A New Approach for Treatment of Woman With Absolute Uterine Factor Infertility: A Traditional Review of Safety and Efficacy Outcomes in the First 65 Recipients of Uterus Transplantation

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infertility fellowship

Abstrac
Uterine transplantation restores fertility in women with absolute uterine factor infertility and allows the
opportunity to conceive, experience gestation, and acquire motherhood.
65 cases : uterus transplantation and IVF
increased risk for further mother and newborn babies .
significant risk:one quarter of grafts are removed because of complications. The risk of the procedure ,gestational and delivery complications.

desire for pregnancy : so strong for some women are willing to risk their health .

Absolute uterine factor infertility (AUFI), which refers to infertility that is completely attributable to the uterine absence (congenital or surgical) or an abnormality (anatomic or functional), affect approximately one in 500 women of childbearing age, or 1.5 million women worldwide .

Uterine factor infertility affect thousands of women worldwide, caused by congenital Müllerian malformations, such as in the MayerRokitansky-Küster-Hauser (MRKH) syndrome, or acquired as in the cases of women suffering from Asherman's syndrome, pregnancy-interfering myomas, or hysterectomies.

women with AUFI have two options: adoption or surrogacy.

Adoption provides legal motherhood.

surrogacy agreement confers genetic motherhood.

after adoption, legal motherhood to infertile mothers. During this process, multiple medical and legal issues may arise.

Maternal surrogacy is forbidden in many countries, including France, Germany, Bulgaria,Croatia, Estonia, Finland, Hungary, Italy, Lithuania, Portugal, Slovakia, Australia, Holland, Spain, Sweden,and Norway. However, there is no legislation or regulation in other countries, leading to conflict between the involved parties.

The evolution of uterine transplantation (UTx) was primarily motivated by the potential to help women suffering from the discrepancy between procreative ability and reproductive aspirations because of AUFI.

Although this procedure is associated with greater risk from multiple major surgeries and exposure to immunosuppressant drugs, UTx is the only option that allows women with AUFI the opportunity to become pregnant and give birth to genetically correlated offspring themselves .

Women who are inspired to pursue uterus transplantation take risks from immunosuppression, a high-risk pregnancy, and at least three surgical procedures.

1)allotransplantation

2)caesarian section to deliver the child (and a second section if a second child is desired)

3)graft hysterectomy after the delivery .

Steps required pre/post the uterus transplantation procedure

The transplant process to successful birth fluctuates from person to person but can take approximately two to five years for many participants .

It includes:

1.Medical evaluation of donor and recipient.

2. Embryo generation: Before the surgery, a woman generates embryos through in vitro fertilization (IVF).

During this process, she should take fertility drugs to produce eggs removed from her ovaries and fertilized

3.Transplantation: The uterus is removed from a donor during a three-hour operation and surgically placed

into the recipient in a six-hour operation. The recipient starts taking immunosuppressive drugs to prevent

rejection of the transplant. These medications should be taken while the transplant is in place and during

