

# Advancements in uterus transplant: new scenarios and future implications

S. ZAAMI<sup>1</sup>, A. DI LUCA<sup>2</sup>, E. MARINELLI<sup>1</sup>

<sup>1</sup>Department of Anatomical, Histological, Forensic and Orthopaedic Sciences, Sapienza University of Rome, Rome, Italy

<sup>2</sup>Institute of Public Health, University of the Sacred Heart, Catholic University of Rome, Rome, Italy

**Abstract:** Women suffering from Uterine Factor Infertility (UFI) arising from congenital conditions (e.g., Rokitansky-Kuster-Hauser syndrome) or hysterectomy can fulfill their wish to achieve motherhood only by resorting to surrogacy, which is, however, banned in most countries. Medical research has long been looking into uterus transplant (UTx), which may constitute a valuable alternative for such patients. Following decades of animal testing and clinical trials, several successful pregnancies have been carried to term. Yet UTx is still to be considered as an experimental procedure. The report's authors believe UTx has the potential to become a mainstream surgical practice, but for the time being, several ethical issues need to be weighed in before it does.

Key Words

UTx historical timeline, Reproductive rights, ASRM report, Uterine tissue engineering

## Introduction

A remarkable innovation in the realm of assisted reproductive technologies is uterine transplantation (UTx), described as 'a new type of quality of life-enhancing, as well as a life-giving transplantation'. The world's first live birth of a child after uterus transplant, using a female living donor and recipient, took place in Sweden in 2013<sup>1,2</sup>. Currently, 12 health care centers perform uterus transplants globally (in Sweden, Germany, Serbia, Turkey, Saudi Arabia, Lebanon, United States, Brazil, China, and India). In June 2018, the first health care institution in Italy dedicated to Utx opened in Catania, and there is already a waiting list for the procedure of women from different parts of Italy. The Italian Utx center will be the second such facility in Europe, after the Swedish one in Gothenburg, and will cater to UFI

sufferers. In the United Kingdom, Womb Transplant UK says that it has enough funds to pay for three transplants but will need hundreds of thousands of pounds more to complete a total of 15 transplants – five of these with living, related donors. UTx's ultimate goal is fertility restoration in female patients with uterus factor infertility (UFI), which is claimed to affect roughly 1.5 million women globally.

Studies have been focused on the significant ethical, legal and policy issue concerns arising from this advancement. Robertson<sup>3</sup> argues that if UTx becomes safe and effective, the case for offering UTx to all women with UFI is strong. Unfavorable medical conditions that affect the uterus, making it impossible to achieve pregnancy, include a lack of uterus following its surgical removal (hysterectomy) and Rokitansky-Kuster-Hauser syndrome (Müllerian agenesis), a rare congenital malformation that carries varying degrees of vaginal or uterine hypoplasia, making the uterus unfit for pregnancy<sup>4</sup>. Women who might benefit from uterus transplant are many. There are estimates 15,000 women with uterine factor infertility in the UK and 50,000 in the USA<sup>5</sup>. Up to 15% of the reproductive population is infertile, and 3 to 5% of all cases of infertility are caused by uterine dysfunction, as those mentioned above<sup>6-8</sup>. This abnormality generally leads women to consider surrogacy or adoption. In many countries, such as Japan, Sweden, and Italy, surrogacy is still heavily restricted or even banned<sup>9</sup>.

## ***Uterus Transplant: a Timeline of Significant Instances***

Pioneering work for UTx comes from the Gothenburg group that has also helped many centers around the world get started. Most recently, this group has also refined the live donor procedure with a robotic approach. Many open questions remain that will need to be answered.

There is a clear demand for a long-term psychological and medical follow-up of donors, recipients, and children. Uterus transplant programs will not only need to assure a multi-disciplinary approach but will also need to implement quality assessment and process improvement measures.

Aspects of donor age, consequences of IRI, uterus-specific aspects of rejection and immunosuppression are some of the critical questions that have not yet been studied enough.

Uterus transplantation provides a unique opportunity with limited time for immunosuppression. Nevertheless, consequences need to be followed and documented long-term after the discontinuation of immunosuppression<sup>10</sup>.

Table I lays out the most remarkable cases, whether successful or not, of UTX performed globally<sup>11</sup>. It is noteworthy that so far, only UTX from live donors has been successful in order to achieve a successful pregnancy, with the sole exception of the one case that occurred at the Hospital das Clínicas in São Paulo, Brazil, on September 2016.

### ***Ethical Concerns Linger***

The uterine transplant has been ethically controversial since the beginning. An initial reaction was that UTX constitutes “technological overkill”: a costly elective procedure so that women might experience pregnancy and deliver their own children when instead less costly and invasive options may be available. One key question that remains unclear is whether the concept of procreative liberty should include a right to ‘gestate’, and, if such a right does exist, whether it should be restricted to women suffering from UFI, while Robertson<sup>3</sup> describes UTX as a ‘technology as less dramatic in scope than other ART innovations, but important for affected women’. In literature exploring the context of assisted reproductive technologies meant to overcome infertility, it has been cogently argued that people have a ‘prima facie’ right to procreative or reproductive autonomy<sup>12</sup>. Dworkin<sup>13</sup> has defined the right of procreative autonomy as “an individual right of people to exercise control and shape their role in reproduction, provided that the State has no compelling reason to deny them such a prerogative. In agreement with that assumption, Harris<sup>14</sup> argues that in all democracies, the “democratic presumption” is that individual choices will not be interfered with unless good and sufficient grounds can be produced for so doing. Based on such democratic precepts, the onus to prove that allowing the exercise of such a right

