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The Montreal Criteria and uterine transplants in transgender women

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Abstract

Ever since its first documented live birth in 2014, the use of uterine transplantation (UTx) for the treatment of absolute uterine factor infertility (UFI) has seen major clinical advances, which include the use of alternative surgical approaches, different donor states, and diverse patient populations. In addition to the thorough research programs that developed the technique, this accomplishment has occurred in large part following a number of ethical frameworks, such as the Montreal Criteria and the Indianapolis Consensus, which paved the way to transition from experimental animal trials to human ones. To date, over 60 uterine transplants have been performed in the world, and at least 18 births have been thus far confirmed. While the procedure remains experimental, the vast knowledge and procedural experience amassed over the last 20 years of rigorous research have hinted at the next step of discovery. In particular, advancing social circumstances have prompted the question regarding the use of this technology in transgender individuals. Though the potential use of uterine transplants in the transgender population has been hypothesized, no in-depth ethical framework has been developed towards this purpose. Herein, we explore the ethical issues revolving around the use of this technology in this patient population and provide key insights that may advance this cause.

KEYWORDS

Montreal Criteria, transgender, uterine transplants

1 | INTRODUCTION

Ever since its first documented live birth in 2014,[1] the use of uterine transplantation (UTx) for the treatment of absolute uterine factor infertility (UFI) has seen major clinical advances, which include the use of alternative surgical approaches, different donor states, and diverse patient populations. In addition to the thorough research programs that developed the technique, this accomplishment has occurred in large part following a number of ethical frameworks, such as the Montreal Criteria and the Indianapolis Consensus,[2] which paved the way to transition from experimental animal trials to human ones. To date, over 60 uterine transplants have been performed in the world, and at least 18 births have been thus far confirmed.[3] While the procedure remains experimental, the vast

[1]Balayla, J., Dahdouh, E. M., Lefkowitz, A., & Montreal Criteria for the Ethical Feasibility of Uterine Transplantation Research (2015). Livebirth after uterus transplantation. *Lancet*, *385*(9985), 2351–2352.

[2]Lefkowitz, A., Edwards, M., & Balayla, J. (2012). The Montreal Criteria for the Ethical Feasibility of Uterine Transplantation. *Transplant International*, *25*(4), 439–447; Del Priore, G., Saso, S., Meslin, E. M., Tzakis, A., Brännström, M., Clarke, A., Vianna, R., Sawyer, R., & Smith, J. R. (2013). Uterine transplantation—a real possibility? The Indianapolis consensus. *Human Reproduction*, *28*(2), 288–291.

[3]Balayla et al., op. cit. note 1.

knowledge and procedural experience amassed over the last 20 years of rigorous research have hinted at the next step of discovery. In particular, advancing social circumstances have prompted the question regarding the use of this technology in transgender individuals. Though the potential use of uterine transplants in the transgender population has been hypothesized,[4] no in-depth ethical framework has been developed towards this purpose. Herein, we explore the ethical issues revolving around the use of this technology in this patient population and provide key insights that may advance this cause.

2 | ETHICAL FRAMEWORK FOR UTERINE TRANSPLANTATION IN TRANSGENDER INDIVIDUALS

UTx for UFI has shown a track-record of successful results, indicating that lacking a functional uterus need not be an impediment to childbearing; contemporary definitions of "success" may expand to include the alignment between physical body and personal identity, rather than achieving gestation, among transgender women. Currently, UTx has been performed only in the context of genetic females (karyotype = XX), as per 'The Montreal Criteria for the Ethical Feasibility of Uterine Transplantation.'[5] The Montreal Criteria outline an ethical framework for patient eligibility to undergo the procedure, including the provision: "1. The recipient is a genetic female of reproductive age with no medical contraindications to transplantation." The stipulation for the patient to be a genetic female inherently disqualifies transgender, some non-binary, gender diverse and cis-gender women who have a non-XX karyotype ("transgender UTx"). As of the present, no successful transgender UTx surgery is known to have occurred. That said, the authors state in their publication that this is an inherent concern regarding research ethics in medicine, and not a reflection of the morality or validity of performing this procedure in the transgender patient population. Indeed, the authors do clarify in their publication that:

> there does not seem to be a *prima facie* ethical reason to reject the idea of performing uterine transplant on a trans patient. A trans patient wishing to gestate a child does not have a lesser claim to that desire than their female counterparts. The principle of autonomy is not sex-specific.

