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Uterus transplantation and fertility preservation

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A B S T R A C T

Absolute uterine factor infertility (AUFI), with uterine absence or presence of a non-functional uterus, was considered untreatable until 2014, when the first child was born after transplantation of a uterus from a postmenopausal woman to a woman of fertile age who was born with no uterus, as a part of the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome. Concerning gynaecological cancer, AUFI may occur after hysterectomy for malignancy or after surgery/radiation that will preserve the uterus but causing non-functionality in terms of future implantation and pregnancy. This review summarises the research preparations that paved the way for the clinical introduction of uterus transplantation (UTx) as a treatment for AUFI. We also summarise the human UTx attempts that have been published as well as the live births reported thus far. The clinical use and procedures for UTx are also proposed for a number of gynaecological malignancies.

Introduction

Successful uterus transplantation (UTx) has recently shown that women with absolute uterine factor infertility (AUFI) can attain both genetic and gestational motherhood [1–3]. In comparison with other types of transplantations, the UTx setting may use both the deceased donor (DD) and live donor

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(LD) concepts. Furthermore, UTx is presently the only ephemeral transplant to remain in situ for a limited time in the recipient and this restricted duration greatly reduces the risk of the well-known long-term immunosuppressive-related side effects.

Cancer treatments for cervical and endometrial cancers are evolving, and the prognoses are continuously improving [4]. Importantly, fertility-sparing strategies are currently routinely discussed, and several options are available, but women undergoing total hysterectomy have been excluded from fertility preservation options [5]. Furthermore, the mean age of women at their first pregnancy and birth has been increasing in many countries during the last decades, which affects the number of women who wish to preserve their fertility at the time of cancer diagnosis/treatment [6]. Hence, fertility preservation has become one of the major concerns of fertile-aged women diagnosed with cancer.

The total prevalence of AUFI is estimated to be approximately 20,000 women of childbearing age in a population of 100 million [7], but naturally, only a minor portion of these women have been treated for malignancy.

UTx – general patient groups and future patient groups for fertility preservation

Women with AUFI have either uterine absence (congenital/surgical) or abnormalities (anatomic/functional) that preclude the implantation of an embryo or completion of a pregnancy.

The most prevalent cause of AUFI is uterine absence because of a hysterectomy performed for benign indications (myoma and bleeding problems). Hysterectomy for these indications is the most frequent major gynaecological surgical procedure that women may undergo [8]. Moreover, massive obstetric bleedings, because of uterine atony, uterine rupture or invasive placentation [9], is not uncommon with invasive placentation becoming more prevalent because of increasing rates of caesarean section.

Hysterectomy during the fertile period, because of malignancy, is much less frequent. The most common malignancies with hysterectomy as a treatment in this age group are cervical cancer, endometrial cancer, epithelial ovarian cancer and non-epithelial ovarian cancer. Very rare causes of hysterectomy are treatment for leiomyosarcoma, endometrial stromal sarcoma and choriocarcinoma/placental site trophoblastic tumour with chemoresistancy and solitary remaining tumour in the uterus. The prognoses and outcomes vary between the different diagnoses with regard to different oncological characteristics, and an experienced gynaecologic oncologist should always be involved in assessing the individual lifetime risk of recurrence when considering future fertility aspects.

Cervical cancer is the fourth most commonly diagnosed cancer in women worldwide, accounting for approximately 8% of all new cancer cases [4], and approximately 25% of women with this cancer type are diagnosed under the age of 40 years [10]. Dargent introduced fertility-sparing options with the trachelechtomy procedure for selective cases of cervical cancer, such as small tumours $\leq$2 cm [11,12]. However, trachelectomy may not be offered to all young women diagnosed with early-stage cervical cancer because of tumour size or other oncological risk factors. Hence, radical hysterectomy may be the recommended treatment for cure, and this will cause AUFI [13]. Furthermore, endometrial cancer may also arise in young women, although not frequently occurring. It has been estimated that 5–29% of endometrial cancers are diagnosed before the age of 40 years [14], and approximately 70% of these women are childless at the time of diagnosis [15]. There are other fertility-sparing options even for young women with endometrial cancer by the use of progestagens and/or surgical resections [16,17], but the internationally recommended treatment is still total hysterectomy and this will cause AUFI.