would cause demonstrable harm is on those who seek to rebut such a presumption<sup>15</sup>. Robertson<sup>16</sup>, a bioethicist at the University of Texas, who has made a substantial contribution to the literature on procreative liberty, has laid out a theoretical framework made up of three fundamental principles. Firstly, a “right” exists to have genetically related children as well as a right to choose not to. As pointed out by the author, the centrality of reproduction to personal identity and dignity means that the moral right to reproduce ought to be respected whenever possible. Secondly, although such a right has “presumptive primacy”, it is not absolute and can and should be limited if the exercise of procreative liberty creates ‘harm’. It is those who seek to limit reproductive choice that should bear the burden of proving that the reproductive actions at issue would create substantial harm and, therefore, could be justifiably limited<sup>17</sup>. Thirdly<sup>18</sup>, Robertson believes the right to procreative liberty should be viewed as a negative one: the State cannot interfere in individuals’ personal reproductive choices, but crucially, it does not have any positive obligations to assist people with their reproductive decisions: it is therefore a matter of broader social policy and resource allocation. Other authors disagreed with those views: Sparrow<sup>19</sup> believes that the right to procreative freedom should be a positive one: the only way to effectively exercise their procreative liberty for those who have issues conceiving or gestating, is through the positive assistance of third parties and state institutions. Aside from financial considerations, as mentioned before, uterine transplantation carries complex ethical issues. The ethical controversy related to uterine transplant arises, in part, from the principles of nonmaleficence and autonomy. The principle of nonmaleficence dictates that unnecessary risk should be avoided and harm minimized, whereas the principle of autonomy advocates for an individual’s right to self-governance. In the case of an individual desiring uterine transplant to align physical body with personal identity but not intending to gestate a child, the ethical demand for respect of autonomy seems equivalent to that of a woman who wants uterine transplant for the purpose of childbearing. However, a significant factor involved in justifying the transplant of this organ is its transitory nature: after the recipient completes her reproductive potential or after she exits child-bearing age, a hysterectomy should be performed so that antirejection medication is no longer necessary. In the case of a person desiring

**Table I.** UTX historical timeline.

| Location/date of surgery  | Type of UTX  | Organ origin   | Outcome  |
|---|--|--|--|
| Dresden Municipal Women's Clinic, Germany 1931                        | <i>The first uterus transplant in history</i>  | Unknown  | Death, on September 13, 1931, three months after the surgery, of cardiac arrest brought on by the infection, after the patient's immune system rejected the transplanted uterus and she developed an infection.              |
| Saudi Arabia April 2000   | A 26-year-old with a history of hysterectomy due to post-partum hemorrhage   | <i>First ever from live donor</i> , a 46-year-old  | Unfavorable: organ had to be removed after 99 days due to blood clots and progressive necrosis   |
| Akdeniz University Hospital in Antalya, Turkey 2011                   | A 21-year-old patient with Rokytanski syndrome   | <i>First ever UTX from deceased donor</i>  | The transplanted uterus was viable and the patient underwent embryo transfer 18 months after the operation, presented two pregnancies spontaneously aborted before 6 weeks of gestational age                                |
| Sahlgrenska University Hospital at Gothenburg University, Sweden 2012 | The first clinical trial involving nine women, receiving uteri from live donors. Among them, two patients, aged 32 and 37 years, both lacked a uterus; one woman had hers removed due to cervical cancer and the other was born without one. | <i>First ever uterine mother-to-daughter transplants</i>   | <i>One of the patients successfully carried a pregnancy to term, giving birth to baby boys by C-section in September 2014 (first birth from live donor UTX)</i>  |
| Cleveland Clinic, United States 24 <sup>th</sup> February 2016        | 26-year-old woman  | From deceased donor, a healthy woman in her 30's, who "died suddenly," according to Clinic   | The transplant failed due to a complication: a yeast infection by <i>Candida albicans</i> had caused damage to the local artery compromising the blood support of the uterus and necessitating its removal on 8th March 2016 |
| Hospital das Clínicas in São Paulo, Brazil September 2016             | The recipient is a 32-year-old who had Mayer-Rokitansky-Küster-Hauser syndrome   | From deceased donor, a mother of three in her mid-40s who died from bleeding on the brain.   | <i>First ever successful pregnancy: a healthy baby girl was born in December 2017, (first birth from deceased donor UTX)</i>   |
| Baylor University Medical Center, Dallas, United States November 2017 | Woman who had been born without a uterus   | Uterus donation from a 36-year-old non-directed living donor   | The first birth as a result of a womb transplant in the United States  |
| Belgrade University Children's Hospital, Serbia March 2017            | 38-year-old patient born without a uterus due to a congenital malformation   | <i>First ever uterus transplant between twin sisters</i>   | Favorable: the patient gave birth on 28th June, 2018 at St. Orsola Hospital in Bologna, Italy  |
| Galaxy Care Hospital in Pune, Maharashtra, India 18th May 2017        | The 26-year-old patient had been born without a uterus   | The donor was the patient's 44-year-old mother   | Successful childbirth through a Caesarean section at Galaxy Care Hospital on October 2018  |
| Bellevue Medical Center, Mansourieh, Lebanon 21st June 2018           | The 26-year-old Jordanian patient suffered from uterine factor infertility   | The patient received her new uterus from her 50-year-old mother (this was the first UTX performed in the Middle East and North Africa) | None reported yet  |

a uterine transplantation for a reason other than gestating a pregnancy, that outcome would not ultimately occur, because such a person would presumably desire to keep the transplanted uterus

indefinitely, whether on self-identity grounds or for different psychological reasons. The weight of the principle of nonmaleficence, which is meant to protect patients from undue risk, ought to be