This right is not absolute, but it is not the business of medicine to decide what is unreasonable to request for a person of sound mind, except as it relates to medical and surgical risk, as well as to distribution of resources. A male who identifies as a woman, for example, arguably has UFI, no functionally different than a woman who is born female with UFI. Irrespective of the surgical challenges involved, such a person's right to self-governance of her reproductive potential ought to be equal to her genetically female peers and should be respected.[6]

The underlying reason behind the Montreal Criteria's requirement for the recipient to be a genetic female stems from Moore's criteria for surgical innovation, which require that the laboratory background be congruent to the clinical application of the procedure.[7] In the case of the uterine transplant, all research attempts had been carried out in genetic females across the different species tested. To satisfy Moore's criteria, it follows that the uterine transplant should be offered to genetic females until such time as enough research background and success can justify the procedure in transgender women. We argue that such time has arrived—and research trials should consider including transgender individuals.

Since pregnancy provides a self-sufficient hormonal environment through placental function, there appears to be no absolute underlying genetic or physiologic contraindication to pregnancy in non-XX individuals who undergo UTx. Transgender UTx hopes to provide therapeutic value to such individuals, in terms of both enabling pregnancy, and also in allowing the patient to attain body-completeness through having a key female reproductive organ. It is understood that the social and political implications of such a surgery require close examination of the ethical factors involved, in addition to those already contemplated by the previous framework. To be clear, when we refer to success we simply refer to "surgical success," where rates of rejection are low and successful pregnancies have been high. In this sense, the success is merely defined as it pertains to surgical and obstetrical outcomes. The outcomes regardless body-completeness have not been studied yet since none of the women undergoing uterine transplantation has been described as having body dysmorphia. In our view, this will be as important an outcome of study as all others if uterine transplantations is ever carried out in transgender individuals.

The Montreal Criteria consider and explore the four main ethical principles of principlism, namely: autonomy, non-maleficence, beneficence, and justice.[8] These factors as expounded remain valid in the case of transgender UTx, with the following added considerations:

1. Normativity in the context of the principle of justice.
2. Body euphoria in the context of the principle of beneficence.
3. Medical risk in the context of the principle of non-maleficence.

[4]Lefkowitz, A., Edwards, M., & Balayla, J. (2013). Ethical considerations in the era of the uterine transplant: An update of the Montreal Criteria for the Ethical Feasibility of Uterine Transplantation. *Fertility and Sterility, 100*(4), 924–926; De Roo, C., Tilleman, K., T'Sjoen, G., & De Sutter, P. (2016). Fertility options in transgender people. *International Review of Psychiatry, 28*(1), 112–119.

[5]Lefkowitz et al., op. cit. notes 2 and 4.

[6]Lefkowitz et al., op. cit. note 4.

[7]Lefkowitz et al., op. cit. note 2.

[8]Lefkowitz et al., op. cit. notes 2 and 4.

3 | NORMATIVITY IN THE CONTEXT OF THE PRINCIPLE OF JUSTICE

In the broad sense, the principle of justice implies that individuals should expect to be able to avail themselves of the normative experiences shared by fellow humans: that key elements of life, be it actual or potential, are accessible, regardless of the circumstances of their birth. While socio-economic circumstances often prevent this from occurring, it does not diminish their worthiness or moral pursuit. In this light, it is normative for an individual to desire to feel complete in his or her body—regardless of gender. It is normative for a person who wishes to reproduce to do so, either as part of a couple or, technological circumstances permitting, as an individual. Said normativity depends on certain background assumptions, i.e., that the person in question has sufficient resources to care for the child, and that the circumstances are such that bringing a child into the world does not compromise the ability of that individual to provide for said child. It then follows that it is normative for a person with a uterus of reproductive age who wishes to become pregnant to do so.

Today, though there remains much progress to make, the rights of transgender people to live and be acknowledged as the gender and sex with which they identify are increasingly evident as advances in the acceptance of transgendered individuals have been well documented.[9]

If a cis-gender person who identifies as female but who lacks a uterus may ethically obtain one, then the principle of justice supports that this opportunity should be available to all such people, regardless of the circumstance of their birth. This is particularly important for transgender individuals who endure significant psychological distress secondary to feeling body-incomplete. The Montreal Criteria were created with the intent of procuring gestation; although they did not address the non-reproductive indications for UTx, these undoubtedly exist. Notwithstanding normativity as it relates to justice for transgender individuals, the use of UTx for non-reproductive purposes must further be studied as per Moore's criteria, prior to its adoption as a treatment for gender dysphoria.[10]

4 | BODY EUPHORIA IN THE CONTEXT OF THE PRINCIPLE OF BENEFICENCE

Patients with a transgender condition report an incongruity between their body's sex characteristics and their identified gender. Gender dysphoria is associated with feelings of sadness, depression, self-harm and suicidality.[11] A key component to gender dysphoria is the sense that one's body is wrong or incomplete—especially in the area of primary sexual characteristics; for male to female transgender people, this often includes the uterus.

