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Uterus transplant update: innovative fertility solutions and the widening horizons of bioengineering

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Abstract. – Uterus transplantation (UTx) aimed at restoring fertility for women suffering from uterine factor infertility has been making significant strides over the past years, leading to the first successful outcome of live birth in 2014. Nonetheless, the ethical issues raised by such a procreative option are uniquely complex and multifaceted. UTx presents unique features, and the most significant risks it entails are the multiple surgeries required and the need for immunosuppressive drugs to prevent organ rejection. Post-transplantation immunosuppressive therapy, rejection monitoring, and immune tolerance are all crucial aspects That affect UTx outcomes and ensuing pregnancy success rates. In time, an alternative tool might become clinically available that could solve all those issues: tissue engineering relying on a combination of cells, biomaterials, and growth factors that harness the body's innate ability to regenerate and repair reproductive organs. Mastering such techniques could lead in the medium-long term to the creation of a bioengineered uterus for the purpose of transplantation, based on scaffolds derived from decellularized organs or tissues that can be recellularized by several types of autologous somatic/stem cells, in particular for uterine tissue engineering.

Key Words:
Uterus transplant, Assisted reproductive technology, Bioengineering, Decellularization, Bioethics.

Introduction

Although research into uterus transplant (UTx) dates back to 1960, the first modern attempt at human UTx did not take place until 2000, in Saudi Arabia. Over the years, clinical research into the challenging procedure gradually gained traction, and in 2014, Brännström et al[1] in Sweden reported the first live birth following living-donor UTx. Research into this treatment for absolute uterine factor infertility has since grown with clinical trials currently taking place across centers in at least thirteen countries worldwide. To provide necessary context, it should be noted that absolute uterine factor infertility (AUFI), i.e., the absence of a functional uterus because of congenital Müllerian malformations or acquired causes, has been described as the only major type of female infertility still deemed to be untreatable[2]. According to estimates, roughly 1 in 500 women worldwide suffer from uterine factor infertility[3]. In addition, UTx may be a solution for patients who had to undergo emergency hysterectomy due to postpartum prothrombin[4] activity, uterine rupture[5], attached placenta, including accreta[6], uterus atony or amniotic fluid embolism[7], among other causes.

UTx Outcomes: an Update on the State of the Art and Immunosuppression-Related Risks

A 2021 prospective study has reported on UTx outcomes at Baylor University Medical Center, Dallas, United States[8]. The study focused on 20 women who received a UTx between 2016 and 2019 in terms of how many successful outcomes, i.e., live births, were achieved in that same group, in addition to taking into account maternal complications, and fetal and newborn outcomes. All pregnancies were brought to term between November 2017 and September 2020. Six graft failures were reported, comprising four due to surgical complications and two caused by inadequate perfusion at the postoperative stage. Out of the 14 successful transplants remaining, at least one live birth was achieved in 11 patients. As of this writ-