deemed prevalent under such conditions, as the risks to the recipient are greater, particularly in the long term. For a person seeking to receive a uterine transplant to improve the alignment between physical body and personal identity, the desire to have a uterus is a first-order desire, whereas the desire to improve the alignment between physical body and personal identity is a second-order desire. The second-order desire could be fulfilled through psychologically based therapies, which entail far less risk than a transplant<sup>20</sup>. However, it is worth pointing out that there does not seem to be a significant ethical reason to rule out the execution of uterine transplant on a male or transsexual patient. Should a male or transsexual individual determined to gestate a child have a lesser claim to the fulfillment of that desire than their female counterparts? In fact, the autonomy principle is not sex-specific. This right is not absolute, but medical science has no bearing in determining what an unreasonable demand is from a person of sound mind, except when it is about medical and surgical risk and the allocation of resources. For instance, a man who identifies as a woman, arguably suffers from UFI, and that condition is no functionally different than the case of a cisgender female with congenital UFI. Regardless of the substantial surgical difficulties involved, such a patient's right to exercise self-governance, when it comes to reproductive potential, should arguably be viewed as equal to her cisgender female peers and considered worthy of respect<sup>21</sup>.

Nonetheless, several analysts have addressed the thorny question of whether a case can be made for the public funding of UTx in countries with publicly funded universal health care coverage, such as the United Kingdom, France, Italy among others<sup>22</sup>. Clearly conflicting views can be observed on that point; we still believe that the responsibility to make such policy decisions ought to rest with national lawmakers to make that determination<sup>23,24</sup>.

In that regard, it is worth considering just how different uterus transplants are from other radical ART techniques such as gestational surrogacy. While both aim to create pregnancies, the reference to other women's wombs in the title points to the concept of disembodiment, which is only true in the case of uterus transplants: UTx, in fact, removes from one woman the organ in which a fetus can grow and implants it in the body of another. Thus, what happens to the donor, the provider of the necessary reproductive organ, removes her from the physical act of gestation and vests that

responsibility upon another woman<sup>25</sup>. On the other hand, a gestational surrogate's body is fully encompassed by her role as a gestational carrier. Her involvement lasts months, and unfolds in a way that is far more invasive and more rife with potential emotional and psychological difficulties for all parties involved. Ultimately, surrogacy is a technique by which a couple that has entered into a relationship and is unable or unwilling to have children (including same-sex partners) turn to a surrogate mother outside the couple in order to have her bear a child conceived via *in vitro* fertilization and possibly using the egg of yet another woman donor and donated sperm as well. After the pregnancy has been carried to term, the newborn will be handed over to the intended parents (the commissioning couple). At that point, the intended parents become the child's legal parents, even though they may share no biological tie with the child whatsoever. Such children may never find out about their genetic origins<sup>26</sup>. So-called surrogacy tourism, however, is not necessarily a viable solution unless the intended parents' home countries legally recognize children born through surrogacy. The European Court of Human Rights has overturned such a ban in France<sup>27</sup>, thus paving the way for children born via surrogacy abroad to be recognized by the commissioning couple's home countries. Countries of origin may also require that the intended parents be married. Israel, for example, has refused to recognize the children of same-sex couples and single women who travelled abroad for surrogacy. As Robertson<sup>28</sup> points out, basically, countries that do not allow repatriation of surrogacy children are transferring surrogacy tasks and responsibilities on to other countries because of the moral and policy objections which they have against hiring a surrogate on their own soil to gestate one's child. UTx may prove vitally important for Muslims whose faith under sharia law forbids surrogacy but not uterus transplant<sup>29,30</sup>. Furthermore, medically assisted procreation leads to the creation of large numbers of supernumerary embryos, which are stored via cryopreservation<sup>31,32</sup>, and at times give rise to conscientious objection issues with health care personnel<sup>33</sup>.

### ***UTx: Not Life-Saving but Life-Enhancing***

Uterine transplants are ethically controversial in part because, unlike most solid organ transplantation, they are not life-saving. Yet they do improve recipient well-being and quality of life in a significant way. This benefit is comparable

to the benefits that recipients of vascularized composite allografts (VCAs, which include hand, arm, face, larynx, and now penis transplants) obtain. No one would suggest that these transplants do not significantly serve the well-being of recipients, although they are not life-saving. Uterus transplant aims at relieving reproductive suffering, which may include ostracism, shame, depression, and sadness. The strongest case for uterine transplant is a patient suffering from severe uterine dysfunction in a country where surrogacy is prohibited or so strictly regulated that it is not practicably accessible. In that case, the uterus transplant provides both the gestational experience and, more importantly, a genetic child, which the transplant recipient would not otherwise be able to have. Even where surrogacy is legally available, in the USA, for instance, a woman might still prefer womb transplant because of moral concerns about using a paid surrogate, the desire to bear her own genetic child, and the psychological and social complications of entrusting her embryo and future child to another woman. Another fear is that the choice to get a uterine transplant may be spurred by an internalized stereotype that a woman is not whole unless she bears and rears her own child, no matter how great the risk posed to her or the donor's health and that of the fetus/child to be. It is also critical to make sure and confirm that the woman herself expresses strong interest in undergoing uterine transplant without pressure from her spouse or family expressing cultural norms and expectations about what it should mean to be a woman and wife.