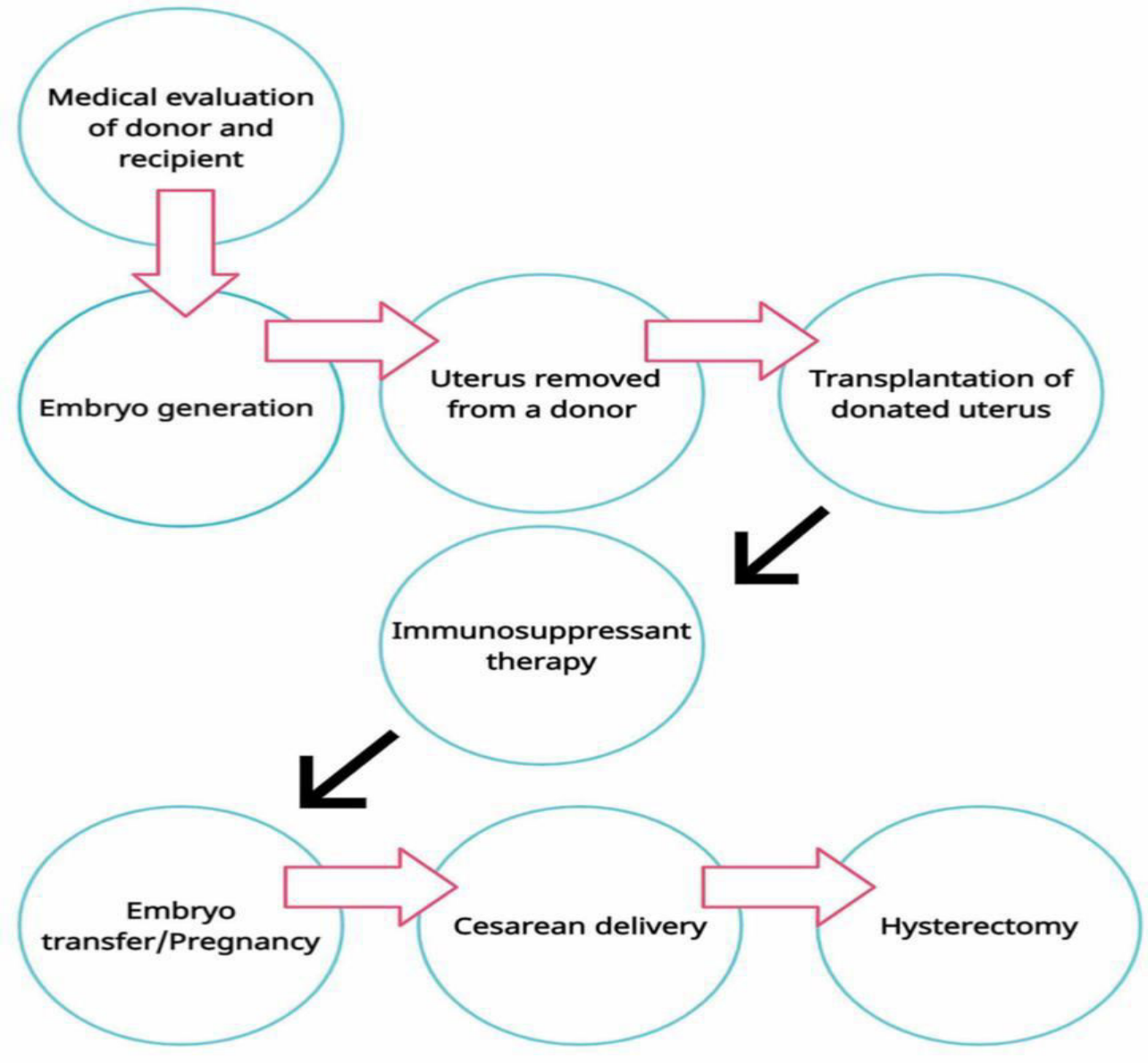
pregnancy .

4. Pregnancy: Several months or a year after the transplant surgery, one of the recipient's embryos will be placed into the uterus. If implantation of the embryo is successful, the recipient will become pregnant. Both baby and mother's health are monitored closely at frequent prenatal care visits with a high-risk obstetrician,known as a maternal-fetal medicine specialist .

5. Delivery: The baby is born as close to term as is possible via a planned cesarean section. If the pregnancy has gone without any complications, and the patient wants one more child, the uterus is left, and immunosuppression medications are continued. Another embryo transfer can be attempted after approximately six months after delivery .

6. Uterus removal: When childbearing is complete, the transplanted uterus must be removed, and immunosuppressive medications should be stopped.

Figure 1: describes in short the steps followed during uterus transplantation procedures.



Possible complications following uterus transplant

it's important to fully consider risks and benefits before deciding the procedure is appropriate for the patient or not (the donor and the recipient at risk).

The Czech Republic :

recipients :vaginal stenosis, vesicovaginal fistula, cytomegalovirus, and herpes infection .

The donors (procedure similar to radical hysterectomy): urinary tract complications is always a concern.

recipient with MRKH syndrome:

fistula formation due to neovagina between organs.

higher risk of thrombosis in anastomotic vessels in UTx because narrower vessels are used compared with those in other organ transplantation.

preventing immunosuppressant-induced infection and pancytopenia are also required.

rebleeding from un-ligated capillaries and the vaginal cuff after reperfusion.