Taken together, these disease-specific treatments are usually associated with an excellent prognosis [4], and these women can now be considered for UTx as a way to restore their fertility capacity.

Radiation in the form of either total body radiation or direct/scattered pelvic radiation may lead to a decrease in uterine blood flow and uterine size, together with endometrial atrophy, which may lead to non-function of the uterus [18]. Radiation treatment will, in most cases, cause ovarian damage and premature ovarian failure, but new strategies are used with cryopreservation of the ovarian cortex, containing the pool of primordial follicles, and subsequent transplantation after cancer treatment. More than 60 births have been reported with this technique [19].

The most evident congenital malformation in the AUFI group is uterine absence as part of the MRKH syndrome, where the woman lacks a vagina above the hymen and with only the rudimentary uterine tissue. The syndrome is present in approximately 1:4500 women [20]. The cause of this Müllerian duct

agenesis is unknown, but it is most likely a combination of genetic and epigenetic/environmental factors during foetal life [20]. It is estimated that the MRKH cohort represents approximately 3% of women with AUFI, and thus far, the vast majority of UTx attempts have been performed in women with this AUFI cause, as described below. The hypoplastic uterus is regarded as a variant of the MRKH, where the uterus is developed but very small. A pregnancy is not possible in such a uterus. Moreover, there exists also a proportion of women with the unification defects of unicornuate and bicornuate uterus who are uterine factor infertile because of implantation failure or early pregnancy loss [21].

Intrauterine adhesions, after curettage or endometritis, could be treated by hysteroscopy and resection, but the majority of cases with severe adhesions remain infertile despite repeated hysteroscopy [22], and UTx is a possible fertility option in such cases.

Preparatory animal studies on UTx

During the last two decades, research on UTx has been conducted in a structured way with the use of several animal models to investigate aspects such as surgery, tolerability to ischemia, detection of rejection, immunosuppression and subsequent fertility [23].

Experiments have been performed with autologous/syngeneic transplantation models to mainly test the results of surgery of UTx, with a uterus with an altered supply and outflow of blood as well as the fixation and position of the uterus. Additional effects of immunosuppression and rejection episodes have been tested in allogeneic UTx models. The ultimate goal of UTx is pregnancy and delivery of a healthy offspring. This has been explored in all the three types of UTx models. The key experiments concerning fertility in animal models are summarised below.

The first demonstration of pregnancy to mid-gestation in a true UTx setting was in the mouse, with the uterus in a heterotopic position [24], using vascular caval–caval and aortic–aortic anastomoses. This initial model was modified somewhat [25], and pregnancies could go to term, with the resultant pregnancy rate being normal in the transplanted uteri. The offspring had a normal growth trajectory to adulthood [25].

In the larger rat, an orthotopic UTx model with an end-to-side anastomoses between the right common iliacs of the graft and the recipient was used [26]. Pregnancy rates, after natural mating, in a syngeneic setting were similar in UTx animals as those of controls [27]. In this species, fertility after allogeneic UTx was reported for the first time [28], and in a follow-up study, pregnancies were allowed to go to term [29]. Birth weights and growth trajectory of the offspring from UTx were normal compared to those of controls.

Fertility in the sheep was first tested in an autologous UTx model, with uterine-tubal-ovarian transplantation and end-to-side vascular anastomoses of the uterine artery, utero-ovarian vein and the ovarian artery, including an aortic patch, to the external iliacs [30]. Approximately three months after auto-UTx, five ewes were placed with rams for mating and 60% of the ewes delivered lambs of normal sizes. Later, an allogeneic sheep UTx model, with cyclosporine immunosuppression, demonstrated live births of normal offspring [31]. This breakthrough result in 2011 was the first live birth from a large animal undergoing allogeneic UTx.