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ing, a 55% live birth rate for each attempted transplant was recorded, and a 79% live birth rate per technically successful transplant. Out of the 14 successful transplants, ten uteri were *inter vivos* and just one from a deceased donor. Pregnancy was achieved through *in vitro* fertilization (IVF) procedures. One instance of organ rejection was recorded during pregnancy and was resolved with steroids. As for the immunosuppression regimen, it was based on tacrolimus and azathioprine as maintenance therapy, while mycophenolate mofetil was discontinued. Such an adjustment enabled earlier embryo transfer, which diminished cumulative exposure to immunosuppression. It is worth noting that the administration of mycophenolate mofetil needs to be discontinued prior to embryo transfer due to its teratogenic nature[9]: an increased risk of first-trimester pregnancy loss and congenital malformations has been reported in relation to the drug[10]. Congenital heart disease, and specifically conotruncal or aortic arch defects, were the most common embryopathies related to mycophenolate, accounting for 33% of reported conditions. Nonetheless, the connection appears to be in need of further investigation: a 2017 retrospective study of kidney transplant recipients showed that birth defects and miscarriages were similar among patients who had ceased the administration of mycophenolate mofetil 6 weeks or less before pregnancy and during the first trimester. On the other hand, discontinuing mycophenolate mofetil during the second trimester or later appeared to heighten the risk of birth defects or even miscarriages[11,12]. In light of the ultimate purpose of UTx, i.e., enabling women to bear children through the ultimate and most rewarding motherhood experience, its immunosuppressive program needs to be specifically targeted and with an adequate degree of specialization[13]. As documented above, immunosuppressive drugs are liable to give rise to perinatal complications and embryopathies; hence such adverse effects need to be tackled by inducing immune tolerance, in the same way in which immune tolerance is developed towards the fetus and placenta during pregnancy, thus preventing their rejection as could happen in cases of miscarriage[14]. Still, the immune mechanisms associated with UTx are still not fully known and understood; hence, if UTx is to become a relatively mainstream procedure anytime soon, new immunosuppressive agents need to be devised and developed, along with assisted reproductive technology procedures aimed at minimizing risks. However, obstacles to UTx use are still considerable and go from infection following immunosuppressive therapy to the development of thrombosis[15]. Despite that, successful births in Sweden, United States, and a recent successful transplant in Catania, Italy (the first in the country[16]), in addition to the development of clinical trials at six additional sites in the U.S. and abroad, offer hope that women with uterine factor infertility will be able to achieve motherhood through UTx. Currently, more than 70 UTx procedures have been carried out globally, resulting in the births of over 30 newborn children. After all, it has been documented that women are deeply, and often severely, impacted by infertility, perceived as a major element of distress in their lives. A thorough risk-benefit analysis should therefore account for such dynamics as well[17]. Surrogacy is an alternative to UTx, but is itself rife with ethical issues, while adoption does not provide for genetically-related offspring[18]. In order to tackle such controversial factors, a carefully drafted and clearly outlined informed consent process is essential in terms of providing a valid ethical response when weighing the risks against the benefits, although inconsistent reasoning, misconception of risks and unrealistic expectations can sway patient decisions, to the detriment of a solid informed consent process[19,20].

Seeking Alternatives in the Ever-Widening Horizons of Bioengineering

Bioengineering strategies have already exhibited a remarkable potential to treat female infertility arising from uterine injuries, major intrauterine adhesions, chemotherapy, fallopian tube occlusion, congenital uterine malformations, and hysterectomy. Medical and biological science has been gaining ever greater awareness and knowledge of the mind-blowing opportunities offered by the revolutionary techniques and interventions aimed at changing the nature of human beings at the level of the infinitely small: the realm of genetic essence.

Bioengineering and biotechnology are scientific specialties capable of harnessing biological sciences and technologies for the purpose of benefiting individual and public health. Research on nucleic acids, for instance, has made it possible to better understand the mechanisms and dynamics relative to major diseases such as neurodegenerative disorders[21], cancer[22-26], and autism spectrum disorders[27]. In the current ongoing pandemic emergency, techniques based

on nucleic acid pre-amplification techniques are under development for diagnostic purposes[28]. That has enabled science to rely on extremely valuable novel diagnostic and therapeutic options for tackling public health issues of considerable magnitude. As for reproductive medicine, a possible alternative to UTx and its many unresolved challenges could be provided by tissue engineering approaches which harness a combination of cells, growth factors, and biomaterials in order to tap into the innate ability of our bodies to regenerate and mend reproductive organs. Research has made giant strides in tissue engineering or whole organ transplant based on autografts or allografts. Various different cell types can be used for tissue engineering, including tissue-specific stem cells, mesenchymal stem cells, and pluripotent stem cells obtained from embryos[29]. Those are the building blocks of currently available regenerative medicine strategies that hold great promise. It is often deemed preferable to use fresh and cryopreserved organ/tissue transplant, by virtue of their ability to retain an intact extracellular matrix (ECM) structure and the natural tissue's complex cellularity[30]. Tissues and organs can either be allogeneic or autologous. Autologous sources are often preferred as they avoid immune rejections and the significant negative effect of immunosuppressive drugs, but autologous organs/tissues' harvest is often difficult to perform. Due to the limited availability of autologous and allogeneic sources, many researchers have turned to the decellularization of tissues or organs, through which it is possible to isolate the ECM of a tissue from its inhabiting cells, thus attaining an ECM scaffold of the original tissue to be used in artificial organ and tissue regeneration. Some of the most widely used decellularized tissue matrices used in female reproductive organ regeneration are porcine small intestinal submucosa (SIS)[31], peritoneum[32], and amniotic membrane[33]. Although decellularization is certainly valuable in terms of preserving the ECM architecture and minimizing the effect of immune rejections, agents related to decellularization can negatively affect the ultrastructure of the decellularized organ. Furthermore, residual cellular components, such as nucleic acid material that are not removed during processing, can trigger adverse effects on the host. This, in addition to the difficulties in retaining exact ECM composition, has led researchers to opt for purified natural or synthetic biomaterials such as alginate, collagen, gelatin, polyethylene-glycol, and polypropylene-fumarate, which enable better control over the composition of biological implants. A 2020 study has reported that engineered tissue was able to develop structures akin to native tissue in rabbits and to support pregnancies which resulted in live births[34]. Certainly, before such groundbreaking technologies become mainstream clinical practice, several issues need to be settled, e.g., identifying the source of the organ and the assessment of the immunogenic effects stemming from allografts. Moreover, the capability of these techniques to harvest whole organ constructs is as yet unproven[35].

