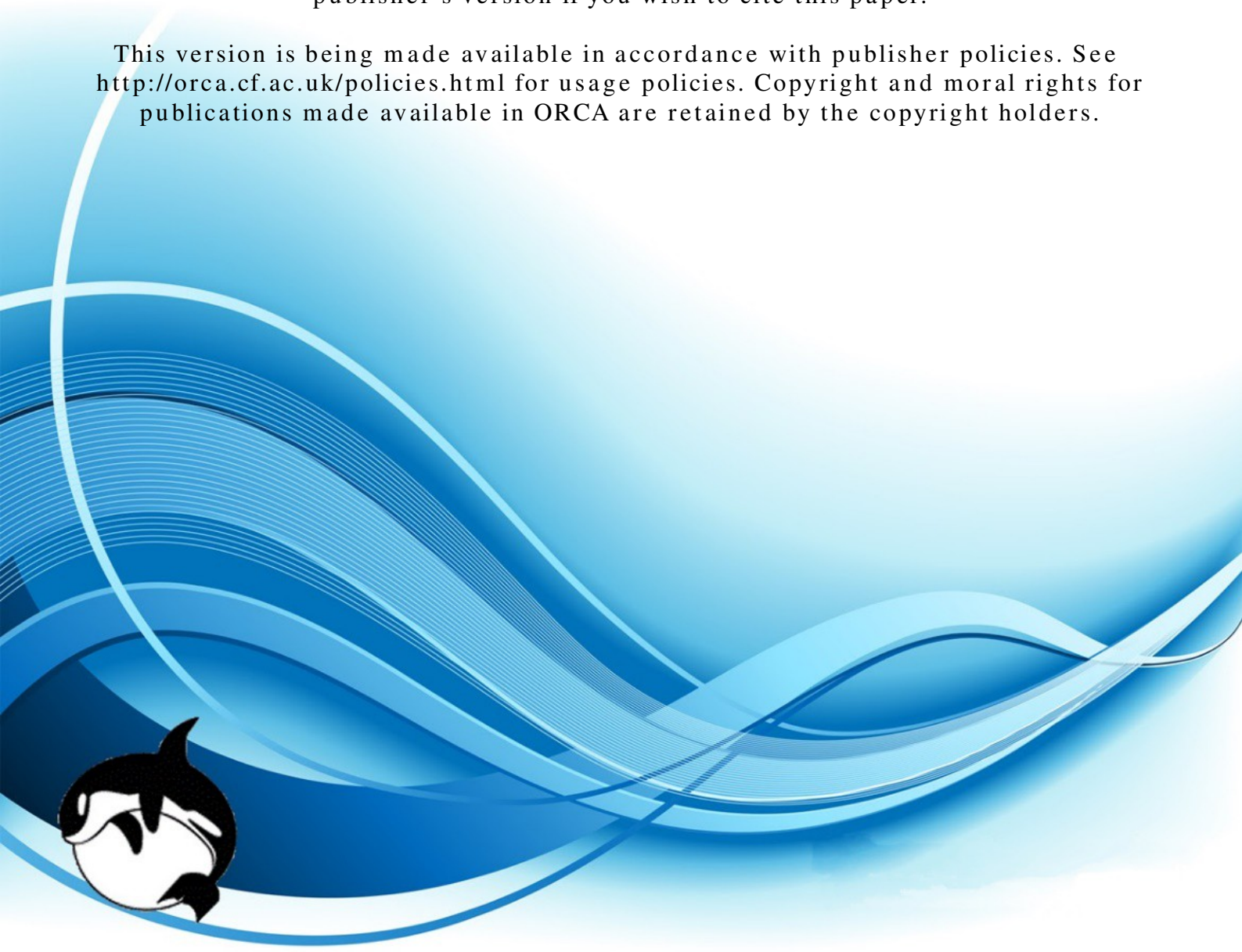

UK Criteria for Uterus Transplantation - Looking Ahead: A review

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Abstract:	Objective: Absolute Uterine Factor Infertility (AUFI) is the final hurdle for assisted reproductive treatments. Uterus transplant trials are being undertaken worldwide; in order to advance the debate around uterine transplantation (UTx) this article considers the selection criteria for clinical trials from a UK perspective and makes recommendations for selection criteria in the future. Methods: A literature based review of uterus transplantation clinical trial selection criteria. Results: Recommendations for future UK eligibility criteria for UTx treatment are advanced including the use of donor eggs, access for single women and women in same-sex relationships, prohibiting the participation of women who are already mothers, and a preference for deceased donors and bioengineered uteri. Conclusion: With UTx on the horizon as a treatment for AUFI it is important to proactively consider the selection criteria for UTx treatment.