### ***The Procedure is Still Hazardous***

Undergoing a uterus transplant procedure would undoubtedly be a difficult choice even if it was shown to be safe and effective: donor participation in a transplant is not devoid of significant physical risks: Robertson et al<sup>34,35</sup> recount many of those risks for living donors, who will have to endure a radical hysterectomy to remove the uterus, given the need to preserve the organ for transplant. This entails known and well documented surgical risks, e.g., post-surgery infections, in addition to the length of surgery (shown in medical literature to last 7-11 hours), the longer duration of anesthesia, unfavorable (and potentially deadly) reactions, the high complexity of the surgery due to the difficulty of separating the aortic arteries and veins that nourish the uterus and supporting structures, potential injury to the

ureters, due to their closeness to vein and artery local systems. Recipients face multiple physical risks too, including lengthy surgery, the need immunosuppressing drugs to stave off rejection of the transplanted organ, potential harm to a fetus growing in a transplanted womb, and as always, the emotional weight of participating in what is currently still an experimental procedure with an unknown outcome, as well as the lengthy, highly complex surgery itself. Consequently, women will have to be carefully screened, in a supportive relationship with a clear understanding of the risks and benefits. For example, uterus transplant may enable them to carry and birth their own child, but because no nerves are reattached, recipients will not feel the movement of the fetus during the pregnancy. Uterus transplants are not life-saving transplants, but they are life-enhancing in the same way as hand, face, penile, and other types of transplants: this must weigh significantly in our balance of whether women should put themselves at risk in order to donate them. The UK, which has close regulation of reproductive technologies in general, presently forbids live donor transplants because of the risk-benefit analysis tips toward only using uteri from cadaveric sources. Beyond the physical risks, well-founded concerns do exist about other ways in which the uterus transplant world could give rise to coercion or exploitation for both donors and recipients. From the donor side, just as legitimate concerns exist about how familial coercion or pressure might weigh on a woman asked to be a surrogate for a close friend or family member, the same holds true in the context of uterus transplants. The lack of compensation does not mean that there will not be pressure to participate in a process that a woman might otherwise identify as completely unworthy of consideration. Emotional risks include the need to ensure that donors and recipients have access to adequate support systems to assist them not only through surgery, but in the long ensuing period of recovery. UTX being a relatively new and experimental procedure, failure is a distinct possibility: a deep sense of anguish and devastation could be experienced when some transplants turn out unsuccessful and have to be removed, as it will inevitably happen, or when pregnancy cannot be achieved even after a successful transplant, or when a fetus is miscarried or stillborn<sup>36</sup>. Women should be informed of the risks and benefits of this still experimental procedure and the many possibilities of failure, but given how fraught the context is and, in some cases, how deeply desired

pregnancy may be, it is inevitable that the free nature of consent might be compromised, at least on some occasions<sup>37</sup>. Uterine transplant, however, is likely to be sought only when other options are not feasible. Without transplantation, a woman without a uterus or suffering from UFI would be left with no alternative to have genetic offspring but a gestational carrier, which is itself viewed by many as ethically objectionable.

### ***UTx From Living or Deceased Donors?***

Because of the risks to donors, the WHO in 2010 issued a recommendation stating that organ donations from deceased donors should always be developed to their maximum potential, to minimize risks to live donors. Yet, because of the shortage of suitable organs from deceased donors, donations from live donor are necessary in order to meet current patient needs<sup>38</sup>. Procurement of the uterus should follow standard protocols in which initial screening is done by the local organ procurement organization (OPO). An acceptable risk/benefit ratio for the recipient does not automatically mean that UTx should become a mainstream therapeutic option. One must also take account of the source of the uterus being transplanted: whether from a living donor or a cadaveric source. Each presents a peculiar set of related issues, and it is too early to establish conclusively which path is preferable in terms of effectiveness. Generally, in organ transplants living donors are preferable, if only because there are so few cadaveric organs available: living donors provide almost 50% of kidney transplants, at relatively small risk to donors (0.03% mortality and <1% risk of major morbidity)<sup>39</sup>. Since a uterus is not necessary for life, as hearts and lungs are, and is routinely removed in hysterectomies, it might be donated by living donors too. Family or friends might choose to do so, particularly if they have completed their own families. Another factor to be accounted for is that most hysterectomies now occur either by laparoscopy, or abdominal surgery. In either case the duration and medical outcomes are likely to be more favorable than the more intensive hysterectomy done for a donation. As Stillman<sup>40</sup> and Gainotti<sup>41</sup> argue, since the mortality and morbidity rate of radical hysterectomy is greater than that of pregnancy, the health risk of living donation should bar living uterus transplants if surrogacy is available. A competent woman's right to donate is rooted in the principle of autonomy, if she finds that the benefits outweigh the risks and a healthcare

team willing to perform the surgery is available. The long-term consequences on donor health from a hysterectomy are low, but uterus donation is much more complicated than even a radical hysterectomy because long veins and arteries must be removed. Psychological factors are also at play with living donation. The donation is not reproductive in itself, since no gametes are donated, and yet it does allow reproduction by the recipient to occur. With uterine transplants, the donor is providing the organ so that the recipient may then gestate and give birth. Yet there are likely to be symbolic and psychological meaning for the donor: in fact, she is the one who provides the actual organ of gestation. Such issues will have to be dealt with prior to donation, so that the donor does not believe that she is "the mother" of the child simply because she provided the organ essential for the recipient's reproduction. Mothers who donate their uterus to their daughters would thus be enabling their daughter to give birth in the same uterus that had nourished her. In some cases, donors may experience even harsher a sense of loss than many women feel when they undergo a hysterectomy. Altruistic stranger donations, common in kidney transplantation, are less likely for uterus donation. Professional or national bans on payments for donor organs would also make living stranger donations unlikely. Counseling will be vitally important in selecting appropriate candidates for transplants. Any candidate receiver must be psychologically prepared to undergo major surgery to receive a uterus from another woman. If surrogacy is available but unacceptable to the patient, she should be willing to cope with the great physical burdens that a living donor friend or family member would incur to help her and the obligations of reciprocity, which would arise from it. Cadaveric donation entails no such issues: there is no risk of injury to the donor, and it may provide more organs than living donors alone would.