Are New Bioethical Frameworks Needed?

Not only can bioengineering and biotechnology yield considerable results in health care, but they run almost the whole spectrum of human life and related activities and processes: agriculture, food processing, environmental science, among others. However, although such advancements have made it possible to create bioengineered organisms that have many benefits, such breakthrough innovations may pose a serious menace to human health and/or the environment. There is no denying that fundamentally modifying and transferring engineered gene assemblies has far-reaching ramifications and entails prospects on which any scientific consensus is extremely far from being reached. After all, technologies that impact the beginning of life stage have long been controversial: *in vitro* fertilization, and medically assisted procedures aimed at enabling couples, or even single individuals, to achieve parenthood have stirred heated debate in scientific communities and societies as a whole[36]. Although such techniques do not entail any genetic intervention or alteration performed on gametes and embryos, they are morally and ethically controversial and have been regulated through various national legislative frameworks[37] with varying degrees of restrictions[38]. Hence, ethical concerns and quandaries do exist with regard to such innovative techniques. Still, it is undeniable that unique complexities arise from what we might refer to as the "hybrid" nature of bioengineering ethics. Bioengineering needs to be consistent and coherent with the ethics of engineering, biology, medicine, and the physical sciences at the same time since all such components interact as bioengineering research develops and evolves. Those specific realms of ethics are, of course,

compatible with general ethics, but at the same time distinct from it and complementary[39]. Each set of ethical precepts is closely related to, and integrated with, the foundational philosophical tenets and principles of each field. In biology and consequently in medicine, knowledge, and research have to be ethically pursued in the context of living organisms, unlike what happens in engineering ad physics. Medical ethics entails fundamental issues such as the limits of therapy, safety, and risk, the Hippocratic precepts, informed consent, the role of physicians and patients, the very nature of life, including the conception of consciousness and awareness, and last but not least, the quandary arising from the identification of individual benefits *vs.* societal ones.

From a historical perspective, biomedical research ethics is meant to address the concerns for the treatment and research uses of "natural entities" deemed to possess, at least to some extent, a moral status worthy of consideration, whether they be human beings, fetuses in utero, animals, embryos, gametes, genes and so forth. We believe that traditional research ethics cannot be enough to cover all of the essential ethical traits inherent to such groundbreaking research. Traditional standards, for instance, focus on informed consent requirements for cell line or gamete donors[40] and uphold their interests relative to privacy[41-43]. Still, if embryos and stem cells can be radically bioengineered, that traditional bioethical approach is totally inadequate[44,45]. Besides, it is worth bearing in mind that bioengineering technologies can mostly be deemed as having a "dual use": while they can greatly benefit science, medicine, and public health, they are also liable to be used with malicious intent. The fundamental question is, therefore, how to put in place effective safeguards against ethical misuse[46]. Such an answer must come from a shared set of norms and ethical guidelines aimed at the highest achievable degree of harmonization among world nations that have in common a foundation of deeply-held core values. Even though an individual country was to ban some of the most controversial and dangerous bioengineering techniques, those could be brought forward elsewhere in the world, and the speed of change and progress in bioengineering has definitely outpaced regulators and lawmakers[47]. Hence, harmonizing the ways in which such practices are governed and regulated is key to ensuring that progress unfolds with all the precautionary measures required by the revolutionary potential of bioengineering innovations without conflicting with well-established bioethical principles.

