

Ethical issues and associated medical risks in uterine transplantation

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Introduction:

In reproductive medicine, a significant portion of female infertility that is incurable is categorised as absolute uterine factor infertility (AUI) (Johannesson et al., 2014). In the world, this disorder affects roughly 1 in every 500 women who are of reproductive age (O'Donovan, Williams and Wilkinson, 2019). It is thought to be due to the absence of an anatomical or functional uterus (Johannesson and Järholm, 2016) and can be a result of congenital malformations for example the Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome, or acquired such as in women who have had a previous hysterectomy (Williams, 2016). These women can also possess a uterus but due to physiological or anatomical defects, it is rendered non-functional (Johannesson et al., 2014). Figure 1 below illustrates the major causes of AUI.

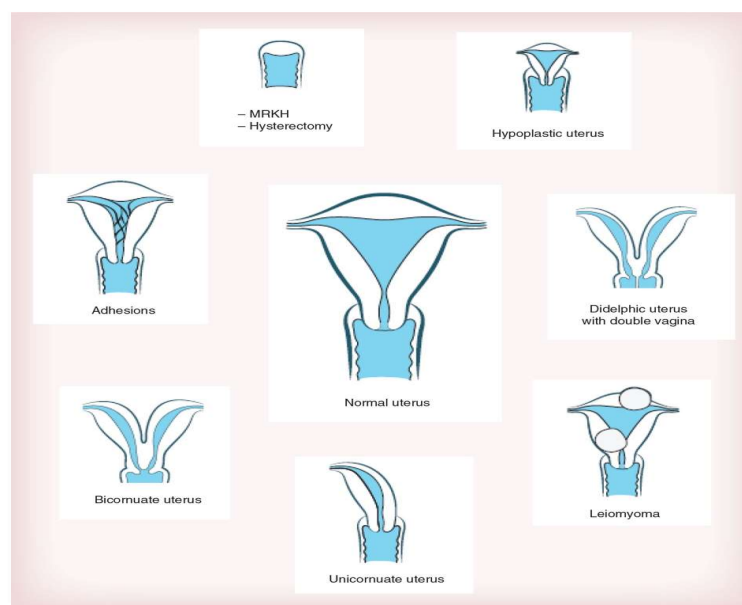


Figure 1. Multiple contributing factors of absolute uterine factor infertility (adapted from (Johannesson et al., 2014)).

Adoption or surrogacy are now the only alternatives available to women with AUF1 who want to become parents (O'Donovan, Williams and Wilkinson, 2019). However, there are ethical, legal, financial and cultural concerns surrounding these procedures with gestational surrogacy currently being illegal in several countries (Saxena, Mishra and Malik, 2012). On the other hand, uterine transplantation (UTx) can offer these women the opportunity to become mothers in a gestational, social and genetic sense (Williams, 2016). Consequently, uterine transplantation models have first been established in smaller and larger animal models before progressing to the experimental clinical stages (Wranning *et al.*, 2006, 2008). Several human uterine transplantation attempts have been carried out and in 2014, a report was published on the first livebirth following uterine transplantation which can be viewed as evidence of UTx as a form of treatment for absolute uterine factor infertility (Brännström *et al.*, 2015).

However, UTx raises several ethical concerns especially as this form of treatment is viewed to be at the forefront of research, falling somewhere between advancements in assisted reproductive technology (ART) and novel transplantation (O'Donovan, Williams and Wilkinson, 2019). The ethical frameworks that currently govern UTx are mostly derived from those that govern solid organ transplantation (Horvat and Iltis, 2019) despite UTx being different from conventional organ transplantation in numerous ways. For example, UTx has the unique feature of being an "ephemeral" transplant with hysterectomy being recommended after a period of time (O'Donovan, Williams and Wilkinson, 2019) which offers the advantage of stopping immunosuppressive medications when the recipient's family is complete (Jones *et al.*, 2021). However, this procedure is not considered to be lifesaving and offer the recipient with no immediate health benefits (Testa and Johannesson, 2017). Therefore, ethical concerns surrounding access to UTx including eligibility, living versus deceased donation, and risks versus benefits, have arisen and pose a great challenge. Additionally, UTx addresses every significant facet of human ethics, such as autonomy, beneficence, justice, dignity, and non-maleficence. In this paper, we will briefly review these key ethical concerns associated with UTx.

Access to UTx

Several concerns arise when considering who should have access to UTx procedures. Questions are raised by UTx regarding the allocation criteria used to create a just system of organ distribution and the selection criteria that

apply to potential patients (O'Donovan, Williams and Wilkinson, 2019). Implementing patient selection criteria seems reasonable, similar to other ART programmes, to guarantee only patients with a reasonable chance of success begin treatment. Within the setting of UTx, these have involved an inclusion criteria of, for example a genetic female which raises a controversial point as to whether women who are genetically XY should be offered UTx (Sampson *et al.*, 2019). It is suggested in transgender women, UTx has the potential to reduce dysphoria that may stem from not being able to become parents (Jones *et al.*, 2021) and because reproductive rights can be viewed as human rights, in accordance with UK legislation, it can be against the law to deny transgender women a uterus transplant based on their gender identity (Jones, Alghrani and Smith, 2019).