### ***Recent Stances From International Medical Institutions on UTx***

In 2006, the World Medical Association issued a Statement on Human Organ Donation and Transplantation, stressing that experimental and/or morally controversial procedures such as Utx need stricter scrutiny and targeted guidelines<sup>42</sup>. A preliminary scientific overview on Utx occurred in 2012, when a multi-national group of four research teams who have worked for over 15 years on bringing UTx to reality for patients issued

the “Indianapolis Consensus” stating that “(...) clinicians have an obligation toward the patients and society, to closely monitor and register the outcome of the procedure and to define a satisfactory outcome as no less than a live birth. If this is not achieved, the procedure should not be allowed to be instituted as a treatment option”. According to the Indianapolis consensus, before becoming an accepted practice, UTx must meet the criteria for any surgical innovation: research background, field strength and institutional stability; and satisfy accepted bioethical principles (respect for autonomy, beneficence, non-maleficence and justice) and their application. Such standards will be espoused by the Montreal Criteria as well. However, the Indianapolis Consensus does not provide exact numbers or gives any other indications in this sense<sup>43</sup>. The “Montreal Criteria for the Ethical Feasibility of Uterine Transplantation”, which were developed at McGill University and published in *Transplant International* in 2012, offer a wide array of standards for the purpose of solving that dilemma: they are a set of criteria deemed necessary for the ethical execution of the uterine transplant in humans. The findings were presented at the International Federation of Gynecology and Obstetrics’ 20th World Congress in Rome in October 2012. In 2013 an update to “The Montreal Criteria for the Ethical Feasibility of Uterine Transplantation” was published in *Fertility and Sterility* and has been proposed as the international standard for the ethical execution of the procedure<sup>44</sup>.

The conditions set by the Montreal criteria for the recipient, the donor, and the health care team, reassert Moore’s criteria regarding institutional stability and the provision informed consent to both parties<sup>45</sup>. These criteria have three components: laboratory background, field strength, and institutional stability.

Moreover, the Montreal Criteria state that a person is only eligible for a uterine transplant if the driving motivation is to gestate a pregnancy, a state in which the risk is justified by the transience of the transplant. Besides, an extremely relevant issue is the one centered on patients who undergo transplants and choose to achieve a pregnancy afterwards, considering the potential damage to the fetus that may stem from immunosuppressive therapies, although current studies do not appear to be conclusive in that regard.

In that respect, the National Transplantation Pregnancy Registry (NTPR), established in 1991, investigates pregnancy outcomes of female trans-

plant recipients. Fetal malformation due to immunosuppressive agents has been observed to be a real concern. In 2016 the US based National Transplantation Pregnancy Registry (NTPR) expanded to include participation worldwide and was renamed the Transplant Pregnancy Registry International (TPR). Data have accumulated for over 2 decades since the establishment of the registry, and the TPR has proposed guidelines for management of pregnancy in transplantation recipients. The NTPR also showed the prevalence of major structural malformations to be 4-5%, whereas that in pregnant women without disease is circa 3%. Risks for obstetric complications during pregnancy, including spontaneous abortion, premature delivery, low birth weight, IUGR, and hypertension/preeclampsia, are greater after organ transplantation<sup>46</sup>.

### ***Immunosuppressive Therapies Entail Risks, However Limited***

Specialists are remarkably experienced in how to plan and manage pregnancies after transplant, considering that over 1200 children were born to women using immunosuppressive agents following a transplant<sup>47</sup>. Even though most maintenance immunosuppressive regimens have not been shown to affect the outcome of posttransplant pregnancies, mycophenolic acid products are associated with an increased incidence of spontaneous abortion and an increase in the incidence and a specific pattern of birth defects. When counseling transplant recipients about a perspective of pregnancy in terms of safety, the health of the mother, her graft, and the developing fetus all need to be taken into account<sup>48</sup>.

Variable degrees of impact have been observed in immunosuppressive drugs. Exposure to azathiopine, prednisone, sirolimus, and other calcineurin inhibitors are believed to cause fewer birth defects or preterm delivery than mycophenolate products such as mofetil. This enables drugs to be used that are less associated with low birth weight and preterm delivery, so that transplant recipients may give birth. In general, physicians have not found that such a ‘higher frequency of pregnancy-associated disorders such as preeclampsia, preterm delivery, acceleration of hypertension, new-onset diabetes mellitus, and newly arising infection’ may take place in pregnant transplant recipients to bar pregnancy. It is a reason to assume that the risk of immunosuppression, which is reasonably tolerable for pregnancy in liver and kidney recipients, ought to

be so for recipients in research studies of womb transplant. Nonetheless, should those risks turn out to be more significant than expected, that could constitute a remarkable factor in arguing against uterus transplant as a mainstream therapy<sup>49</sup>. Several systematic studies have assessed immunosuppressant drugs during pregnancy in transplanted women, in terms of their safety, on the basis of a United States Food and Drugs Administration classification scale; based on that standard, there is no evidence associating the use of steroids to any risk in humans and no evidence of teratogenicity for steroids (FDA classification: B), whereas the use of Cyclosporine, Tacrolimus, Everolimus/Sirolimus may entail a degree of risk (classified by the FDA safety classification as “C”), specifically preterm birth, transient hyperkalemia and renal impairment, although insufficient data are available on the use of mTOR (mammalian target of rapamycin) inhibitors in pregnant women<sup>50</sup>. Azathioprine and mycophenolate mofetil (MMF), as potentially the riskiest type of immunosuppressants, are classified as “D” (i.e., presenting positive evidence of risk), and could determine prematurity and low birth weight have been observed in pregnancies with azathioprine medication, whereas the use of MMF is strictly contraindicated in pregnancy and has been associated with miscarriage as well as various types of malformations in the fetus<sup>51,52</sup>.