Conclusions: Caution and Graduality Are Key, Both Ethically and Clinically

At a National Academy of Sciences conference in Washington, United States, in 2015, Jennifer Doudna (Nobel Prize winner for chemistry, along with Emmanuelle Charpentier, for their groundbreaking research findings on genome editing techniques), along with 500 other scholars and ethicists, urged the scientific community to refrain from embryo editing, at least for the moment, since science is still unaware of how to safely and ethically make germline changes, which are heritable, i.e., passed on to future generations[48].

In addition, another concern has been expressed in relation to bioengineering applications and the beginning of life[49,50], arising from the prospect of editing embryos or gametes for non-therapeutic purposes, in order to enhance human capabilities or selecting specific traits of humans yet to be born[51]. Under this scenario, parents could choose a variety of options for their unborn children, including everything from cosmetic traits, such as hair or eye color, to endow their offspring with greater intellectual or athletic ability. While transhumanists may consider making changes at the embryonic level as a great opportunity[52], most philosophers, bioethicists and theologians view the prospect of having "designer children" as akin to eugenics, a 19th-century and early 20th-century philosophical movement that inspired forced sterilization laws in several countries, and even provided some of the abhorrent and catastrophic intellectual frameworks for the Nazi dictatorship and its horrific pursuit of racial purity[53]. Those conflicting views highlight just how essential it is to build a solid consensus and regulatory frameworks based on international harmonization if we are to take full advantage of the amazing opportunities offered by such scientific breakthroughs for the good of all humankind while preserving and upholding human dignity and the values we as a society hold dear[54,55].

