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Comment on the article by Del Rio et al. Uterus transplant update: innovative fertility solutions and the widening horizons of bioengineering. Eur Rev Med Pharmacol Sci 2021; 25(9): 3405-3410

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I have read with great interest the article by Del Rio et al, titled "Uterus transplant update: innovative fertility solutions and the widening horizons of bioengineering[1]". Still, I do feel it may be worth adding a few elements of discussion to that insightful piece of research, particularly in regard to uterus transplantation (UTx) and the risks entailed by the possible alteration of extremely complex immunological dynamics between the fetal and maternal systems, in addition to brief remarks on UTx and its distinctive traits and peculiarities. UTx is in fact likely to gain an increasingly significant a role in the realm of assisted reproductive technologies. Given how fast such techniques have been developed, experimented on, and improved, UTx may soon provide a valuable medical option for more and more women suffering from absolute uterine factor infertility (AUFI). Clinical AUFI can be the result of genetic disorder (such as Mayer-Rokitansky-Küster-Hauser Syndrome), hysterectomy, intrauterine adhesions or other severe conditions making the womb unfit for pregnancy[2]. UTx can make it possible for women with AUFI, which reportedly accounts for three per cent of all infertility in women[3], to have a pregnancy and biological offspring[4]. UTx techniques have undergone a gradual and substantial evolution since the first live birth in 2014, and so has the ethical debate centered around such a controversial, and in many respects unique, kind of human transplant[5]. UTx has in fact distinctive traits that set it apart from any other kind of transplantation: although it is not non-lifesaving, it may be viewed as "life-giving", aimed at enabling the recipient to achieve motherhood[6]; it is also ephemeral, i.e., meant to be removed after birth[7], unlike kidney or liver transplants for instance, experimental, and rather costly by health care spending standards, with clear and well-established alternatives. Moreover, its success cannot be based on allograft survival alone, but rather on whether it is effective at restoring the ability of the recipient to bring to term a pregnancy and give birth to a healthy child. Few examples exist of transplantations involving reproductive organs, among which ovarian tissue, first case in 2004[8], and testicles in 2001, when a patient underwent the surgical removal of his testicular tissue prior to being treated for cancer and transplanted back after the chemotherapy cycles[9]. The patient even succeeded in fathering a child. Functional restoration, rather than mere technical success, is in fact the fundamental goal of such an intervention, and if that fails, UTx hardly retains any merit at all[10].

The Distinctive Traits of UTx Make it Hard to Lay Out a Thorough Risk-Benefit Analysis

To lay out a risk-benefit analysis of a surgical intervention such as UTx, in light of its unique multi-layered complexities, it is worth bearing in mind that such a procedure entails considerable risks for the recipient, mostly stemming from multiple surgeries and the need for immunosuppression in order to prevent organ rejection and throughout the pregnancy. On the other hand, infertility has been shown to constitute a majorly distressing element in the lives of millions of women all over the world[11]. Unlike adoption, UTx can provide for genetically related offspring. Surrogacy may be viewed as an alternative in that regard, but that too raises ethical and legal quandaries of significant magnitude[12,13], which is why surrogacy is banned in many countries, and in almost all European nations[14]. Even though patient decisions are liable to be affected by inconsistent reasoning

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and inaccurate assessment of risks, a thorough informed consent process certainly constitutes a fundamental element and cornerstone of a viable risk-benefit assessment. Although there is no evidence of increased risks for children born from uterus transplant, it must be considered that in order to achieve pregnancy through UTx, the uterine vessels have to be connected to those of the recipient through a highly complicated procedure which does entail risks of altered blood supply and blood clots, both of which can negatively affect fetal growth. Furthermore, the already mentioned need for immunosuppression throughout gestation to prevent rejection of the organ is risky in itself. Though no conclusive evidence exists as to immunosuppressive medications increasing the rate of birth defects, several are associated with low birth weight and preterm delivery. For living donors, the risks of hysterectomy are known and must be thoroughly expounded upon to rely on a thorough informed consent process. As for the procurement of uteri from deceased donors, the way in which deceased donor organs should be allocated needs to be determined, as guidelines for other organs cannot readily be applied. Such difficulties have been denounced in Italy by hospital management at the only Italian institution that performs UTx in the country, where the first ever UTx in Italy has been successfully performed in August 2020 on a 29 year old with Müllerian agenesis[15]. According to hospital officials, a shortage of organs allocated from deceased donors (*inter vivos* UTx has not been authorized by health authorities in Italy) is making it harder and harder to stay on schedule and enroll more patients[16]. The Italian patient is now ready to have her own oocytes implanted, which had been frozen in advance through another ART procedure, elective egg freezing[17,18]. Furthermore, countries where assisted reproductive techniques are not covered by national health care systems, costs will be a major issue, as the procedure is considerably expensive.