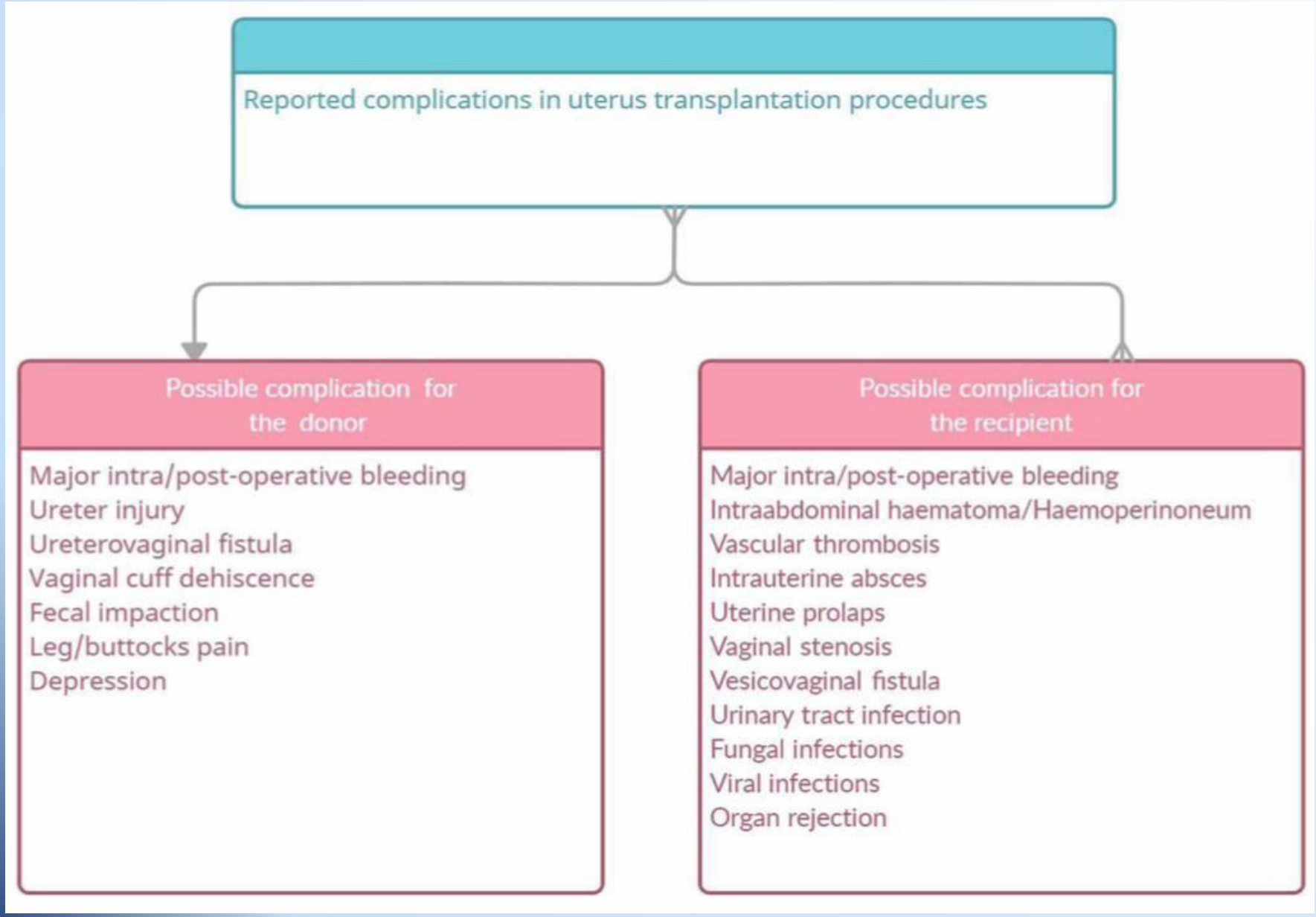
Insufficient hemostasis may cause postoperative intraabdominal complications or retroperitoneal hematoma.

The likelihood of rejection transplanted uterus unclear.

rejection detected with cervical bx for many transplanted uteruses .

Some patients develop rejection before and during pregnancy, which is managed with immunosuppressant medication .

Figure 2: summarizes reported complications faced by donors and recipients during and after the procedures needed for uterus transplantation.



Review (Methods)

literature search on Google, Google Scholar, PubMed, and non-PubMed indexed journals.

searched terms: "uterus transplantation," "uterus transplantation and complications," "first uterus transplantation," "babies born after uterus transplantation."

included criteria: full text available ,English language, human models.

excluded criteria: studies on animals.

first uterus transplantation: *Saudi Arabia.*

first human uterine transplantation : April 6, 2000.

first human recipient : 26-year-old, who lost her uterus six years earlier due to delivery complicated with post-partum hemorrhage.

first donor was a 46-year-old patient with multiloculated ovarian cysts, underwent a hysterectomy to preserve tissue and vascular integrity.

The donor uterus was connected to the recipient's vaginal vault with additional fixation using a shortened uterosacral ligament. The uterine arteries and veins were connected to the external iliac arteries and veins using segments of the great saphenous vein .

Immunosuppression maintainance:oral cyclosporine A, azathioprine, and prednisolone.

An acute rejection episode was treated and controlled on the ninth day with anti-thymocyte globulin (ATG).