The most relevant and recent analysis centered on UTx is the September 2018 report from the American Society for Reproductive Medicine, which outlines a range of key points (Table II).

Moreover, the ASRM outlines several advantages and disadvantages according to UTx from living or deceased donors (Table III).

Ultimately, however, the ASRM points out three lingering doubts as to uterus transplant feasibility and its potential to become standard surgical practice.

Firstly, which approach is to be deemed preferable between living and deceased donor?

Secondly, it is not clear whether, in living donors, utero-ovarian veins can be used in place of the uterine veins for the entire venous return of the uterus: a key point, in light of the procedure’s complexity that arises, in part, from the uterine vascular structures. Lastly, as previously highlighted, consequences (particularly long term) of anti-rejection therapies need to be assessed and thoroughly supervised, for both mothers and babies. Uterus transplantation has advanced rapidly from an experimental procedure in animals to a

**Table II.** ASRM key points on UTx.

|  |
|--|
| <ul style="list-style-type: none"> <li>• Neonatal and long-term pediatric outcomes need to be collected.</li> </ul>  |
| <ul style="list-style-type: none"> <li>• Uterus transplantation should be performed within an Institutional Review Board (IRB) – approved research protocol.</li> </ul>  |
| <ul style="list-style-type: none"> <li>• Uterus transplantation is an experimental procedure for the treatment of absolute uterus-factor infertility (UFI).</li> </ul>   |
| <ul style="list-style-type: none"> <li>• Uterus transplantation teams should be well-coordinated and multidisciplinary.</li> </ul>   |
| <ul style="list-style-type: none"> <li>• Surgical training with animal models and/or cadaver labs is necessary prior to attempt transplantation in human subjects.</li> </ul>  |
| <ul style="list-style-type: none"> <li>• The organ used during uterus transplantation can be from living or deceased donors.</li> </ul>  |
| <ul style="list-style-type: none"> <li>• Transparent inclusion and exclusion criteria should guide selection of transplantation recipients.</li> </ul>   |
| <ul style="list-style-type: none"> <li>• Standardized reporting on outcomes of uterus transplantation is desirable to assess the true risks, benefits, and outcomes associated with this procedure.</li> </ul>                                       |
| <ul style="list-style-type: none"> <li>• Consistent with all organ transplantations, the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) is the supportive organization for data collection.</li> </ul> |

successful clinical application. Nevertheless, for the time being, UTx should still be considered a clinical experimental procedure until a sufficient amount of experience has been collected from clinical trials, expected to take place over the next 1-2 years. Given the clinical demand, the volume is expected to rise, and programs have already initiated in various facilities worldwide.

***A Future Prospect for UTx: Organ-Engineering Technology***

A future prospect for Utx comes from some Swedish researchers, who are looking into tissue engineering principles in general and in particular strategies on how to create a bioengineered uterus that could be used for transplantation, without risky donor surgery and no need for immunosuppression in recipients.

Studies regarding the decellularization of organs/tissues which may be recellularized using autologous somatic/stem cells, seem promising. Organ-engineering, while still at the experimental stages, makes it possible, at least hypothetically, to pursue a twofold solution: one involving organs unfit to be transplanted (and that are eventually decellularized) and one that uses a synthetic scaffold. Those two different kinds of framework will then be transplanted after a recellularization



**Table III.** Comparison of living vs. deceased-donor models.

| Donor type          | Pros  | Cons   |
|---------------------|---|--|
| From living donor   | <ul style="list-style-type: none"> <li>• Ability to rely on detailed medical/surgical history</li> <li>• Donor and recipient's physical closeness</li> <li>• More flexible scheduling and assessment process</li> </ul> | <ul style="list-style-type: none"> <li>• Pelvic surgery and correlated hazards</li> <li>• Coercion or pressure to become a donor</li> <li>• Psychological distress and sense of guilt with unfavorable outcomes</li> <li>• Higher risk relative to older organ</li> <li>• Oophorectomy may be needed in cases of use of ovarian vessels</li> </ul> |
| From deceased donor | <ul style="list-style-type: none"> <li>• No risk for donors</li> <li>• Organs from younger donors</li> <li>• A wider variety of vascular pedicles and ovarian vessels available</li> </ul>                              | <ul style="list-style-type: none"> <li>• Preoperative assessment may turn out incomplete</li> <li>• Dearth of transplantable organs and unsuitable scheduling and location</li> <li>• May turn out difficult to gain consent from next of kin</li> </ul>   |

procedure by the recipient's stem cells, hopefully becoming as functional as any transplanted organ; the greatest benefit would be to eliminate the need for immunosuppressive therapy<sup>53</sup>.

In particular, uterine decellularization and recellularization protocols have been tested in the rat: bioengineered tissue was used to mend uterine defects. The patched rat uteri had been capable of carrying pregnancies to term.

Spanish and American researchers in 2016 carried out the decellularizing of pig uterus, the first pilot study with large whole reproductive organs.

This field has to be explored further in several animal models, including nonhuman primates, before any possible clinical trial<sup>54</sup>.

## Conclusions

Will advancements make UTx obsolete? Innovative techniques may eventually be instrumental in solving ethical and medicolegal issues posed by UTx and transplantations in general. Technological advancements are known to often entail bioethical quandaries, and yet, in the case of UTx, the opposite may become true: bioengineering would make resorting to donors (and related risks) unnecessary, by using autologous cells, and might eliminate the need for immunosuppression and the correlated complications, as well as the complexities inherent to gaining a truly informed consent. It is reasonable to assume that UTx might soon, and hopefully, become an outdated practice.