Another general inclusion criterion is the woman should have the capacity to raise children although this can prove to be highly divisive. In the UK, a "welfare of the child" evaluation which is mandated by the Human Fertilisation and Embryology Act 1990 is carried out before treatment and is described as a better threshold selection requirement (O'Donovan, Williams and Wilkinson, 2019). Additionally, global differences exist in the inclusion and exclusion criteria. The criteria in Sweden, for instance, require the recipient to be part of a stable relationship; UK standards do not. Furthermore, Swedish standards seem to focus solely on biological parenthood, in contrast to the UK, which bar applicants who have already had children (Hammond-Browning, 2019). Such inconsistencies highlight the ethically challenging task of creating inclusion and exclusion criteria in UTx clinical trials, coupled with the challenge of determining who would be given priority for a transplant should UTx become the norm in clinical practice (Koplin and Kendal, 2020).

With regards to justice, the current guidelines for organ transplantation are designed to foster equality and justice; for example organs are assigned based on medical urgency rather than financial means (Koplin and Kendal, 2020). However, these well-established guidelines do not neatly apply to UTx. The concept of "sickest first" allocation is not adhered to in UTx; prognosis and standards of living benefits from UTx transplants, are more difficult to measure than from donations that directly address medical needs; and infertility cases that are more or less "urgent" do not exist. (Koplin and Kendal, 2020).

This may create allocation bias which can have an impact on who has access to UTx as a form of treatment.

Concerns about justice are also pertinent to the debate over whether UTX should get government funding. Thus, the question of whether to fund UTX will eventually have to be decided upon by publicly funded healthcare systems like the National Health Service (NHS) in the UK. This raises controversy as funding for current ART such as IVF already generates hostility in the public with some people arguing allocating funding to ART entails sacrificing advances in other areas of health (Devlin and Parkin, 2003). One main argument to consider is whether infertility should be perceived as a disease. In response to this, a comprehensive survey on general population views regarding infertility and its treatment, was carried out by Adashiet *al.* across Australia, several European countries, and the USA, with just 38% of respondents, agreeing with the statement that "infertility is a disease" (Adashiet *al.*, 2000). The question's implications are apparent: if AEFI is regarded as a sickness, state funding for its management is justifiable; the only thing left to decide is how important it is to prioritise it in comparison to other necessary treatments. If not, public funding of UTX may be deemed unjustifiable (Wilkinson and Williams, 2016) although this argument is implausible on the basis that AEFI has distinct biological causes and thus effects and these can then be exacerbated by social factors such as pronatalist beliefs (Wilkinson and Williams, 2016).

Living vs deceased donation

The preference for either living or deceased donors is a matter on which scientists involved in UTX strongly differ. Approximately 75% of the documented cases of UTX procedures have used living donors, the majority being close family members of the recipient with only 25% using uteri from brain-dead (deceased) donors (O'Donovan, Williams and Wilkinson, 2019). Thus, there has been much discussion on the relative importance of each model and, consequently, which model should be chosen, presuming that both are eventually shown to be adequately safe and effective.

A major factor that influences the type of model donor to use is the clinical benefits and risks associated with each (O'Donovan, Williams and Wilkinson, 2019). The possible benefits of using a deceased donor model for UTX include a lower risk of complications such as thrombosis seen in live donor models due to the surgeons being able to recover longer lengths of vasculature which are obtained from the deceased donor more efficiently (Del Priore and Gudipudi, 2014).

Additionally, in response to the claims that living donors are more suitable with regard to long-term graft survival, it can be argued the benefits are minimal as UTX is intended to be ephemeral (Williams, 2016). The transplantation procedure in a deceased donor model is also considered to be more simplified with shorter durations and therefore poses a lower anaesthesiologic risk in patients (Johannesson and Järholm, 2016).

Nevertheless, despite these benefits, most doctors conducting UTX trials believe that the living donor model is likely to offer more advantages such as; the uterus being of a higher quality due to considerably reduced cold and warm ischaemia times, a closer tissue match when related donors are used, and the ability to set a convenient date and time to allow sufficient time for the donor and organ to be thoroughly evaluated prior to transplantation (Johannesson and Järholm, 2016). It is also easy to argue that allowing living donor model takes into account the autonomy of those who decide to donate by giving them the opportunity to do so (O'Donovan, Williams and Wilkinson, 2019). However, this position is thought to be more complicated in reality. A small number of clinicians argue that living donation is unsuitable due to the risks and harms involved, in addition to the doctor's responsibility of non-maleficence and UTX being viewed as a quality-of-life transplant rather than a lifesaving one (O'Donovan, Williams and Wilkinson, 2019). However, others argue this risk has to be weighed against the advantages UTX offers (Williams, 2016).