UK Criteria for Uterus Transplantation - Looking Ahead: A review

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Abbreviations:

ART – Assisted Reproductive Treatment
AUFI - Absolute Uterine Factor Infertility
UTx – Uterus Transplantation

Abstract:

Objective: Absolute Uterine Factor Infertility (AUFI) is the final hurdle for assisted reproductive treatments. Uterus transplant trials are being undertaken worldwide; in order to advance the debate around uterine transplantation (UTx) this article considers the selection criteria for clinical trials from a UK perspective and makes recommendations for selection criteria in the future.

Methods: A literature based review of uterus transplantation clinical trial selection criteria.

Results: Recommendations for future UK eligibility criteria for UTx treatment are advanced including the use of donor eggs, access for single women and women in same-sex relationships, prohibiting the participation of women who are already mothers, and a preference for deceased donors and bioengineered uteri.

Conclusion: With UTx on the horizon as a treatment for AUFI it is important to proactively consider the selection criteria for UTx treatment.

Main text:

Introduction:

Uterus transplants (UTx) came to the world's attention in October 2014 when a team of researchers in Sweden announced the first birth following UTx.[1] Heralded as a treatment for women who suffer from Absolute Uterine Factor Infertility (AUFI), some women may consider UTx as their only reproductive option; adoption or surrogacy may not be a viable option for them, whether due to personal, legal, financial, ethical, or religious reasons. Prior to the first research trial in Sweden, there had been two previous attempts at human UTx. The first, conducted with a living donor in Saudi Arabia in 2000, was removed after 99 days, the second occurred in Turkey in 2011 with donation from a deceased donor.[2] The latter has resulted in two early pregnancies that have ended in miscarriage.[3] The first UTx in the U.S. occurred in February 2016 at the Cleveland Clinic, closely followed by Baylor University Medical Center at Dallas performing four transplants from anonymous living donors in September 2016.[4,5] Two births to date have been reported by the Baylor team.[6,7] The first baby to be born following UTx from a deceased donor was born in Brazil in 2017.[8] The UK team, Womb Transplant UK, is to start clinical trials in the UK imminently. With research teams worldwide it is evident that there is considerable medical interest in developing UTx as a treatment for AUFI.

In order to advance the debate around this ephemeral transplant parts of the UK selection criteria for UTx clinical trials is examined, with the aim to explore how the medical criteria for recipients may need to be transformed to comply with the UK

legal framework when UTx becomes a safe and effective treatment for AUFI. The selection of donors for UTx is then considered. Recommendations for future UK eligibility criteria for UTx treatment are advanced. By engaging with the selection criteria for UTx this is an original contribution to the relevant literature.

Selection Criteria to Participate in a Uterus Transplant Clinical Trial

FIGO published limited guidelines for UTx in 2009, followed in early 2012 by the Montreal Criteria, which were the first criteria to consider the ethical feasibility of UTx.[9] Criteria were more broadly agreed in Indianapolis at a large meeting of medical experts and stakeholders in 2011 and published November 2012. A number of *'way markers'* were agreed that needed to be *'…considered to provide sufficient scientific and ethical justification for taking human UTn from a rare oddity, to a recognized and reasonable addition to the armamentarium of assisted reproductive technologies...'*[10] These 'way markers' make up what is commonly known as the Indianapolis Consensus, and include the need for women to provide their own eggs, a recommendation of 2-3 years to be in receipt of the donated uterus, the need to remove the donated uterus after a successful pregnancy, and to encourage women to pursue alternatives to UTx. These 'way markers' have been used as a guide for UTx research. Worldwide, eligibility criteria have developed along these lines and in accordance with the laws of the relevant jurisdiction (for example, see Table 1).

UK Selection Criteria

a) Own ovum

The UK criteria, as with all UTx trials worldwide, require all potential recipients to be able to produce their own ovum. According to the Swedish team, the reasons that recipients need to undergo IVF is *'…to exclude any sterility factor related to fertilization failure and to cryopreserve embryos for transfer more than 12 months after transplantation…'*[13] In addition, there is an upper age limit of 38 years (40 years if embryos frozen before 38 years of age), presumably because the women that participate have to be able to produce their own ovum, and the number, as well as their quality, declines rapidly from 35 years onwards.[14] As noted by Huet, *et al.,* '*…patients older than 35-40 years are not ideal candidates for UTx at the present time. Such patients are more prone to multiple complications of pregnancy. …Furthermore, the ovarian reserve diminishes beyond age 35, thus increasing the possibility of a poor response to ovarian stimulation…'*[15] So at present, any woman who lacks ovaries as well as a uterus is not eligible for the UK research trial.