The Key Role Played by Immunological Factors

Pregnancy is fundamentally based on a harmonious coexistence of the maternal system and the hemiallogeneic fetus developing in the womb. As such a multi-layered, elaborate process unfolds, a coordination takes place of several mechanisms involving the mother, the fetus, and placenta which "cooperate" to preserve the fetus from rejection through allogeneic immune responses[19]. It is therefore worth briefly expounding upon the unique complexities inherent in UTx, which are closely linked to the key role played over the pregnancy by maternal immune cells within the decidua, which interact with fetal trophoblast cells to foster placentation and tolerance towards the semi-allogeneic fetus. Such a highly complex immunologic environment may be altered and upset, to a degree, by the uterine allograft, which constitutes a foreign, non-self-organ from a genetic standpoint; such alterations might at least theoretically bring about unintended effects both on the pregnancy and on the transplant itself[20]. It behoves us to point out that pregnancies in solid organ transplantation recipients are generally deemed high-risk compared to pregnancies in non-transplanted women who do not undergo immunosuppression. Increased rates of pre-eclampsia have been observed in the former, along with preterm delivery and lower birth weights. Those complications may apply to UTx pregnancies as well. Hence, establishing a robust degree of immune tolerance is key to resolve such potentially harmful effects[21].The degree and scope of immunological complexity relative to UTx when encountering a semi-allogeneic fetus in a uterine allograft is still undetermined, and no conclusive findings are available, particularly in terms of the multi-layered dynamics that come into being among the various factors of the fetal-maternal interface. It is however well-known that effective decidualization constitutes the very first stage of any healthy pregnancy, in that it lays the groundwork for a favorable ecosystem for embryo implantation by turning the endometrial stroma into the decidual matrix that fosters embryo implantation and eventual placenta formation[22], mostly through the differentiation of endometrial stromal cells (EnSCs) into secretory decidual cells[23]. In UTx, alloimmune processes may be triggered or facilitated by ischemic incidents causing tissue hypoxia and the enhanced degree of immunogenicity to which allografts are exposed. Such dynamics have been reported both in experimental[24,25] and clinical solid organ transplantation[26,27] (SOT). In addition, local tissue injury and systemic sterile inflammation can be sparked by metabolic alterations and blood shears during reperfusion in the micro-circulation of capillaries. In SOT, Ischemia/Reperfusion Injury (IRI) manifests as delayed graft function[28] (DGF), which as observed in various pre-clinical animal models can also affect UTx[29,30]. IRI is triggered by tissue ischemia due to inadequate

oxygen supply and ensuing reperfusion, which can give rise to a broad-ranging sequence of inflammatory responses liable to worsening local injury as well as disabling remote organ function. In addition to that, over the long term IRI has been linked to acute rejection and chronic graft dysfunction in kidney transplantation recipients, because of interstitial fibrosis and tubular atrophy. How graft viability is negatively affected by IRI has been further shown by experimental trials on UTx sheep models[31], with the animals developing interstitial tissue edema affecting the uterus in all its layers[32], severe epithelial cell damage in addition to other metabolic alterations[33]. In clinical UTx, it has been recommended that ischemic times should not exceed 6 hours, although a clear baseline has yet not been identified[34]. Hence, although further research is needed to shed a light on such crucial aspects, it could be assumed that some unsuccessful UTx attempts involving deceased donors may have been related to protracted ischemic spells[35]. Overall, injuries augmenting alloimmune responses and/or inflammation linked to IRI could result in lower degrees of endometrial receptiveness and affect menstrual cycles. That could in part explain the lower success rates, in terms of achieving pregnancy, in UTx from deceased donor, which has anyway already led to live births[36].

Beyond Clinical Complications, Ethical Unique Traits Arise

In light of the clinical complexities briefly mentioned herein, there is no denying that UTx constitutes the juxtaposition of two extremely controversial areas in terms of ethics and morals: Medically-assisted procreation (MAP) and organ transplantation. As far as the organ transplantation realm is concerned, UTx is somewhat akin to composite tissue transplants such as face and limb grafts, thus raising several of the same ethical concerns ascribed to such non-life saving, but rather life-enhancing (or as UTx has been characterized, "life-giving"), interventions. UTx within the MAP framework constitutes one more potentially viable avenue by which infertile women may achieve motherhood. Still, as other MAP procedures, UTx involves major complexities that have to do with the limits of reproductive autonomy, among other aspects[37]. As UTx is likely to increasingly establish itself as a real and viable alternative for women suffering from AUFI, it is in our view essential to start a broad-ranging discussion as to how UTx ought to be regulated. To that end, it must be taken into account that unlike other allografts, UTx from live donors impacts three individuals: the donor, the recipient and the child-to-be. Hence, the physical, psychosocial and ethical risks and benefits of uterus transplantation for all three parties involved need to thoroughly inform the discussion of the regulatory and legislative implications. Would children born *via* a transplanted donated uterus have the right to know the organ donor or should anonymity be preserved, as it is for gamete donors partaking in assisted reproductive techniques[38,39]? The main difference between the two situations is that the children are not biologically related to the UTx donor as they are to the gamete donors, but it can be argued that being born through a donated womb can in itself establish a connection between the child and the donor of the womb which made his or her birth possible. Moreover, and just as importantly, how ethically sustainable is it to jeopardize the health of the donor for the benefit of the recipient? Based on utilitarian ethics, organ transplants are generally viewed as ethically justified, although they do run counter to the principle of non-maleficence ("first, do no harm") as well as Kantian principle, considering that a living donor is made into "a means to an end"[40-42]. Still, would an ephemeral and non-lifesaving transplant such as UTx still meet that utilitarian principle?[43]

Conclusions: a Llife-Giving Transplantation Consistent With Moral And Ethical Precepts?

Certainly, an essential argument in favor of living UTx is grounded in the fundamental respect for individual autonomy, according to which the right of everyone to form personal opinions, make decisions and ultimately act upon personal beliefs and convictions must always be upheld and acknowledged. Irrespective of the risks UTx undoubtedly entails, in fact, organ donors could benefit emotionally and psychologically from fulfilling their wish to donate and enable a woman to achieve motherhood. Studies centered around kidney donors have in fact shown that they have reported higher levels of self-esteem, happiness, and even better quality-of-life following donation. The same dynamics could apply to uterus donors, particularly if the technique is further improved with even better chances of viable pregnancy and childbirth. Albeit not a life-saving transplantation, in fact, UTx is after all meant to be "life-enhancing" and "life-giving".

Conflict of Interest

The Author declares that she has no conflict of interests.

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