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## Editorial

# Uterus transplantation: Questions and future prospects



## Introduction

Since 2000 and the first human uterus transplant [1], this new assisted reproduction technology has resulted in the birth of 12 children [2]. Uterus transplantation (UTx) is the only method that enables women with uterine factor infertility to attain both biological and gestational motherhood. Although there is a strong demand among these women, few candidates can benefit from UTx, as it is still at the developmental stage.

This article addresses questions that need to be resolved in order to better standardize UTx and thereby increase its chances of success.

*What is the maximum cold ischaemia time tolerated by the uterus?*

Cold ischaemia time is the duration of *ex vivo* hypothermic organ storage, from the time it is flushed with cold preservation solution until the start of vascular anastomosis in the recipient. The maximum tolerated cold ischaemia time varies between organs, and that of the uterus is as yet unknown.

Several animal and human studies have investigated uterine tolerance to prolonged cold ischaemia. In an ovine autotransplantation model, our team found no significant difference in the degree of apoptosis after 3 h versus 24 h of cold ischaemia [3]. In human studies of uterine tolerance to cold ischaemia following multi-organ retrieval, no histological changes were found after 12 h or 24 h of cold ischaemia [4]. Sieunarine et al. found no histological changes in samples of human uterine tissue after 48 h of cold ischaemia [5]. Finally, in 2005, Wranning et al. concluded that the human uterus could tolerate 6 h of cold ischaemia when stored in Perfadex or University of Wisconsin (UW) solution [2].

To date, the longest cold ischaemia time that resulted in successful UTx followed by the birth of a child was 6 h 20 min, performed in Brazil using a deceased donor (unpublished data). The increasing use of brain-dead donors for UTx will improve our understanding of uterine tolerance to cold ischaemia. Data from the Czech uterus transplantation trial (e publication ahead of print) with 4 successful deceased donor uterus transplant will be interesting [6].

In summary, the uterus appears to tolerate at least 6 h of cold ischaemia.

*Which preservation solution should be used in UTx?*

The graft is stored throughout the period of cold ischaemia in a preservation solution to minimize hypoxic injury and to aid resumption of function. The teams that have obtained livebirths following UTx (Sweden, USA, Brazil) all used histidine-tryptophan-ketoglutarate (HTK), a solution initially used in heart transplantation. HTK was also used by Wei's team in China and Brucker's team in Germany [2]. HTK appears suitable for UTx, but additional comparative studies are needed to determine the best preservation solution.

No particular preservation solution can currently be recommended.

*Which immunosuppression protocol should be used for UTx?*

Most of the immunosuppression protocols used in UTx have been similar to those used in kidney transplantation. They combined thymoglobulin, tacrolimus, mycophenolate mofetil (MMF) and a corticosteroid [1]. The Swedish team tried discontinuing MMF and continuing tacrolimus alone in 4 patients. However, cervical biopsies showed signs of inflammation and azathioprine and prednisolone were therefore reintroduced [7]. A recent study demonstrated strong HLA sensitization in the uterus necessitating complex immunosuppression protocols, as is also the case in kidney transplantation [8]. The data on the effects of immunosuppressant use during pregnancy on the mother, the fetus and the transplant are reassuring.

In summary, UTx is a "young" transplantation field. The uterus is an immunogenic organ. The immunosuppression protocol currently used is based on the experience acquired with kidney transplantation. Identification of biomarkers would enable laboratory-based monitoring of the graft.

*What is the optimum interval between UTx and embryo transfer?*

Gestation is only possible after UTx through IVF. The fallopian tubes are not transplanted due to the risk of necrosis and tubal adhesions, potentially increasing the risk of ectopic pregnancy. In most of the uterus transplants performed in humans, embryo transfer was performed 1 year after transplantation, or 18 months later in the case of the Turkish team. The American Society of Transplantation recommends a minimum interval of 1 year

between solid organ transplantation and pregnancy [9]. This interval allows sufficient time to stabilize the graft and immunosuppressant therapy.

The Dallas team shortened this interval to 6 months and a healthy baby was born [10].

An interval of 1 year is currently recommended between UTX and embryo transfer, as a precautionary measure. It should be possible to shorten this interval in the future, informed by the experience gained from various clinical cases.

### Future prospects

Although UTX is still at the developmental stage, some teams are already working to take it to the next stage.

#### *Improved tolerance to cold and warm ischaemia*

A recent study showed that the addition of acetyl L-carnitine to HTK improves its efficacy by limiting the formation of free radicals [11]. The impact of warm ischaemia can also be reduced through the use of pharmacological adjuvants: several animal studies have demonstrated attenuation of ischaemia-reperfusion injury by tacrolimus [12], MMF [13], remifentanyl [14] or a combination of oxytocin and kisspeptin [15]. It is uncertain however whether this effect will transpose to humans.

The use of haemoglobin from the marine worm *Arenicola marina* has also proven effective during the cold ischaemia phase in lung and kidney transplantation. Studies are in progress in humans.

All these adjuvants could be incorporated into UTX to increase the chances of graft success.

#### *Use of minimally invasive surgery in UTX*

An open abdominal approach has been used in both donor and recipient surgeries due to the complexity of the vascular dissections in the former and vascular anastomoses in the latter. Wei et al. have performed uterine retrieval by robot-assisted minimally invasive surgery [1]. Retrieval took 6 h and no complications occurred. Unlike most teams, the Chinese team retrieved the utero-ovarian veins rather than the uterine veins for venous drainage of the graft. Dissection of the uterine veins is a complex surgical procedure that can cause complications and has only been performed until now via open abdominal surgery. Dissection of the utero-ovarian veins is more straightforward. However, this required the Chinese team to perform bilateral oophorectomy on the 42-year-old donor, resulting in premature menopause. The Swedish team is currently conducting a study on the feasibility of uterus retrieval with robot-assisted dissection of the uterine veins. However, Testa et al. recently published the first birth in the US of a child born after UTX in which the utero-ovarian veins were used to provide venous drainage for the graft. This study indicates that utero-ovarian veins provide sufficient drainage provided for graft viability and raises the possibility of laparoscopic uterus retrieval, since dissection of the utero-ovarian veins is straightforward, without necessarily removing the donor's ovaries [10]. The donor's utero-ovarian veins will not always be usable however, as they often have varices and a small diameter. High-quality preoperative vascular imaging will be important, in order to choose the best retrieval procedure.

In the future, uterus retrieval for UTX will be more reproducible and less invasive for living donors. Robotic surgery and use of the utero-ovarian venous system are interesting prospects.

### *Ex vivo uterus generation*

UTx may only be a transient phase in the treatment of uterine factor infertility. The future will probably involve *ex vivo* organ generation through tissue bioengineering to avoid the need for immunosuppressants and invasive procedures and to overcome the organ shortage. A new viable organ can be generated by decellularizing an organ and repopulating the scaffold obtained with a patient's own stem cells. No immunosuppression is required because the cells that make up the organ were derived from the recipient. Brännström's team in Sweden is investigating the use of tissue bioengineering to generate a uterus *ex vivo*, and their initial experiments in mice have already resulted in pregnancies and births [16].

### Conclusion

UTx is a promising technology for treating uterine factor infertility. Many technical questions remain to be answered however. An increasing number of uterus transplants performed within the confines of research protocols, especially as part of an international registry, and experimental research will advance knowledge in this field. As with any new assisted reproduction technology, UTX must be regulated by clear bioethics legislation to ensure that it is used appropriately.

### Declarations of interest

None.

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