ABSTRACT: A group of experts gathered in Indianapolis in December 2011 to address lingering concerns related to uterus transplantation (UTn). They represent a multi-national group of four research teams who have worked for over 15 years on bringing UTn to reality for patients. Presented here are a set of parameters that must be considered in order for UTn to become an acceptable procedure in the human setting. UTn has been proposed as a potential solution to absolute uterine factor infertility (AUIF). Causes of AUIF include congenital uterine factors (i.e. absence or malformation) or acquired uterine factors (e.g. hysterectomy for uncontrollable hemorrhage) rendering a woman ‘unconditionally infertile’. Current estimates are that in the USA, up to 7 million women with AUIF may be appropriate candidates for UTn. As a result of a first human attempt in 2000, investigators have responded with a plethora of publications demonstrating successful UTn attempts, including pregnancies, in various autogeneic, syngeneic and allogeneic animal models. Before UTn can become an accepted procedure, it must satisfy defined criteria for any surgical innovation, i.e. research background, field strength and institutional stability. Equally important, UTn must satisfy accepted bioethical principles (respect for autonomy, beneficence, non-maleficence and justice) and their application (informed consent, appropriate assessment of risk and benefit and fair selection of individuals). Furthermore, we believe that a defined number of transplants should not be exceeded worldwide without a successful term delivery, to minimize proceeding in futility using current techniques. Even if UTns were to become relatively common, the following research objectives should be continuously pursued: (i) additional pregnancies in a variety of large animal/primate models (to search for unanticipated consequences), (ii) continuous assessment of women diagnosed with AUIF regarding UTn, (iii) continuous assessment using ‘borrowed’ psychological tools from transplant centers, adoption agencies and assisted reproductive technology centers with potential recipients and (iv) continuous careful ethical reflection, assessment and approval.

Key words: female infertility / transplantation / uterus

Background

A group of experts and other ‘stake holders’ gathered in Indianapolis in December 2011 to assess the state of the art of human uterus transplantation (UTn) and address any lingering concerns. Experts involved in UTn research discussed the necessary steps, presented here as a set of ‘way markers’, that must be considered to provide sufficient scientific and ethical justification for taking human UTn from a rare oddity, to a recognized and reasonable addition to the armamentarium of assisted reproductive technologies (ART).

Speakers and participants represented areas of law, ethics, medicine, hospital administration, lay public and the social sciences. Specialists present included doctors of transplant medicine and surgery, infertility, gynecology, oncology, maternal-fetal medicine and others. The entire recorded conference is available for anyone to draw their own conclusions (Appendix). The deliberations of this meeting...
are summarized here, including areas of consensus and conflict. We hope that this document can ultimately assist numerous institutions to participate in treating absolute uterine factor infertility (AUFI) by UTn.

**History of UTn**

UTn was first performed in humans in Saudi Arabia in 2000 on a 26-year-old woman who had her uterus removed as a result of post-partum hemorrhage (Fageeh et al., 2002). The transplanted uterus failed after 3 months. Although controversial and appearing without precedent at the time, animal work had been performed for decades before.

In the 1960s and 1970s, UTn and other female reproductive organ transplantations were investigated as potential treatments for ovarian, tubal and uterine infertility (Eraslan et al., 1966). UTn was subsequently ignored for two decades following progress of alternative and modern ART, which was often equally controversial. UTn came back into focus at the beginning of this century secondary to the development of related fertility-preserving procedures (Smith et al., 1997) in gynecological oncology and the realization that a significant number of infertile women suffered from AUFI (Nair et al., 2008; Brannstrom et al., 2010).

**Potential indications**

Causes of AUFI include congenital uterine factors (i.e. absence or malformation) or acquired uterine factors (e.g. hysterectomy for uncontrollable hemorrhage), rendering a woman ‘unconditionally infertile’ (Nair et al., 2008; Brannstrom et al., 2010). Current estimates are that in the USA, up to 7 million women, aged 15–34 years, with AUFI may be appropriate candidates for UTn (Nair et al., 2008; Brannstrom et al., 2010). As witnessed similarly with the advent of ART in the 1980s, the extent of the likely disease population enlarges at the introduction of any potential therapy. As a result of this realization, investigators have responded with publications demonstrating pregnancies in various autogenic, syngeneic and allogeneic UTn animal models (Díaz-García et al., 2010; Ramirez et al., 2011; Wranng et al., 2011).