The initial offspring reported in a non-human primate species was obtained after autologous UTx in the cynomolgus macaque [32] and auto-transplantation, with unilateral preservation of the oviduct. Pregnancy occurred after natural mating, and because of signs of partial placental abruption, a caesarean section was performed preterm but with delivery of a live offspring.

Living donor UTx in patients with MRKH

It is estimated that the MRKH cohort represents approximately 3% of women with AUFI, and thus far, the majority of UTx attempts have been performed in these women.

The first clinical UTx trial, initiated in 2012 in Sweden following agreed psychological [33] and medical screening [34], included eight patients with the MRKH syndrome. Six of the eight women who donated their uteri to patients with MRKH of this study were related (five mothers and one sister), one was a family friend and the other one was a mother-in-law. Four of these donors were postmenopausal, and all had had only uncomplicated pregnancies to term. The (midline incision) retrieval surgery

comprised dissection of the uterus and the bilateral uterine arteries and deep uterine veins, with segments/patches of the internal iliac vessels. The surgery of deep dissection of the uterine veins and ureters was difficult, complex and time consuming, and the total surgical duration of the retrieval surgery was 10–13 h [34]. The more undemanding surgery of the recipient took 4–6 h and included bilateral end-to-side anastomosis of segments of the internal iliac arteries and veins of the graft to the external iliacs. After uterine blood flow in recipient had been established, the graft was anastomosed to the vagina and then attached to the pelvis by the sacrouterine ligaments and round ligaments and to the cleaved residual uterine tissue on the pelvic sidewalls.

The 6-month outcome [34] of these eight transplants was that six out of eight uteri remained viable. The reasons for the two subsequent uterine removals were bilateral thrombotic uterine vessel occlusion within a week in one patient and persistent intrauterine infection, developing into an intrauterine abscess at approximately 3 months after UTx, in the other patient. The recipients and their partners showed general psychological well-being and stability during the initial post-transplantation year, although some worry existed about organ survival during this time [35]. All donors were also in good medical and psychological health at one year post donation [36].

The first human live birth after UTx occurred in a patient with MRKH in September 2014 after an UTx procedure in February 2013 [1]. The donor was a family friend who was 61 years at donation. There was a period of 1 year from UTx until attempts to initiate pregnancy to minimise and optimise the immunosuppression. This patient became pregnant after her first embryo transfer. Preeclampsia occurred at week 31 + 5, and one day later, we delivered a healthy boy by caesarean section. The second UTx baby [2], also from a patient with MRKH, was delivered two months later after the pregnancy had been initiated at her first ET attempt. The uterus was from the grandmother of the newborn child. During the period from 2014 to 2017, a total of six healthy children were born from the cohort of six women with MRKH undergoing the full procedure of IVF, UTx and ET in this initial UTx trial [37].

The next living donor UTx attempt with a woman with MRKH took place in China in late 2015 [38], when a mother (age 42 years) donated her uterus to her daughter with MRKH. The procedure included complete robotic-assisted laparoscopic retrieval surgery, and the sole venous outflows were the ovarian veins. The use of ovarian veins greatly simplified surgical dissection, but it necessitated oophorectomy, which is not without risks for subsequent cardiovascular and cognitive morbidity. One year after transplantation, the uterus was reported to be viable [38]. Thus far, there have been no publications concerning any pregnancy resulting from this procedure.

In 2016, three separate trials on LD UTx with involvement of patients with MRKH were initiated.

The first to start was in the Czech Republic and has thus far involved five women with MRKH, with donors being mothers in four cases and a mother's sister in one case [39]. All donors were peri/postmenopausal, and this allowed the usage of only ovarian veins as outflow, with accompanying oophorectomy, in the majority of cases. One uterus was removed two weeks post-UTx because of vascular thrombosis. Initial ET attempts have not yet lead to any pregnancy.

Later, in 2016, an UTx trial was initiated in Germany. The surgery and initial follow-up of the first two patients with MRKH have been reported [40]. Spontaneous menstruation occurred after some months, but no pregnancy has yet been reported.