The Swedish team require recipients to produce ovum in order to rule out infertility for reasons other than AUFI. It is noticeable that there is no requirement for the recipient to have a partner who is able to produce healthy sperm for the IVF process. However, for those who lack a uterus (compared to those who have an apparent non-functioning uterus), the reasoning behind the criteria appears irrelevant. Even if they are able to produce their own ovum, they cannot gestate. If fertilisation of eggs is found to be the cause of a woman's infertility rather than having a non-functioning uterus, this can be more easily remedied through the use of IVF techniques, rather than undergoing UTx.

All potential recipients have to undergo IVF to produce a minimum of 10 embryos prior to transplantation. It is foreseeable that a recipient's supply of frozen embryos will run out before a successful pregnancy is achieved. No literature states what happens in this situation. It is predicted that the recipient would be required to go through more cycles of ovarian stimulation in order to continue to comply with the inclusion criteria although this may be medically difficult to achieve due to the implanted uterus. Once the UK team demonstrates proof of concept, it will be difficult to justify limiting UTx to women able to produce their own ovum due to the legal recognition of, and access to, donor gametes. Donor sperm is permitted in the UK trial; the requirement for the recipient to produce her own ovum is not legally justified, as other infertile women can use donor ovum in other assisted reproductive treatments (ART). However, in a clinical trial setting this may be medically justified.

From published literature it is uncertain why the use of donor ovum is prohibited in the UK clinical trial. The prohibition conflicts with the reproductive regulations that permit gamete donation for reproductive purposes in the UK.[16] Women who are unable to produce their own genetic material are unfairly excluded from the clinical trial, but looking to the future ought not to be excluded from UTx treatment.

It is recommended that all recipients should have the opportunity to utilise donor gametes at any point in the UTx process. This corresponds with the UK legislative provisions as well as promoting the reproductive liberty of recipients. Unless medically justified, the inability to produce your own ovum should not act as an exclusion criterion.

b) Requirement to have a partner

For the UK trial, it is *preferable* that the recipient is in a stable and loving relationship at the time of the procedure due to the support needed after surgery; donor sperm may also be used, thereby opening up the research trial to single women and female same-sex couples.[17] The preference for a partner recognises the support needed for the complex, invasive and lengthy process and operations involved. Before commencing ART in the UK, there is a legal requirement to take account of the welfare of any child who may be born as a result of the treatment, including the need of that child for supportive parenting.[16] It is not necessary for a woman to have a sexual partner to provide that support, nor is there a requirement to have two parents. Therefore, so long as the recipient has a good support system around her, then she should be able to participate in the research trial.[18] Prima facie, the preference for a partner requirement in the trial setting appears inconsistent with UK policy and legislation, and would need special justification if it were to continue as an eligibility criterion beyond the research realm. Whilst the same arguments can be presented with regards to research trials, I recognise that the UK team have received research ethics committee approval on the basis of the agreed eligibility criteria and so must be adhered to during the clinical trial. As with all high-risk procedures, it is preferable for potential recipients to show that they have support, whether that is from a sexual partner, a family member, or a close friend. If UTx is proven to be safe, then in order to promote the procreative autonomy of all women affected by AUFI, there should not be a requirement to have a partner.

The UK criteria have been amended over time to be more inclusive; an earlier version of the patient information sheet stated that the need to use donor eggs or sperm would exclude participants from the research trial, and recipients must have a long-term partner.[19] The change allowing the use of donor sperm aids access for single women with AUFI, as well as women with AUFI in a same-sex relationship or whose male partners are unable to produce sufficient good quality sperm for IVF. This reflects both the regulatory and the societal position in the UK; the use of donor gametes is well regulated, widely recognised and socially accepted.

Therefore, it is recommended that women with AUFI are able to access UTx regardless of their relationship status, although account must be taken of the welfare of the child that may be born as a result of treatment. The ability to demonstrate a support network is a more suitable criterion and would conform to the legislative framework.

c) Age and Female

The UK trial explicitly requires that recipients are female and aged 24-38 yrs. With the requirement to use ones own ovum, the age limit is medically justified due to the decrease in pregnancy success rates with increasing maternal age. Nevertheless, if donor ovum is permitted, or the recipient's ovum was frozen before the upper age limit, then the upper age limit may need to be revised. An appropriate guide is 42 years if NHS funded (in accordance with NICE guidelines on access to IVF), and 50 years if privately funded.