The transplanted uterus responded well to combined estrogen-progesterone therapy, with endometrial

proliferation up to 18 mm, which resulted in withdrawal bleeding upon cessation of the hormonal therapy, 99 days after transplantation, vascular thrombosis developed, and hysterectomy was necessary.

Macro- and microscopic histopathological: acute thrombosis in the uterine body vessels, which resulted in infarction.

Both fallopian tube:no evidence of rejection.

Inadequate uterine support caused acute vascular occlusion, led to probable tension,torsion, kinking the connected vascular uterinegrafts.

first human case failure but inspired researchers around the world to initiate new studies on uterus transplantation, immunosuppression, rejection, pregnancy outcome.

The second uterus transplantation: *Turkey* ,from a deceased donor,2011.

recipient: a 22-year-old woman with MRKH syndrome.she underwent vaginal reconstruction with jejunum segment two years before transplantation.

donor : a 22-year-old nulliparous, brain death after a car accident.

The retrieval procedure:radical hysterectomy, dissection of vascular pedicles, including hypogastric, uterine artery, and ovarian vessels, from surrounding tissues.the bladder

peritoneum's anterior reflection was dissected and included within the retrieved uterus.

The anastomosis between the recipient's external iliac vessels and the hypogastric artery pedicle of the donor.

20th month of postoperative , the recipient did well with no signs of rejection,continuing to menstruate.

Six IVF cycles were attempted, one chemical pregnancy and three missed abortion(two had fetal cardiac activity).

elected a deceased donor main advantage:possibility of achieving longer and enhanced vascular grafts within a significantly short time.

the first heart beating pregnancy following deceased donor, an important step. these pregnancies missed abortion.

previous vaginal reconstruction with intestinal flap might have impeded the implantation process,similar to the adverse effect of hydrosalpinx on in vitro fertilization (IVF) cycles.

intestinal neovagina: fecal storage function nl, NL bacterial flora may have diminished endometrial receptivity and abnormal expression of factors related to implantation.

in her 28th week of pregnancy,she gave birth on June 4, 2020, to a

healthy baby boy, with the help of plastic surgeon Dr. Ömer Özkan of Akdeniz University in Antalya province. After successful birth, the uterus was removed .

The first clinical trial of uterus transplantation:in *Sweden* in 2013, nine live donor procedures, nine recipients (27-38 years of age), with eight having MRKH syndrome, the ninth patient had a radical hysterectomy because of cervical cancer seven years before UTx.

The donors: in seven genetically related and two non-genetically related.
The donors' age: 37 to 62 years(five being postmenopausal).

Surgical success was established in eight of nine.

one graft was removed three days post-op :bilateral a-v thrombosis.

one recipient :intrauterine infection two months after UTx>>>treatment antibiotics and surgical drainage>>> hysterectomy had to be 3/5m later when septicemia developed.

Seven patients:regular menstruations during the initial year >>> embryo transfer 12 months post-transplantation.

first U-T: a 35-year-old woman with Rokitansky-Mayer syndrome.

donor : living, 61-year-old, two-parous woman.

first menstruation:43 days after U-T.

regular mens: median of 32 days.

One year after U-T:first single ET,successful,viablepregnancy.

Triple immunosuppression(tacrolimus, azathioprine,corticosteroids): continued during pregnancy>>>3 mild rejection incidents>>>one occurred during pregnancy, managed by corticosteroid.

31 W+5D>>> preeclampsia>>>cesarean due to Ab NL NST.

A healthy baby boy, nl wt for GA (1,775 g),APGAR: 9, 9, 10.

two successful births followed within that trial in November 2014.

first U-T: surgeon-operated robots in Sweden Oct 2017, no complications,with a one cm incision in the abdomen of the donor,Two robot arms managed by a human surgeon.

uterus direct transferred to the recipient via open surgery by humans.

10m after transplantation, the recipient became pregnant via IVF.

The pregnancy without any complications, a baby boy delivered by c/s.

U-T December 2019 in Sweden, for the first time :deceased donor. who had previously birth and in fertile age at the time of her sudden death.

recipient :30y.

10m after surgery, attempts will be started to make the woman pregnant.

2014 first baby was born, another eight babies, including three sibling pairs, were born in Sweden; latest birth in January 2020.

in June 2020 that >10 babies were born in Sweden from U-T.

U-T ,*China* in 2015. recipient 22y. donor: 43 y.

robotic-assisted laparoscopic uterus retrieval.

FET successfully implanted in June 2018, after the fifth attempt.

in early pregnancy,3 episodes of vaginal bleedings were treated with corticosteroids and tacrolimus .