The first LD UTx trial in the USA initially included five patients with MRKH. The first three recipients lost their grafts during the initial two weeks because of vascular complications [41]. However, subsequently, two cases were uneventful and functioning grafts were reported 3–6 months after transplantation. One of these latter UTx cases became pregnant at her first ET attempt 6 months post-UTx and delivered a healthy baby in late 2017 [3]. This UTx procedure used only the utero-ovarian veins for venous outflow.

In 2017, a partially laparoscopic-assisted LD UTx case was undertaken in India. A 21-year-old patient with MRKH received a uterus from her mother, with vessel dissections including the ovarian veins and uterine arteries being performed laparoscopically [42]. The surgical duration was shortened by this approach, with exclusive use of ovarian veins as outflow.

Deceased donor UTx in patients with MRKH

All the seven reported DD UTx cases worldwide have involved patients with MRKH as recipients. The first DD UTx attempted was performed in Turkey in 2011, when a 21-year-old woman with MRKH

received a uterus from a 22-year-old nulliparous brain-dead woman [43]. The retrieval surgery lasted for 2 h and the transplantation, with bilateral end-to-side anastomosis of the internal iliac vessels of the graft to the external iliac vessels, lasted for 5 h. No live birth was reported from this case.

The second DD UTx, also involving a patient with MRKH, was in the USA in early 2016 [44]. The cold ischemic time was long because of a large distance between the site of procurement and transplantation. The graft had to be removed two weeks after transplantation because of fungal infection involving the uterine vessels.

Four DD UTx attempts in a series with MRKH recipients (age 17–21) were performed in the Czech Republic [39], with the initial case in the first half of 2016. The donors were in two cases postmenopausal and with previous normal vaginal births. The other two donors were 20–25 years old and nulliparous. Surgical time of the recipient was 6–8 h, with two uterine veins being used in all cases and, additionally, two ovarian veins in two cases. One uterus was removed after one week because of thrombosis and another after 7 months because of degenerated endometrium, secondary to primary herpes simplex virus infection. No pregnancy has yet been reported.

The first successful DD UTx case was performed in Brazil in September 2016 when a 32-year-old woman with MRKH received a uterus from a brain-dead 45-year-old para three donor who had died of a subarachnoid haemorrhage [45]. In situ flushing was performed through the common iliacs, with clamping of the external iliacs, and this perfusion was performed before flushing of other organs. However, retrieval of the uterus was after procurement of the heart, liver and kidneys to minimise the ischemic time for these vital organs. The back-table preparation lasted for 1.5 h, with care taken to dissect all vessels including the uterine arteries and veins, as well as the ovarian veins. Bilateral salpingectomy and oophorectomy were also performed on the back-table. The cold ischemic time was 6 h and 20 min, which is substantially longer than that in LD UTx surgery.

The recipient surgery included bilateral anastomosis of the uterine vessels to the external vessels. After unclamping, a substantial flow was seen through the preserved ovarian veins, and consequently, these veins were also anastomosed to the external iliac veins at a more cranial position to facilitate venous outflow. After that, the vagina was opened and the vaginal rim of the uterus was attached to the vagina of the patient, followed by fixation of the uterus to the ligaments. The surgical time of the recipient was more than 10 h and with a blood loss of more than 1 L. The long duration and substantial blood loss were due to substantial bleeding from open vessels of the graft, and these openings were then closed by cautious use of bilateral diathermy, with avoidance of damaging the blood supply and normal outflow from the uterus.

Six months after UTx, one blastocyst was transferred in the natural cycle and the uterus recipient became pregnant at this initial ET attempt. Elective caesarean section was performed at week 35 and three days, and a healthy baby girl was delivered. Hysterectomy was performed after delivery. Notably, prominent intimal fibrous hyperplasia of the uterine arteries was observed. The reason for this is unclear, and it has not been noted in the published LD cases with hysterectomy after birth. The postnatal growth and development of the child was normal during the first 7 months.

The importance of this case is the proof of concept of DD UTx as an alternative to LD UTx, which will open up the possibility for more women with AUFI to have this only available infertility treatment in the future.