Currently, there are medical and anatomical reasons for limiting UTx to biological females; however, the medical barriers to UTx in transgender women and men do not appear to be insurmountable.[20,21] Continuation of the debate around UTx and access for transgender women (and men) is fundamental; the use of donor ovum alongside UTx could provide an opportunity for transgender women to gestate their own genetically related child, (if sperm was frozen prior to gender reassignment surgery). Under the Equality Act 2010 transgender people are afforded explicit protection from direct and indirect discrimination, as such it will be legally impermissible to deny access to transgender women purely because of their gender identity. However, if the goal of UTx is reproduction, this may justify limiting UTx to cisgender women, this is because legally all recipients of UTx in the UK must be biologically female. UK law prohibits the transfer of human embryos to anyone other than a woman who has been a woman from birth.[16] Therefore, even if medically feasible and ethically supported, UTx would not be able to serve its reproductive purpose in transgender women. Conversely, if UTx has goals other than reproductive, such as offering an opportunity to realign gender identity and to feel 'complete', then it could be considered appropriate to provide UTx to transgender women, men, and to women with AUFI who do not seek to reproduce.

I acknowledge the emerging debate around transgender women and UTx, however, legally all recipients in the UK must be biologically female as UK law prohibits the transfer of human embryos to anyone other than a woman who has been a woman from birth. Human rights challenges are likely and proactive debate is needed before UTx for transgender women (and men) proceeds. Currently, even if medically feasible and ethically supported, UTx would not be able to serve its reproductive

purpose in transgender women. As such the existing UK medical criteria for UTx legally conform, and would need to continue in this form when UTx is provided as a reproductive treatment option for AUFI.

It is recommended that research teams investigate the legal frameworks within which they are working; if it is legally prohibited to transfer embryos to anyone other than a biological female then medics either need to work with legislators to reform the law (if desired) or cease work that is intentionally designed to perform UTx in biologically male bodies.

d) Not already a mother

Adoption and surrogacy are options available to women with AUFI in the UK. Potential recipients must be fully informed of the alternative paths to parenthood open to them and this is something that research teams around the world include in their procedures.[13] Gestational surrogacy achieves the same outcome as UTx, a genetically related child. It is equally important that adoption is taken seriously as an option to become a parent, as these are children already in existence who need a stable family environment.[22]

It is recognised that adoption and surrogacy may not be a simple option to pursue. Although altruistic surrogacy is legally permitted in the UK, it lacks legal certainty for intended parents. Unenforceability of surrogacy arrangements, birth mothers recognised as the legal mother, and the need for parental orders to transfer legal parenthood, can result in apprehensive and reluctant intended parents.[16,23,24]

Equally, women may not feel comfortable shifting the burden of gestation to another woman, in order to achieve her own personal aim of becoming a mother, or they may desire the social experience of pregnancy. The adoption avenue may not be open to some women, does not have enough 'desirable' babies for adoption, or is very difficult to access due to restrictions in the adoption process.

Even where surrogacy and adoption are accessible and may have been used to achieve motherhood, some women may strongly feel that gestating their own child is the only option for them, and so UTx is the sole solution.

The medical motivation for conducting UTx is to find a treatment for women with AUFI. The goal is to successfully perform UTx and to have a live birth, thereby providing another route to motherhood, in addition to surrogacy and adoption. Motherhood was the early motivation for pursuing UTx, not gestation. In 2008 it was stated that, "*Uterine transplantation would not be undertaken to fulfil a woman's desire to experience pregnancy. It would not be performed to allow a woman to carry a pregnancy, or to give birth per se, but rather to allow the couple to have a child and thereby a family*"[25] This is a rare example in the scientific literature unambiguously stating that motherhood is the medical aim of UTx.[26] This is further evidenced by the UK criteria explicitly excluding recipients who are already mothers, including by adoption or surrogacy, and the recipients in the Swedish trial had no previous children.[12]

The importance of gestation must not be underestimated; the first woman to undergo UTx in the U.S. chose to volunteer, and was accepted, for a UTx trial even though

she and her husband were already parents to three adopted children.[27] A recent quantitative study also supports the view that women with AUFI who are already mothers are interested in accessing UTx.[28]

As noted, Womb Transplant UK is excluding from their trial any woman who is already a mother. If account is taken of existing children of the family, the medical risks of this experimental procedure justify excluding women who are already mothers.