The success of gender confirmation surgery (also called "sex reassignment surgery") demonstrates that surgical intervention for severe gender dysphoria relating to primary sexual characteristics is largely effective.[12] To date, however, no surgical solution for people who feel they are missing a key body part—their uterus—has been available. The expectation is that real psychological benefit is to be had by the patient in feeling complete by having this organ. Thus the principle of beneficence supports that, as the welfare of the patient will be improved, this treatment should be made available to those suffering from gender dysphoria.

5 | MEDICAL RISK IN THE CONTEXT OF THE PRINCIPLE OF NON-MALEFICENCE

Like conventional UTx, transgender UTx poses risks to the recipient, the donor (if living) and fetus, should a pregnancy ensue. Risks to the donor are identical to those of a conventional UTx and thus are already covered by the Montreal Criteria and a body of literature.[13] Risks to the recipient and fetus must be weighed with consideration to the special circumstances posed by a transgender recipient. If these risks can be mitigated such that they are outweighed by the benefits, then the principle of beneficence would overshadow any non-maleficence, thereby supporting the availability of UTx to transgender recipients.

From a purely clinical standpoint, the welfare of the fetus is primarily dependent on its genetic makeup; with the uterine environment serving simply as the incubator during pregnancy. So long as the uterus is well perfused in a hormonal environment that promotes uterine growth and quiescence during pregnancy, the fetus and its placenta should live out their potential. Thus far, no fetal complications directly attributed to the uterine graft have been described. With the limited number of uterine transplants thus far carried out, this will be certainly a question that will need to be re-visited in the future. It should be noted that any pregnancy inherently carries substantial risk—even for non-UTx cis-gender women. Although uncommon in well-equipped modern hospitals, pregnancies can and do still result in the death of the mother and/or infant.[14] It would thus follow that it cannot be demanded that a transgender UTx pregnancy be risk-free; instead, the principles of equity and justice support that

[9]Witeck, B. (2014). Cultural change in acceptance of LGBT people: Lessons from social marketing. *The American Journal of Orthopsychiatry*, *84*(1), 19–22.

[10]Hammond-Browning, N. (2019). UK criteria for uterus transplantation: A review. *BJOG*, *126*(11), 1320–1326.

[11]Peterson, C. M., Matthews, A., Copps-Smith, E., & Conard, L. A. (2017). Suicidality, self-harm, and body dissatisfaction in transgender adolescents and emerging adults with gender dysphoria. *Suicide & Life-Threatening Behavior*, *47*(4), 475–482.

[12]Smith, Y. L., Van Goozen, S. H., Kuiper, A. J., & Cohen-Kettenis, P. T. (2005). Sex reassignment: Outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychological Medicine*, *35*(1), 89–99.

[13]Testa, G., Koon, E. C., Johannesson, L., McKenna, G. J., Anthony, T., Klintmalm, G. B., Gunby, R. T., Warren, A. M., Putman, J. M., DePrisco, G., & Mitchell, J. M. (2017). Living donor uterus transplantation: A single center's observations and lessons learned from early setbacks to technical success. *American Journal of Transplantation*, *17*(11), 2901–2910; Bruno, B., & Arora, K. S. (2018). Uterus transplantation: The ethics of using deceased versus living donors. *American Journal of Bioethics*, *18*(7), 6–15.

[14]Callaghan, W. M. (2018). Foreword: Maternal mortality and severe maternal morbidity. *Clinical Obstetrics and Gynecology*, *61*(2), 294–295.

the risks encountered should be within the range encountered during adverse conventional pregnancies that may be considered normative.

Unlike genetic female patients, transgender recipients are expected to have anatomical and physiological considerations that differ from cis-women. This poses several potential problems, some of which include: the availability of space within the abdomen to accommodate the graft and potential pregnancy; the availability of suitable vascularization to support the organ; and variance in the hormonal environment of the recipient during pregnancy.

Anatomical concerns regarding the introduction of a uterine graft into the pelvis of an XY trans-woman have been addressed in the literature before by a leading surgical team in England, which concludes: "despite a number of anatomical, hormonal, fertility, and obstetric considerations that require consideration, there is no overwhelming clinical argument against performing UTx as part of gender re-assignment surgery."[15]

There is no expectation that a transgender UTx recipient would be able to deliver a pregnancy through a neo-vaginal canal. Nevertheless, given surgical concerns, particularly regarding the cervico-vaginal anastomosis, vaginal delivery is contraindicated even amongst XX women with natural-born vaginal canals who undergo UTx. As such, issues with the narrowness of a virilized pelvis and comparative inflexibility of contemporary neo-vaginas should not be taken into account when considering UTx in trans-women.[16]

Successful implantation of a transplanted uterus requires that the organ be adequately vascularized within the host environment. If successful, then the development of a fetus will place further demands on the blood supply of the host to sustain both organ and fetus. The abdominal and pelvic cavities of both sexes are well supplied with nearly identical vasculatures.