Additionally, in the case of living and deceased models, there is a chance the uterus may have been donated without adequate high-quality consent (Koplin and Kendal, 2020). External factors, including pressure from relatives to inquire about UTX or peer pressure to donate their own uterus, carry some risk in both the case of living donors and receivers, thus affecting the quality of the consent obtained (O'Donovan, Williams and Wilkinson, 2019). Similarly, one could also question whether wider societal factors such as a pro-natalist ideology could jeopardise autonomous consent with pronatalism being linked to a greater social pressure to have children who are genetically related, which may have a large impact on a woman's choice to get UTX or to give her daughter, a loved one or even a stranger her own uterus (Koplin and Kendal, 2020). The degree to which informed consent for UTX is threatened by these social influences remains a crucial ethical concern that necessitates further evaluation.

Risks versus benefits

The balancing act of risks and benefits is viewed to be more complex in UTX compared to other forms of organ transplantation. For instance, since neural innervation is currently impossible in UTX and numerous sensations related to pregnancy would be absent, there is a higher chance that as a result, recipients will feel a sense of disappointment even in the chance of a live birth as the full experience of pregnancy is just as important to some individuals (Catsanos, Rogers and Lotz, 2013). It is important to note an analysis of the risks and benefits associated with UTX includes four parties; the recipient, the recipient's partner, the donor and the prospective child (Johannesson *et al.*, 2014). In UTX, given the recipient undergoes the risk of pregnancy, immunosuppression, and surgery, she is the one who is most at risk (*ibid*). However, in contrast to other organ transplantations, UTX poses a risk to other parties in particular the prospective child who would undergo immunosuppressive treatment while still in utero (Arora and Blake, 2014) which can lead to a greater risk of premature birth, intrauterine death and a low birthweight (Benedet, 2019).

The benefits of UTX are also distinct from those of other types of organ transplantation. In contrast to for example a heart transplant, UTX is viewed as a life enhancing rather than a lifesaving procedure (Koplin and Kendal, 2020). However, it can be viewed as a way for women with AEFI to become parents with objectives that involve assisting them in becoming emotionally, visually, and socially recognised as pregnant (Arora and Blake, 2014). These objectives set UTX apart from other organ transplantation procedures as well as from other AEFI-related ways to become a parent, such as adoption or surrogacy (Koplin and Kendal, 2020). However, this raises the question of to what extent can these risks be accepted to achieve these goals.

In terms of the procedure itself, the duration of surgery is a major concern, with research now focussing on robotic assisted procedures in order to reduce operative times (Fornalik and Fornalik, 2018) and make it less invasive (Benedet, 2019). Post-operative complications such as infection, thrombosis, fistula, and uretic damage also pose further risks to the health of the recipient (Kisuet *et al.*, 2018). Women who undergo organ transplants also undergo immunosuppressive therapy with potential complications for the recipient including an increased risk of malignancy, nephrotoxicity and bone marrow toxicity (Benedet, 2019) thus the adverse risks of this form of therapy should be followed up in the long term.

In addition, there are more widespread concerns such as the psychological issues following transplant surgery for all four parties with emphasis placed on an assessment carried out pre-and postoperatively by a certified psychologist (Johannesson and Järholm, 2016). Taking everything into account, more information is needed to truly comprehend the potential risks associated with UTX with a focus on safety and efficacy before it is widely adopted in routine clinical practice. Determining whether the benefits of UTX outweigh the risks involves the ethics of beneficence and non-maleficence and these will still be relevant when UTX becomes the norm in clinical practice (Koplin and Kendal, 2020).

Conclusion

Uterine transplantation was revolutionary in the world of reproductive medicine and has had remarkably positive results thus far. However, it does raise significant social, legal, and ethical concerns. As more data emerges regarding the benefits and risks associated with this procedure, solutions to these concerns will become apparent and policy adjusted accordingly. This pertains specifically to concerns about using living or deceased donors, meeting financial requirements, and recipient allocation criteria. When comparing UTX to other alternatives for AEFI, a major distinctive feature of UTX that warrants special consideration is the opportunity for the recipient to become socially and genetically related to the child. How much value we can attribute to this unique feature is dependent on all four facets of human ethics—beneficence, non-maleficence, autonomy, and justice.

Therefore, a solid ethical foundation is required in this rapidly evolving area to govern guidelines and laws before UTX becomes the norm in clinical practice. The prospective future of uterine transplantation will possibly involve establishing and implementing robust consent processes, laparoscopic methods to minimise risks and duration of surgery, organ engineering technology with the aim of eliminating the use of immunosuppressive therapy which will all hopefully lead to UTX being introduced in a wider general setting.

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