33w+6d due to contraction c/s. A healthy baby boy (2,000 g),APGAR 10.

uterus kept for a possible second pregnancy.

two U-T were done in China using a living donor, but full details unknown.

USA :first U-T , February 2016.

recipient 29y,donor a deceased 30y. March 7, began bleeding,artery connected to supply the uterus damaged and remove the organ.

cause :Candida infection from the transplanted uterus.

Doctors at Baylor University Medical Center, USA,4 U-T September 2016, but only one successful. This was the first living-donor U-T in the USA .recipient :MRKH syndrome,29y,November 2017,born a healthy baby boy.

Two important modifications in this U-T:

1.U-T had only the utero-ovarian vein as venous outflow.

2.the time from U-T to ET was shortened from prior protocols,shorter exposure to immunosuppressant drugs by the patient, minimized the risk for potential advers effects .

2016 to 2020, 20 U-T ,20 women with a median age of 29.7 y, 10 in first and 10 in second phases.

2 recipients : congenital absence of the uterus.

Eighteen recipients received a uterus from living donors and two from deceased donors.

In phase one, 50% of recipients had successful uterus transplant,90% in phase two .

hysterectomy U.T: 5 cases robot-assisted , 13 cases by open laparotomy . Uterus removal was required due to:

vascular thrombosis in 4recipients.

graft ischemia in 2 recipients.

postoperative hemorrhage in 1 patient.

One recipients gave birth to the second baby girl in December 2020.

fifth woman to undergo U-T from a living donor,no complication, the first baby girl was born in 2018.

20 U-T;13 babies born .

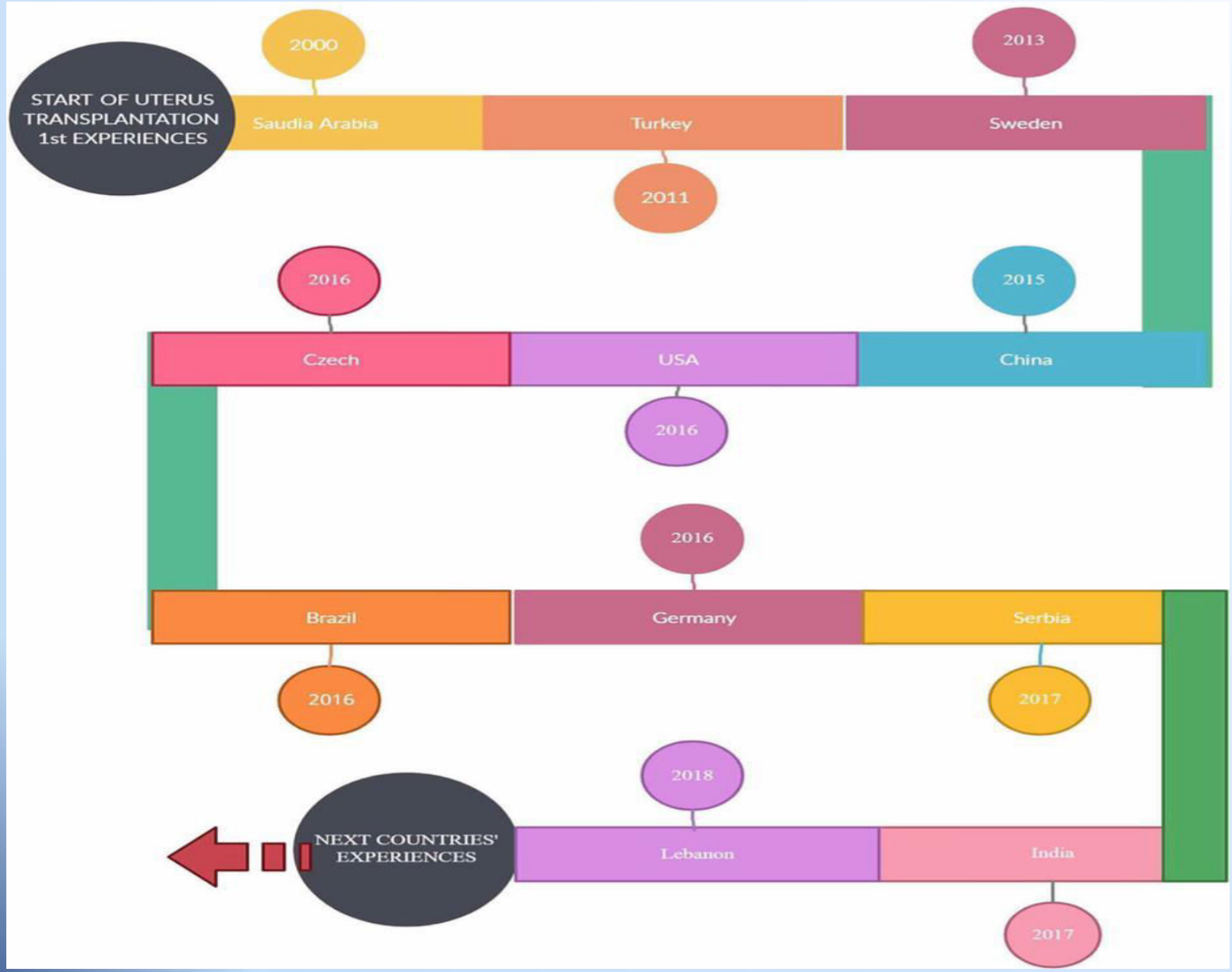
October 2015 to October 2023;10 U-T; This study has seven phases: primary and secondary screening, medical evaluation, IVF, transplantation, embryo transfer, pregnancy/delivery, and follow-up after delivery. Women will undergo deceased donor uterine transplantation after IVF .