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Brännström M, Johannesson L, Bokström H, Kvarnström N, Mölne J, Dahm-Kähler P, Enskog A, Milenkovic M, Ekberg J, Diaz-Garcia C, Gäbel M, Hanafy A, Hagberg H, Olausson M, Nilsson L. Livebirth after uterus transplantation. Lancet 2015; 385: 607-616.
2) Hellström M, El-Akouri RR, Sihlbom C, Olsson BM, Lengqvist J, Bäckdahl H, Johansson BR, Olausson M, Sumitran-Holgersson S, Brännström M. Towards the development of a bioengineered uterus: comparison of different protocols for rat uterus decellularization. Acta Biomater 2014; 10: 5034-5042.
3) O'Donovan L, Williams NJ, Wilkinson S. Ethical and policy issues raised by uterus transplants. Br Med Bull 2019; 131: 19-28.
4) Zhang Y, Yan J, Han Q, Yang T, Cai L, Fu Y, Cai X, Guo M. Emergency obstetric hysterectomy for life-threatening postpartum hemorrhage: a 12-year review. Medicine (Baltimore) 2017; 96: e8443.
5) Machado LS. Emergency peripartum hysterectomy: incidence, indications, risk factors and outcome. N Am J Med Sci 2011; 3: 358-361.
6) Radnia N, Manouchehrian N, Shayan A, Shirmohamadi N, Eskandarloo T, Otogara M. Frequency and causes of emergency hysterectomy along with vaginal delivery and caesarean section in Hamadan, Iran. Electron Physician 2017; 9: 4643-4647.
7) Frati P, Foldes-Papp Z, Zaami S, Busardo FP. Amniotic fluid embolism: what level of scientific evidence can be drawn? A systematic review. Curr Pharm Biotechnol 2014; 14: 1157-62.
8) Johannesson L, Testa G, Putman JM, McKenna GJ, Koon EC, York JR, Bayer J, Zhang L, Rubeo ZS, Gunby RT, Gregg AR. Twelve live births after uterus transplantation in the Dallas UtErus Transplant Study. Obstet Gynecol 2021; 137: 241-249.
9) Anderka MT, Lin AE, Abuelo DN, Mitchell AA, Rasmussen SA. Reviewing the evidence for mycophenolate mofetil as a new teratogen: case report and review of the literature. Am J Med Genet A 2009; 149A: 1241-8.
10) Kylat RI. What is the teratogenic risk of mycophenolate?. J Pediatr Genet 2017; 6: 111-114.
11) King RW, Baca MJ, Armenti VT, Kaplan B. Pregnancy outcomes related to mycophenolate exposure in female kidney transplant recipients. Am J Transplant 2017; 17: 151-160.
12) Coscia LA, Armenti DP, King RW, Sifontis NM, Constantinescu S, Moritz MJ. Update on the Teratogenicity of Maternal Mycophenolate Mofetil. J Pediatr Genet 2015; 4: 42-55.
13) Zhang R, Deng SL, Lian ZX, Yu K. Immunosuppression in uterine transplantation. Transpl Immunol 2020; 63: 101335.
14) Williams Z. Inducing tolerance to pregnancy. N Engl J Med 2012; 367: 1159-1161.
15) Zaami S, Di Luca A, Marinelli E. Advancements in uterus transplant: new scenarios and future implications. Eur Rev Med Pharmacol Sci 2019; 23: 892-902.
16) Web24 News. First uterus transplant in Italy, the operation performed in Catania. Issued on 22nd August 2020. Available at: https://www.web24.news/u/2020/08/first-uterus-transplant-in-italy-the-operation-performed-in-catania.html
17) Testa G, Johannesson L. The ethical challenges of uterus transplantation. Curr Opin Organ Transplant 2017; 22: 593-597.
18) Piersanti V, Consalvo F, Signore F, Del Rio A, Zaami S. Surrogacy and "Procreative Tourism". What does the future hold from the ethical and legal perspectives? Medicina (Kaunas) 2021; 57: 47.
19) O'Donovan L, Williams NJ, Wilkinson S. Ethical and policy issues raised by uterus transplants. Br Med Bull 2019; 131: 19-28.
20) Zaami S, Marinelli E, di Luca NM, Montanari Vergallo G. Ethical and medico-legal remarks on uterus transplantation: may it solve uterine factor infertility? Eur Rev Med Pharmacol Sci 2017; 21: 5290-5296.
21) Idda ML, Munk R, Abdelmohsen K, Gorospe M. Noncoding RNAs in Alzheimer's disease. Wiley Interdiscip Rev RNA 2018; 9: 10.1002/wrna.1463.
22) Piergentili R, Zaami S, Cavaliere AF, Signore F, Scambia G, Mattei A, Marinelli E, Gulia C, Perelli F. Non-coding RNAs as prognostic markers for endometrial cancer. Int J Mol Sci 2021; 22: 3151.
23) Grillone K, Riillo C, Scionti F, Rocca R, Tradigo G, Guzzi PH, Alcaro S, Di Martino MT, Tagliaferri P, Tassone P. Non-coding RNAs in cancer: platforms and strategies for investigating the genomic "dark matter". J Exp Clin Cancer Res 2020; 39: 117.
24) Vallone C, Rigon G, Gulia C, Baffa A, Votino R, Morosetti G, Zaami S, Briganti V, Catania F, Gaffi M, Nucciotti R, Costantini FM, Piergentili R, Putignani L, Signore F. Non-coding RNAs and endometrial cancer. Genes (Basel) 2018; 9: 187.
25) Anastasiadou E, Jacob LS, Slack FJ. Non-coding RNA networks in cancer. Nat Rev Cancer 2018; 18: 5-18.
26) Gulìa C, Baldassarra S, Signore F, Rigon G, Pizzuti V, Gaffi M, Briganti V, Porrello A, Piergentili R. Role of non-coding RNAs in the etiology of bladder cancer. Genes (Basel) 2017; 8: 339.
27) Zhang SF, Gao J, Liu CM. The role of non-coding RNAs in neurodevelopmental disorders. Front Genet 2019; 10: 1033.
28) Zaami S, Piergentili R, Marinelli E, Montanari Vergallo G. Commentary – CRISPR-based techniques: Cas9, Cas13 and their applications in the era of COVID-19. Eur Rev Med Pharmacol Sci 2021; 25: 1752-1761.

29) Memi F, Ntokou A, Papangeli I. CRISPR/Cas9 gene-editing: research technologies, clinical applications and ethical considerations. Semin Perinatol 2018; 42: 487-500.

30) Abdal Dayem A, Lee SB, Kim K, Lim KM, Jeon TI, Seok J, Cho AS. Production of mesenchymal stem cells through stem cell reprogramming. Int J Mol Sci 2019; 20: 1922.

31) Antfolk M, Jensen KB. A bioengineering perspective on modelling the intestinal epithelial physiology in vitro. Nat Commun 2020; 11: 6244.

32) Inci I, Norouz Dizaji A, Ozel C, Morali U, Dogan Guzel F, Avci H. Decellularized inner body membranes for tissue engineering: a review. J Biomater Sci Polym Ed 2020; 31: 1287-1368.