If existing motherhood is to be utilised as an eligibility criteria beyond research trials, clarification is called for with regards to the goal of UTx. Gestation and motherhood appear inextricably linked; it may seem inconceivable that someone would want UTx without subsequently attempting gestation. Yet there may be some women, including transgender women, who may desire UTx without subsequent gestation.

Lotz suggests that UTx has three goals '*(a) to become a parent and raise a child; (b) to have a biologically related child; and (c) to experience gestation'.*[22] Moving forward, if it is recognised that one of the goals of UTx is to experience gestation, this calls for UTx to be available to all women with AUFI who have not had the opportunity to experience gestation. In contrast, if the goal of UTx is motherhood, eligibility criteria could be used to exclude women who are already mothers by any means.

There is a need for a clear definition that addresses the medical goal of UTx as well as the goal(s) of the potential recipients. Due to a likely lack of available uteri, scarce

resources, and the risks to recipients, it is recommended that at this time UTx be only offered to women who are not already mothers.

e) Donors

It should not be forgotten that UTx involves two women – a recipient and a donor. Whether there should be a preference for living or deceased donors is subject to ethical and medical debate; research trials vary.[29] The Swedish trial succeeded with known living donors. In the U.S., Baylor Medical Center has performed UTx with anonymous living donors and has had two births to date. In Turkey, the first transplant from a deceased donor has so far failed to result in a successful pregnancy, and in 2016 the Cleveland Clinic in the U.S. had to remove a uterus from a deceased donor soon after transplantation. As yet unpublished, proof of concept with UTx from a deceased donor has now been shown with a birth in Brazil. Womb Transplant UK has approval to conduct research trials with both deceased and living donors.

Obviously, the removal of a uterus from a deceased donor is the least medically risky option, *'…the surgery for retrieval of organs being far less complex, and there being no risk of harm to the donor.'*[29] The principal (non-medical) concern with deceased donation is the consent process; Caplan *et al.,* have noted that *'Obtaining the uterus from a deceased donor raises some unique ethical issues.'*[30] They argue that few women would have thought about donating their uterus upon their death, and that a woman may not be as willing to donate her reproductive organs, as she may distinguish it from her other organs.[31] As such, they argue that 'explicit consent' for

uterus donation prior to death should be preferred. In a recent French study that sought explicit consent from family members to retrieve uterus from brain dead donors, none of the families asked refused consent.[32] As such, provided that explicit consent has been obtained from either the donor prior to death or family members, the use of uteri from deceased donors is legally and ethically unproblematic. England and Wales operate two different organ donation schemes, the former requires donors to opt-in, whilst the latter operates an opt-out deemed consent scheme. However, even under the deemed consent scheme, explicit consent is required for the donation and transplantation of a uterus from living and deceased donors.[33,34,35]

Ethical concerns and medical complications increase with the use of living donors. The need to preserve vascular support to ensure successful transplantation requires that a radical hysterectomy be performed; this is highly invasive and complex encompassing a range of risks that even in skilled hands cannot be completely avoided. As with all surgeries there is a risk of complications, the willingness of women to act altruistically and subject themselves to risks when there is no corresponding medical benefit to them is admirable, yet should raise concerns. Altruism in the medical context is highly regarded, but social influences and factors along with donor motivations must be investigated prior to inclusion in a trial.

If the living donor is a relative, then particular care must be taken with the consent of the donor due to the risk of emotional pressures and coercion within the familial environment as well as societal pressures.[36] In the Swedish trial, one donor suffered a uretic complication that was described by the Swedish team as 'low risk'. However, this has been challenged, *'…given the immediate and long-term implications of such*

an injury in any context, but particularly in the case of an elective procedure.'[37] Research highlights other risks for living donors including complications with the hysterectomy, ovarian dysfunction, a decrease in quality of life, mental problems, and sexual dysfunction.[38]

The advantage of living donors is time; allowing for necessary medical checks, and scheduling of the surgeries. It is vital that the donors are fully aware of the health risks that they are consenting to, as well as the time commitment that they are making for the pre-surgery tests, the surgery itself, and the recovery period. The donor may also feel conflicted about donating an organ that she no longer needs but which is a symbol of femininity.[39,40] With increasing awareness of UTx as a treatment for AUFI, there may be a corresponding social influence for female relatives to donate to a family member with AUFI. Whilst it is clear that donors can withdraw their consent at any time prior to the donation, donors may feel unable to do so, particularly if they know the potential recipient. As Kisu *et al* argue, support systems must be established *'…to ensure voluntary decision making and long-term follow up and care for donors, similar to the support available for recipients.'*[38]