first one:failure

8 U-T :6 successful,2 hysterectomies soon after transplantation .

first baby girl born in 2019.(first baby in North America delivered by a mother who received a deceased donor's uterus transplant).

Figure 3: schematically shows countries that started performing uterus transplantation from 2000 to 2020.



U-T in *Czech Republic*:July 2015.

first UTx in April 2016 with a living donation from mother to daughter, first deceased donor (DD) UTx was performed in June 2016.

in total, nine transplantations: 4 from deceased and 5 from living donors (LDs).

All recipients were healthy,all of them MRKH syndrome.

Donors aged 18 to 60 y.

LDs examination: having a normal uterus, without a history of cancer, diabetes,hypertension, any other serious disease & infectious diseases.

DDs had a normal uterus and no history of cancer, diabetes,chronic or infectious diseases.

maximum 4 deliveries, including one C/S,accepted for uterine donation.

Both LDs and DDs had TVS,hysteroscopy,P/S before UTx

in 2 recipients, transplant from NP DDs.

Mild rejection episodes occurred seven times in three recipients.

moderate rejection occurred only once.

Two uterine grafts were removed on day seven (DD) and day 15 (LD) after UTx due to vascular thrombosis discovered by regular clinical examination and transabdominal Doppler ultrasound .

One successful DD UTx was removed on month seven due to HSV-2, destroyed the uterine cavity and cervical canal.

Histopathology:fibrotic obliteration of the cervical canal ,signs of rejection in the myometrium.

Partial postoperative stenosis of the uterine-vaginal (or vaginal-vaginal) anastomosis in 3 recipients,between first and second months after UTx. most caused: discrepancy between the large uterine cervix and the narrow and tough vaginal vault.

Spontaneous menstruation started within five to 14 weeks post-transplant in all six recipients with a functional uterus.

In August 2016; 26y with MRKH syndrome was fourth person worldwide who received a U-T from a deceased donor.

donor :24y ;brain-dead NP.

fifth FET successful, a clinical pregnancy, 3w later, an intrauterine GS containing an embryo with FHR was detected, the pregnancy resulted in missed abortion.

Brazil

first worldwide case of a live birth after U-T from a DD happened in Brazil.

A 32y with MRKH ,U-T in Brazil.

September 2016, a 45y died of SAH with 3 NVD.

recipient discharged after 8 days .

Immunosuppressive drugs were begun with prednisolone, thymoglobulin, and continued tacrolimus and mycophenolate mofetil (MMF).

Five months post-transplantation, azathioprine replaced MMF.

First mens;37 D post-transplantation,regular (every 26-32 days).

first ET seven months post-transplantation.

No fetal growth impairments during pregnancy.

No rejection episodes after transplantation or during gestation.

C/S December 15, 2017, near 36w, girl 2,550 g , APGARof 9,10.

7m pp,uterus removed,immunosuppressive therapy was suspended.

Germany :October 2016, the first UTx.

In total,4 pairs of uterus recipients and living donors underwent UTx Oct 2016 and Jan 2019.

Recipients :23 to 35 y, MRKHS.

Donor:32 to 56 y, (only one postmenopausal donor). All at least two children, maximum 4 deliveries .

donor surgery: harvesting the uterus with its blood vessels without the ovaries; the Fallopian tubes removed to avoid EP.

arterial vasculature : deep uterine artery bilaterally with a segment of internal iliac arteries.

the venous vasculature connected to the uterine graft to be harvested one or two deep uterine veins on both sides, connected to a segment of the internal iliac vein, and/or the proximal parts of the utero-ovarian branch, divided proximally to the inlet of the ovarian veins, to preserve the ovaries in situ.