UTx in non-MRKH benign cases

There are only two reports of UTx attempts in patients without MRKH with benign disease leading to AUFI. Both of these reports were with the LD concept.

The first UTx attempt was an LD UTx case, performed in 2000 in Saudi Arabia [46]. An unrelated peri-menopausal donor gave her uterus to a woman who had experienced an emergency peripartum hysterectomy. A necrotic uterus was removed 99 days post UTx with the presence of bilateral uterine vessel thrombosis. Inadequate uterine structural support may have led to prolapse with associated tension and kinking of the vessels.

The second UTx attempt in this category was made in 2017, with a 26-year-old woman with severe Asherman syndrome, who received a uterus from her mother [42]. The procurement of the uterus from

the donor was by a combination of laparoscopy and laparotomy. Because the sole venous outflow parts were the ovarian veins, the donor surgery was relatively fast, but the surgery necessitated oophorectomy.

UTx after gynaecologic malignancy

One out of the nine recipients of the Swedish trial had undergone a radical hysterectomy 7 years before UTx to treat her cervical cancer [34]. That patient was diagnosed with a 3 cm large, cervical tumour, stage 1B1, at the age of 25 years. Because of a tumour size larger than 2 cm, she was not recommended fertility-sparing surgery with trachelectomy, and a radical hysterectomy with pelvic lymph node dissection was performed. The pathology report showed adequate surgical margins and negative lymph nodes, and she was followed up for 5 years with no evidence of disease (NED). She was well informed about the UTx trial at the planning stage and wished to participate with her 51-year-old mother as the donor. After careful psychological and medical screening of the patient and her mother, she accepted to participate in the trial. Importantly, repeated vaginal cytology showed that she was negative for HPV infection, and after 7 years, she still showed NED. The UTx surgery was performed according to our standard method. She became pregnant at her 4th embryo transfer attempt and delivered a healthy boy in November 2014 by caesarean section. In January 2016, she delivered a healthy daughter and is thus the first patient with UTx in the world with two deliveries after UTx. The uterus was removed at the second caesarean section, and immunosuppression was immediately withdrawn.

Summary

UTx is still at the early clinical experimental stage. Success has been demonstrated after both LD and DD UTx, and more than 10 babies have been born worldwide. Thus far, only one patient with previous gynaecological malignancy has had success after UTx. This patient had cervical cancer. It is likely that UTx in the future will include fertility preservation/restoration in new categories of patients with gynaecological cancer as outlined above. An important factor with regard to UTx in cancer victims is that it is well known that the long-term use of transplantation-related immunosuppression medication leads to an increased risk of certain malignancies such as skin cancer and haematological malignancies. There may also exist a risk that immunosuppression would be able to trigger the recurrence of the specific malignancy that in some patients caused the AUFI condition. Thus, a patient with cancer history should only be subjected to UTx at a time when it is fully clear that there is almost no risk for recurrence of the disease. Importantly, the uterine graft and immunosuppression is only temporary, until one or two children have been born, and then the uterus will be removed and medication will be stopped. Another aspect that has to be considered is that the presence of epithelial dysplasia of the outer genital tract is fairly common in immunosuppressed women, and thus, a transplanted woman has to be monitored closely with cytology and colposcopy of the cervix, vulva and vagina.

We foresee a future with a gradual and well-controlled expansion of UTx for fertility preservation in patients with previous malignancies.

Practice points

- Uterus transplantation (UTx) has successfully been conducted in humans after more than a decade of animal-based research in several species.
- Techniques for successful UTx, resulting in live births, have been developed for organs of both deceased and living donors.
- UTx will most likely be expanded to several new patient groups, including women with lack/damage of the uterus after cancer treatment.

Research agenda

- Long-term effects (psychological and medical) should be evaluated for recipients, partners, living donors and children after uterus transplantation.
- Studies should be conducted towards non-invasive techniques to evaluate rejection.
- Clinical studies with application of minimally invasive surgery for living donor surgery and in the longer future, also for recipient surgery, should be started.

Conflicts of interest

None.

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