As noted by Catsanos *et al,* anonymous living donation could reduce the risk of coerced consent, whereas Dickens questions the motivations behind anonymous donation: *'Outside a family relationship or close friendship, the willingness of a woman to undertake hazards of non-therapeutic removal of her uterus to promote an unrelated woman's childbearing raises questions of her motivation.'*[41,42] Whilst questions over coercion may be resolved with anonymous donation, the health risks

of a complex hysterectomy procedure must not be overlooked when informing, and obtaining, express consent.

The use of deceased donors or a bioengineered uterus would overcome all of the concerns expressed in relation to living donors. At present, provided that express consent has been given, and the removal of life saving organs remains a priority, deceased donation is preferred. With the recent birth of a child after UTx from a deceased donor, research teams worldwide may start to find it harder to justify the use of living donors in trials. In the future, bioengineered uteruses will remove the need for immunosuppressant drugs (if the recipient's own cells are used to grow the bioengineered uterus), uteri can be grown 'to order', and surgery can be scheduled. There would be no risks to a living donor, no familial or social pressure to donate, and no questions around appropriate consent. For these reasons, the Swedish team has already started research in animal models to grow and transplant bioengineered uteruses.[43]

In light of all the risks for living donors, it is recommended that UTx be performed with deceased donors who have expressly given consent for uterus donation, or bioengineered uteruses.

Conclusion

Successful UTx and live births is a major breakthrough for women with AUFI who desire gestate in order to achieve motherhood. Questions have been raised with

regards to the eligibility criteria for recipients for UTx when it becomes available as a treatment for AUFI.

Nonetheless, based on the development of other reproductive treatments and the rapid progress being made in UTx, it is highly likely that UTx will one day soon come to fruition as a treatment. In order to continue the debate, I have examined the UK selection criteria for UTx trials and made recommendations going forward (Table 2). These include the use of donor eggs, access for single women and women in same-sex relationships, prohibiting the participation of women who are already mothers, and the inclusion of deceased donors and bioengineered uteri.

This original analysis builds upon the work in this fledgling area of healthcare, bioethics and law. These recommendations are important for formulating regulatory and ethical frameworks in which UTx can proceed.

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Tables:

Country	Sweden[11]	UK[12]
Inclusion Criteria for Recipients	• Suffer from childlessness due to uterine infertility that cannot be remedied • Feel a strong desire to become a biological parent • Live in a stable couple relationship • Be younger than 37 years of age • Have healthy ovaries • Have her own donor	• Female • AUFI • Normal ovarian reserve and function • Aged 24–38 years (40 if embryos frozen <38 years) • Normal length - no skin/intestinal neovaginas • Body mass index <30 kg/m^2 • Lives in UK as a resident • Fluent in the English language • Sufficient embryo quality/quantity (minimum number of 10 satisfactory quality embryos)
Exclusion Criteria for Recipients	Should not have or have had – • Cancer within last five years • Chronic infections such as HIV, tuberculosis or hepatitis • Severe illnesses which are sensitive or worsened by pregnancy or immunosuppressant medication	• Previous children including adopted or born by surrogacy • Previous multiple major abdominal/pelvic surgery • Premature ovarian failure with no frozen mature eggs/embryos • Severe endometriosis • Significant medical problems including renal pathology, thrombophilia • Previous cancer <5 years in remission • History of significant psychiatric illness

Table 1: Recipients eligibility criteria for uterus transplant research trials in Sweden and the UK

Inclusion Criteria	Exclusion Criteria	Donors

• Female with AUFI including women in a heterosexual relationship, single women, women in a same-sex relationship • Produce own eggs OR use donor eggs • If NHS funded - Age 42 yrs if own eggs frozen before age 40 or donor eggs used • If privately funded – Age 50 yrs if own eggs frozen before age 40 or donor eggs used • Support - not necessarily a sexual partner • Able to give informed consent	• Already a mother • Significant ill health • No support network	• Preference for deceased donors • If known living donors are involved, issues of familial pressure must be explored • Bioengineered uteruses to be explored further as a potential source

Table 2: Summary of recommended eligibility criteria for UTx treatment