33) Khosravimelal S, Momeni M, Gholipur M, Kundu SC, Gholipourmalekabadi M. Protocols for decellularization of human amniotic membrane. Methods Cell Biol 2020; 157: 37-47.

34) Magalhaes RS, Williams JK, Yoo KW, Yoo JJ, Atala A. A tissue-engineered uterus supports live births in rabbits. Nat Biotechnol 2020; 38: 1280-1287.

35) Kuo CY, Baker H, Fries MH, Yoo JJ, Kim PCW, Fisher JP. Bioengineering strategies to treat female infertility. Tissue Eng Part B Rev 2017; 23: 294-306.

36) Negro F, Varone MC, Del Rio A. Advances in medically-assisted procreation technologies: can malpractice claims and "reproductive damage" be identified. Clin Ter 2020; 171: e225-e228.

37) Frith L, Blyth E. Assisted reproductive technology in the USA: is more regulation needed? Reprod Biomed Online 2014; 29: 516-523.

38) Montanari Vergallo G, Zaami S, Bruti V, Signore F, Marinelli E. How the legislation in medically assisted procreation has evolved in Italy. Med Law 2017; 36: 5-28.

39) Taylor DA, Caplan AL, Macchiarini P. Ethics of bioengineering organs and tissues. Expert Opin Biol Ther 2014; 14:879-882.

40) Zaami S. Assisted heterologous fertilization and the right of donorconceived children to know their biological origins. Clin Ter 2018; 169: e39-e43.

41) Hadizadeh-Talasaz F, Simbar M, Latifnejad Roudsari R. Exploring infertile couples' decisions to disclose donor conception to the future child. Int J Fertil Steril 2020; 14: 240-246.

42) Pennings G. Disclosure of donor conception, age of disclosure and the well-being of donor offspring. Hum Reprod 2017; 32: 969-973.

43) Montanari Vergallo G, Marinelli E, di Luca NM, Zaami S. Gamete donation: Are children entitled to know their genetic origins? A comparison of opposing views. The Italian State of Affairs. Eur J Health Law 2018; 25: 322-337.

44) Morsy A, Flexman J. Ethics in biomedical engineering. Annu Int Conf IEEE Eng Med Biol Soc 2008; 2008: 3823.

45) Montanari Vergallo G, Busardò FP, Zaami S, Marinelli E. The static evolution of the new Italian code of medical ethics. Eur Rev Med Pharmacol Sci 2016; 20: 575-580.

46) Baker HB, McQuilling JP, King NM. Ethical considerations in tissue engineering research: case studies in translation. Methods 2016; 99: 135-144.

47) Napoletano S, Piersanti V, Rallo G. CRISPR -Cas9: a groundbreaking new technique which ushers in new prospects and just as many doubts. Clin Ter 2021; 171: e52-e54.

48) Sanders R. CRISPR inventor calls for pause in editing heritable genes. Berkeley News. Issued on 1st December 2015. Available at: https://news.berkeley.edu/2015/12/01/crispr-inventor-calls-for-pause-in-editing-heritable-genes/

49) Ricci G, Campanozzi LL, Marinelli S, Midolo E, Ruggeri L. The human embryo, subjectivity and legal capacity. Notes in the light of art. 1 of the Italian law on "medically assisted procreation". Clin Ter 2019; 170: e102-e107.

50) Greely HT. CRISPR'd babies: human germline genome editing in the 'He Jiankui affair'. J Law Biosci 2019; 6: 111-183.

51) Marinelli S, Del Rio A. Beginning of life ethics at the dawn of a new era of genome editing: are bioethical precepts and fast-evolving biotechnologies irreconcilable? Clin Ter 2020; 171: e407-e411.

52) Porter A. Bioethics and transhumanism. J Med Philos 2017; 42: 237-260.

53) Almeida M, Diogo R. Human enhancement: genetic engineering and evolution. Evol Med Public Health 2019; 2019:183-189.

54) Montanari Vergallo G, Ciallella C. Comment on the article by Zaami S, et al. "Advancements in uterus transplant: new scenarios and future implications". Eur Rev Med Pharmacol Sci 2019; 23: 892-902. Eur Rev Med Pharmacol Sci 2019; 23: 10178-10181.

55) Guntram L, Zeiler K. The Ethics of the Societal Entrenchment-approach and the case of live uterus transplantation-IVF. Med Health Care Philos 2019; 22: 557-571.