## Authors' contributions

Liaoning Provincial Science and Technology Department - Jinzhou Medical University Joint Fund Project (No. 20170540336).

## Conflict of Interests

The authors declare no conflicts of interest.

## References

- 1) DAHM-KÄHLER P, DIAZ-GARCIA C, BRÄNNSTRÖM M. Human uterus transplantation in focus. *Br Med Bull* 2016; 117: 69-78.
- 2) 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.
- 3) ROBERTSON JA. Other women's wombs: uterus transplants and gestational surrogacy. *J Law Biosci* 2016; 3: 68-86.
- 4) 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.
- 5) GRADY D. First uterus transplant in U.S. bolsters pregnancy hope of many, *New York Times*, Feb. 25, 2016.
- 6) WATANABE K, KOBAYASHI Y, BANNO K, MATOBA Y, KUNITOMI H, NAKAMURA K, ADACHI M, UMENE K, KISU I, TOMINAGA E, AOKI D. Recent advances in the molecular mechanisms of Mayer-Rokitansky-Küster-Hauser syndrome. *Biomed Rep* 2017; 7: 123-127.
- 7) FLYCKT R, DAVIS A, FARRELL R, ZIMBERG S, TZAKIS A, FALCONE T. Uterine transplantation: surgical innovation in the treatment of uterine factor infertility. *J Obstet Gynaecol Can* 2018; 40: 86-93.
- 8) MILLIEZ J. Uterine transplantation FIGO committee for the ethical aspects of human reproduction and women's health. *Int J Gynaecol Obstet* 2009; 106:270.
- 9) RICCI G, DELBON P, CONTI A, SIRIGNANO A. Literature review and state of the art of the Italian law on medically assisted reproduction. *Clin Ter* 2015;166: 234-241.

- 10) BRÄNNSTRÖM M, DAHM KÄHLER P, GREITE R, MÖLNE J, DIAZ-GARCÍA C, TULLIUS SG. Uterus transplantation: a rapidly expanding field. *Transplantation* 2018; 102: 569-577.
- 11) FAGEEH W, RAFFA H, JABBAD H, MARZOUKI A. Transplantation of the human uterus. *Int J Gynaecol Obstet* 2002; 76: 245-251.
- 12) LEE R, MORGAN S. *Human fertilization & embryology, regulating the reproductive revolution*. Blackstone Press, Oxford, 2001.
- 13) DWORKIN R. *Life's dominion: an argument about abortion, euthanasia, and individual freedom*. Vintage Books, New York, 1993.
- 14) HARRIS J. No sex selection please, we're British. *J Med Ethics* 2004; 31: 286-288.
- 15) HARRIS J. Sex selection and regulated hatred. *J Med Ethics* 2005; 31: 291-294.
- 16) ROBERTSON JA. Procreative liberty and the state's burden of proof in regulating noncoital reproduction. *Law Med Health Care* 1988; 16: 18-26.
- 17) ROBERTSON JA. Liberalism and the limits of procreative liberty: a response to my critics. *Wash Lee Law Rev* 1995; 52: 233-267.
- 18) ALGHRANI A. Uterus transplantation: does procreative liberty encompass a right to gestate? *J Law Biosci* 2016; 3: 636-641.
- 19) SPARROW R. Is it 'every man's right to have babies if he wants them?' Male pregnancy and the limits of reproductive liberty. *Kennedy Inst Ethics J* 2008; 18: 275-299.
- 20) MULLER S. Body integrity identity disorder (BIID) — is the amputation of healthy limbs ethically justified? *Am J Bioethics* 2009; 9: 36-43.
- 21) LEFKOWITZ A, EDWARDS M, BALAYLA J. Ethical considerations in the era of the uterine transplant: an update of the Montreal criteria for the ethical feasibility of uterine transplantation. *Fertil Steril* 2013; 100: 924-926.
- 22) WILKINSON S, WILLIAMS NJ. Should uterus transplants be publicly funded. *J Med Ethics* 2016; 42: 559-565.
- 23) BALAYLA J. Public funding of uterine transplantation. *J Med Ethics* 2016; 42: 568-569.
- 24) ALGHRANI A. Yes, uterus transplants should be publicly funded! *J Med Ethics* 2016; 42: 566-567.
- 25) MUTCHERSON K. Reproductive surrogates, risk, and the desire for genetic parenthood. *J Law Biosci* 2016; 3: 389-394.
- 26) 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: 1-16.
- 27) MENNESSON VS. France, App. No. 65192/11 Eur. Ct. H.R., HUDOC (Sept. 26, 014), <http://hudoc.echr.coe.int/sites/eng/pages/search.aspx?i=001-145389>.
- 28) ROBERTSON JA. 'Surrogacy, Israel, and the Nepal earthquake', bill of health, <http://blogs.law.harvard.edu/billofhealth/2015/06/04/surrogacy-israel-and-the-nepal-earthquake>
- 29) ARAMESH K. Iran's experience with surrogate motherhood: an Islamic view and ethical concerns. *J Med Ethics* 2009; 35: 320-322.
- 30) ISLAM S, BIN NORDIN R, BIN SHAMSUDDIN AR, BIN MOHD NOR H, AL-MAHMOOD AK. Ethics of surrogacy: a comparative study of Western secular and Islamic bioethics. *J IMA* 2013; 44. pii: 44-1-5920.
- 31) MONTANARI VERGALLO G. Negligence and embryo protection: a new frontier for medical law? *Med Law* 2014; 33: 2-13.
- 32) ZAAMI S, BUSARDÒ FP. Elective egg freezing: can you really turn back the clock? *Eur Rev Med Pharmacol Sci* 2015; 19: 3537-3538.
- 33) MONTANARI VERGALLO G, ZAAMI S, DI LUCA NM, MARINELLI E. The conscientious objection: debate on emergency contraception. *Clin Ter* 2017; 168: 113-119.
- 34) ROBERTSON JA. Impact of uterus transplant on fetuses and resulting children: a response to Daar and Klipstein. *J Law Biosci* 2016; 3: 710-717.
- 35) TANEJA A, DAS S, HUSSAIN SA, MADADIN M, LOBO SW, FATIMA H, MENEZES RG. Uterine transplant: a risk to life or a chance for life? *Sci Eng Ethics* 2018 Feb 8. [Epub ahead of print].
- 36) KENNEDY M. 1st U.S. uterus transplant fails amid 'sudden complication', NPR NEWS, Mar. 10, 2016.
- 37) CATSANOS R, ROGERS W, LOTZ M. The ethics of uterus transplantation. *Bioethics* 2013; 27: 65-73.
- 38) WHO GUIDING PRINCIPLES ON HUMAN CELL, TISSUE AND ORGAN TRANSPLANTATION. Sixty-third world health assembly, World Health Organization. *Cell Tissue Bank* 2010; 11: 413-419.
- 39) SEGEV DL, MUZAALE AD, CAFFO BS, MEHTA SH, SINGER AL, TARANTO SE, MCBRIDE MA, MONTGOMERY RA. Perioperative mortality and long-term survival following live kidney donation. *JAMA* 2010; 303: 959-966.
- 40) STILLMAN R. Gestational surrogacy vs. uterine transplant: a medical and ethics based debate, inaugural NFI. Stockholm, Sweden, Dec. 4th, 2001.
- 41) GAINOTTI S. From experimental procedure to clinical practice: how much evidence do we need in uterine transplantation? Istituto Superiore di Sanità, 26th June 2018.
- 42) WORLD MEDICAL ASSOCIATION. World Medical Association Statement on Human Organ Donation and Transplantation. Adopted by the 52nd WMA General Assembly in Edinburgh, Scotland during October 2000 and revised by the WMA General Assembly, Pilanesberg, South Africa, October 2006.
- 43) DEL PRIORE G, SASO S, MESLIN EM, TZAKIS A, BRÄNNSTRÖM M, CLARKE A, VIANNA R, SAWYER R, SMITH JR. Uterine transplantation—a real possibility? The Indianapolis consensus. *Hum Reprod* 2013; 28: 288-291.
- 44) LEFKOWITZ A, EDWARDS M, BALAYLA J. The Montreal criteria for the ethical feasibility of uterine transplantation. *Transpl Int* 2012; 25: 439-447.
- 45) MOORE FD. Ethical problems special to surgery: surgical teaching, surgical innovation, and the