In particular, both sexes have external iliac arteries, the vessel to which a uterine artery from the donor graft is now commonly anastomosed,[17] and which has shown success in allowing a pregnant womb to grow and nourish a fetus. Akin to cis-recipients, it is obligatory that the adequacy of blood flow be ascertained prior to attempting a pregnancy, and that pregnancy not be attempted if the demands of a fetus could not be sustained by the available environment.

Depending on where an individual is in their transition process, they may be undergoing estrogen replacement and/or testosterone suppressing therapy. The potential confounding influence of persistent masculine sex hormones from transgender patients who retain their testes may require that transgender UTx recipients have undergone an orchiectomy prior to attempting pregnancy, until it can be shown that the hormonal environment will not be adversely affected. These risks are theoretical and will need to be addressed during trials in this population.

As the practice of UTx in transgender patients is still theoretical, one cannot accurately quantify the added risk, if any, of transgender women over cis-gender women undergoing UTx, with regards to carrying a pregnancy and the impact on the fetus. Though we address the possible complications that might arise from the anatomical differences, however, this is again hypothetical, given that though the theoretical scientific background exists one cannot predict the exact outcomes and implications. In addition, any potential risk that might arise from immunosuppressant use should be identical to both cis- and trans-gender women.

6 | GENDER OF XY INDIVIDUALS SEEKING UTx

In an evolving social world where traditional biological stereotypes are increasingly being broken down, it bears considering the hypothetical situation of an XY cis-male wanting to undergo UTx solely so that he may carry a pregnancy. In our view, though the surgical and medical considerations for pregnancy would be similar to a trans-female (XY) seeking UTx, the underlying indication for such a request is significantly different. The clinical scenario whereby a transgender woman seeks to undergo a UTx would be consistent with the natural premise that women carry pregnancies, and that such individuals identify as females—a role that would therefore correspond to them. In the transgender case, UTx would serve two inter-connected purposes—body completeness (and all of the psychological benefits that would ensue) as well as pregnancy. As we mentioned previously, though UTx may well be transitory to void the need for lifelong immune-suppression, the gender re-assignment surgery and orchiectomy needed to ensure the success of UTx are permanent—a consideration that would not apply to cis-males who would seek to carry pregnancies without transitioning.

Indeed, the ready convenience of access to the uterine cavity both for embryo transfer and biopsy via the cervix prefers that a transgender patient seeking to become pregnant through UTx should have previously undergone surgical construction of a neo-vagina that may be connected to the transplanted canal and cervix. Such a reality would only apply to trans-females and not cis-males.

It bears nevertheless stating that the aforementioned procedures can be conducted trans-abdominally—an IVF pregnancy has been successful brought to term in a woman with congenital cervical atresia[18]—thus full reconstructive gender confirmation surgery is not seen as a strict necessity, but rather a risk mitigating

[15]Jones, B. P., Williams, N. J., Saso, S., Thum, M. Y., Quiroga, I., Yazbek, J., Wilkinson, S., Ghaem-Maghami, S., Thomas, P., & Smith, J. R. (2019). Uterine transplantation in transgender women. *BJOG*, *126*(2), 152–156; Hammond-Browning, N. (2019). Uterine transplantation in transgender women: Medical, legal and ethical considerations. *BJOG*, *126*(2), 157.

[16]Balayla, J. (2016). Uterine transplants in the Canadian setting: A theoretical framework. *Journal of Obstetrics and Gynaecology Canada*, *38*(10), 955–960.

[17]Ibid.

[18]Lai, T. H., Wu, M. H., Hung, K. H., Cheng, Y. C., & Chang, F. M. (2001). Successful pregnancy by transmyometrial and transtubal embryo transfer after IVF in a patient with congenital cervical atresia who underwent uterovaginal canalization during Caesarean section: Case report. *Human Reproduction*, *16*(2), 268–271.

factor, which would bring the transgender case closer to that which we have experience with, namely, the UTx is cis-females with UFI.

All in all, a more in-depth analysis of the ethical issues surrounding UTx in transgender women reveals no clear added obstacle to its execution relative to cis-gender females. Progressive integration of these ethical issues into clinical practice may very well allow a transgender woman to undergo a UTx in the near future.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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