Recipient surgery : dissection of the vaginal vault and ext iliac vessels.

Anastomoses end to the side from the segments of the graft's deep uterine arteries to the recipient's ext iliac arteries and segments of graft's internal iliac veins to the recipient's ext iliac veins.

In recipients with a thin deep uterine vein on one side, the proximal part of the utero ovarian vein was used for an additional venous outflow, either by anastomosis onto the graft segment's internal iliac veins or directly onto the external iliac veins. After proper reperfusion, the recipient's vagina was opened, and vaginal-vaginal anastomosis was performed. The uterus affixed to the sacro-uterine and round ligaments, bladder's peritoneum of sutured with the recipient's bladder.

no complications intra or postop, except in one recipient, who impaired arterial flow on the RT side intraoperatively, necessitating re anastomosis.(RT U.A end to side onto the ext iliac artery in addition to a segment of int iliac artery adjacent prox vesical artery) .

Immunosuppressive regimens for UTx adopted kidney transplantation .

Induction therapy :anti-thymocyte globulin (ATG) for 3D, parallel start of a tacrolimus, MMF, prednisolone. MMF replaced after 6M with azathioprine for at least 3-6M given a planned pregnancy.

To improve tolerability, tacrolimus replaced by cyclosporin.

donor's and recipient's CMV prophylaxis with valganciclovir for 3-6M done.
cotrimoxazole for6M for Pneumocystis jirovecii prophylaxis .

Two mild rejection in two recipients.

one recipient developed a CMV infection 7m post-op successfully treated with valganciclovir.

After the third single-ET in 17m, one recipient pregnant, Abort 8w.

After next IVF, she and another recipient , a freshsingle-blastocyst transfer, successful intrauterine pregnancies in both .

two mothers (25 and 26 y) gave birth to the 15th and 17th children globally.

first baby at 35w +1d after pprom And no signs of infection or labor>>>c/s.

the second 36w c/s elective.

Serbia:March 2017,a 38y received a U-T from her twin sister. (by the Swedish medical team).

uterus extraction lasted 10 hours, transplant lasted 5 hours.

No complications.

Doner has three children.

After transplant, the woman traveled to Stockholm to perform IVF .

After IVF , she gave birth to a healthy baby boy in Italy .

India:U-T;May 18, 2017;21 y,congenital absence of the uterus.
Donor: her mother's uterus(41y), laparoscopic surgery.(4/5h)
transplant surgery :9 h.

May 19, 2017, a second U-T: by the same team.
recipient:21y.Donor:45y.
transplant surgery :9 h.

third successful U-T; January 2018: by the same team.
transplant surgery :6 h.

All three transplants: laparoscopic surgery.

April 2018:2 successfulU-T in another hospital.

2patients: 30y,one patient: 24 y.(MRKH syn).

Donor:LD, their mothers of 48 and 47 y.

The IVF protocols and results are not mentioned in the paper .

Retrieval of organs: mini-laparotomy and laparoscopic intervention.

The ovarian veins used as outflow channels, allowed to avoid the challenges in dissection along the int iliac vein ,harvesting the donor int iliac artery reduced the tension on the vascular anastomosis.

immunosuppression:tacrolimus,MMF; 24 h before surgery start.

Everolimus a month later to prevent rejection and decrease tacrolimus dose.

IV dexa add postop and tapered and replaced by prednisolone.

valganciclovir and cotrimoxazole postop to prevent opportunistic infections.

s.c heparin for 3w,replaced by aspirin.(antithrombotic prophylaxis) .

Both recipients started menstruating within two months of surgery.

Oct 2018, first baby girl,C/S,17m after U-T, 34 w due to mother's blood pressure rise, AF started to reduce .(second U-T)

Lebanon: first U-T;June 11, 2018 ,doctors from Lebanon-Sweden.

recipient:24y(MRKH syn).

donor:50y,multiparous.

retrieval and transplantation :laparotomy.

Donor's uterus isolated:UA,UV, round lig, USL,bladder peritoneum .

immunosuppression:tacrolimus,azathioprine,thyroglobulin(daily for 5D), methylprednisolone.

Mycamine antifungal prophylaxis, daily valganciclovir 6m for CMV prophylaxis.

trimethoprim/sulfamethoxazole :Pneumocystis jirovecci3m.

first mens 3w after UTx, reg,28 to 30 days.

developed vaginal stenosis, required manual dilations TDS.

