a clinical setting, where
a more rapid decision to perform hysterectomy may be beneficial to
the patient.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

The study was designed by M.B. C.K collected and compiled the
data, and C.K and M.B worked together on the data analysis. J.M and
V.B contributed with histopathological assessments of graft failures.
C.K prepared a preliminary draft and M.B, P.D-K, N.K participated
in a critical discussion about the content, with individual additional
contributions. All authors have participated in completing and read-
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