- surgeon in managed care. *Arch Surg* 2000; 135: 14-16.
- 46) MCKAY DB, JOSEPHSON MA. Pregnancy in recipients of solid organs effects on mother and child. *N Engl J Med* 2006; 354: 1281-1293.
- 47) COSCIA LA, CONSTANTINESCU S, DAVISON JM, MORITZ MJ, ARMENTI VT. Immunosuppressive drugs and fetal outcome. *Best Pract Res Clin Obstet Gynaecol* 2014; 28: 1174-1187.
- 48) BLUME C, PISCHKE S, VON VERSEN-HÖYNCK F, GÜNTHER HH, GROSS MM. Pregnancies in liver and kidney transplant recipients: a review of the current literature and recommendation. *Best Pract Res Clin Obstet Gynaecol* 2014; 28: 1123-1136.
- 49) ROBERTSON JA. Impact of uterus transplant on fetuses and resulting children: a response to Daar and Klipstein. *J Law Biosci* 2016; 3: 710-717.
- 50) ØSTENSEN M, KHAMASHTA M, LOCKSHIN M, PARKE A, BRUCATO A, CARP H, DORIA A, RAI R, MERONI P, CETIN I, DERKSEN R, BRANCH W, MOTTA M, GORDON C, RUIZ-IRASTORZA G, SPINILLO A, FRIEDMAN D, CIMAZ R, CZEIZELA, PIETTE JC, CERVERA R, LEVY RA, CLEMENTI M, DE CAROLIS S, PETRI M, SHOENFELD Y, FADEN D, VALESINI G, TINCANI A. Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res Ther* 2006; 8: 209.
- 51) BLUME C, PISCHKE S, VON VERSEN-HÖYNCK F, GÜNTHER HH, GROSS MM. Pregnancies in liver and kidney transplant recipients: a review of the current literature and recommendation. *Best Pract Res Clin Obstet Gynaecol* 2014; 28: 1123-36.
- 52) DEL PUP L, PECCATORI FA, LEVI-SETTI PE, CODACCI-PISANELLI G, PATRIZIO P. Risk of cancer after assisted reproduction: a review of the available evidences and guidance to fertility counselors. *Eur Rev Med Pharmacol Sci* 2018; 22: 8042-8059.
- 53) JOHANNESSON L, JÄRVHOLM S. Uterus transplantation: current progress and future prospects. *Int J Womens Health* 2016; 8: 43-51.
- 54) CAMPO H, BAPTISTA PM, LÓPEZ-PÉREZ N, FAUS A, CERVELLÓ I, SIMÓN C. De- and recellularization of the pig uterus: a bioengineering pilot study. *Biol Reprod* 2017; 96: 34-45.