Due to persistent anemia,EPO two times a week and oral ferrous sulfate with vitamin B12 three m before ET due to low HB.

ET;10 m after U-T, successful, positive pregnancy test after 14 days.

35 w,C/S due to short uterus cervix and PLP.

female fetus was delivered 15 min after the skin incision.

Table1: summarizes the outcomes and complications resulting from U-T in countries that have done the procedure. Based on published data, 65 UTx procedures were done from 2000 to 2020 in 11countries; 16 (24.6%) were unsuccessful.

Country	Year of UTx	LD/DD	Reported complications of the recipients
Saudia Arabia	2000	LD	Inadequate uterine support caused acute vascular occlusion, thrombosis-hysterectomy was necessary.
Turkey	2011	DD	No complications were reported.
Sweden	Clinical trial started in 2013	9 LD	One graft was removed three days postoperatively due to bilateral arterial and venous thrombosis. Another recipient developed an intrauterine infection and sepsis two months after UTx- both needed hysterectomy
	2017	LD	No complications were reported.
	2019	DD	No complications were reported.
China	2015	LD	No complications were reported.
	N/K	LD	N/K
	N/K	LD	N/K
USA	Clinical trial started in 2016 (Cleveland Clinic)	8 DD	First UTx failed due to Candida infection found in donor's uterus, which caused erosion of uterine artery and intraabdominal bleeding-hysterectomy was necessary. Additionally, another hysterectomy was necessary; the full information is N/K.
	The first clinical trial started in 2016 to 2018, second trial from 2018 to 2020 (Baylor University Medical Center)	18 LD 2DD	Uterus removal was required due to vascular thrombosis in four recipients, graft ischemia in two recipients, and postoperative hemorrhage in one patient.
Czech Republic	Clinical trial started in 2016	5 LD / 4 DD	Two uterine grafts were removed on day seven (DD) and day 15 (LD) because of vascular thrombosis. Another graft (DD) was removed on post-transplant month seven due to Herpes simplex virus-2 (HSV-2), which destroyed the uterine cavity and cervical canal. Partial postoperative stenosis of the uterine-vaginal anastomosis developed in three recipients, which were found between the first and second months of the postoperative period.
Brazil	2016	DD	No complications were reported.
Germany	Clinical trial started in 2016	4 LD	One recipient showed impaired arterial flow on the right uterine side intraoperatively, necessitating re-anastomosis.
Serbia	2017	LD	No complications were reported.
India	2017	2 LD	No complications were reported.
	2018	3LD	No complications were reported.
Lebanon	2018	LD	Vaginal stenosis, which required manual dilations three times. Anemia.
In total		65 UTx (47LD/ 18DD)	16 uterus grafts were removed post-UTx due to complications.

Limitations of this review

This review article is a traditional review and, therefore, does not follow the standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews.

Further research

U-T rapidly spreading worldwide and is starting to be recognized as a new ART. However at the experimental stage and has many medical, technical, and ethical issues.

U-T procedure is a constant risk for further mothers, starting with transplantation, an immunosuppressive status, and ending with the C/S and hysterectomy.

babies born as a result of U.T should be born prematurely at less than 37W, as specialists are concerned that as the uterus grows, this can affect the uterine vascular supply.

babies at risk :apnea of prematurity,RDS,infections or neonatal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, jaundice, and anemia,NICU admition.

long-term challenges : intellectual and developmental disabilities.

Long-term observation and control of babies of U-T(LD-DD)preferable.

case-control studies between babies born naturally and babies born after uterus transplantation.

Further studies :

safest operation method to minimize complications(donor-recipient).

on immunosuppressive protocol before and during pregnancy.

Long-term observation of recipients after hysterectomy is demanded(U-T big intervention):

changes the anatomy of pelvic floor muscles.

direction of ureters,place of ovaries>>predispose pelvic organ prolapse and urinary tract infections with further kidney damage.

affect the vascular supply of pelvic organs and lower limbs.

no clear information: *(*further research is still needed)

how many weeks gestation a transplanted uterus can tolerate.

newly formed vaginal vault.

deranged pelvic floor.

is there any chance for a twin pregnancy?

Conclusions

U-T:new treatment approach of absolute uterine factor infertility,proceeded rapidly from an experimental procedure in animals .

at this time, U-T considered a clinical experimental procedure until sufficient clinical trials during the next years.

There is a significant clinical demand for U-T;it is expected the number of procedures will increase.

thanks for attention

VRHRC.TUMS.AC.AR