After more than a decade of published research from multiple independent institutions, it is now verifiably possible for a surgeon, with no significant prior research in the area, to successfully perform UTn, as shown by a case in August 2011 from Turkey (Mats Brännström to Giuseppe Del Priore, personal communication, June 2012).

UTn might be safely performed today because of important developments in transplantation surgery including complex quality-of-life enhancing procedures. These are exemplified by multi-visceral, hand, larynx and face transplants (Vianna et al., 2009; Pomahac et al., 2012). Unlike in these other non-vital transplants, the grafted uterus (and the necessary immunosuppressants) would only be in place for the 2–3 years that are necessary for pregnancy to be achieved. Early UTn recipients would have agreed to only one viable birth and minimal time constraints. This would include imaging, as well as tests to rule out HPV infection, cervical dysplasia, leiomyoma and endometrial polyps. On the other hand, the advantage of using a deceased donor lies with zero surgical risk to the donor and a more extensive dissection of the vascular tree on the uterine graft when compared with a live donor. A more radical dissection would lead to the recovery of larger arteries and veins, thus allowing for a technically easier vessel anastomosis. A disadvantage with using a deceased donor, compared with a live donor, is that graft survival may be negatively affected at brain death by major systemic inflammatory changes (Brännström et al., 2012).

We envisage that following a successful pregnancy, a total abdominal hysterectomy would be performed approximately 6 weeks post-delivery or at the time of Cesarean section. At the time of Cesarean section, preparation for emergent hysterectomy should be contemplated. An alternative option would be to stop the immunosuppressants and simply allow the graft to atrophy within the pelvis. At Cesarean section, there is a theoretical risk of abnormal placenta, but this has not been seen in the numerous animal experiments that have addressed altered blood supply, impact of different anastomoses, various immunosuppression regimes and other variables. However, potential obstetrical complications are not limited to the placenta. Specialist in high-risk obstetrics would need to call upon all their experience in balancing the risk to the mother and fetus.

Impaired quality-of-life due to infertility demands that UTn becomes a safer and more valid treatment option. Surrogacy and adoption will remain treatment alternatives of choice, but the risks associated with the former and the obstacles with the latter mean they may not be satisfactory to everyone. Regardless, the majority of women with AUFI should be counseled and encouraged to pursue alternatives to UTn.

Adoption is an excellent option, but can be a challenging process, where parents face substantial expenses and sometimes evolving dilemmas. A current debate in the UK is whether to encourage easier adoption of children from one ethnic background by adoptive
parents of a different ethnic background. Surrogate births are mostly uncomplicated, but the practice has faced controversy, with it being illegal in most of the world and many states in the USA. In the UK, the surrogate delivers and the genetic parents legally adopt, so there is scope for the surrogate to refuse to give up the baby. A need exists for additional relief options, where surrogacy and adoption cannot suffice, in this case UTn. However, the 2009 ethics statement from the International Federation of Gynecology and Obstetrics advised against a premature move to human application (Milliez, 2009). However by 2012, other ethics groups were calling UTn ‘a good option’ under certain circumstances (Lefkowitz et al., 2012). UTn would be ethically acceptable whenever and wherever several recognized criteria are satisfied. We, therefore, treat the news of other successful UTn with cautious optimism, while awaiting news of long-term survival and a successful pregnancy (Lefkowitz et al., 2012).

**Ethics of UTn**

UTn would need to satisfy, as any surgical innovation would, criteria as defined by FD Moore, i.e. laboratory background, field strength and institutional stability (Moore, 2000). Progress in multiple solid organ transplants has made UTn well within the technical capabilities of many transplant centers. For instance, the uterus graft from a deceased donor may have only one large anastomosis (aorta/cava). However, even if two smaller smaller anastomoses are used, they would be well within the experience of bowel and multi-visceral and certainly pediatric transplant centers. Pediatric transplants also provide reassurance regarding the vascular supply to the growing gravid uterus. Under physiologic control, pediatric anastomoses grow with the organ in a normal physiologic order. Animal transplants have confirmed that the fetus develops normally with no prematurity or growth restriction, regardless of the vascular reconstitution. This is the case even in primates, where Mihara et al. performed auto-UTn in non-human primate model (cynomolgus macaque) with anastomosis of two uterine arteries to the external iliac artery and achieved pregnancy for the first time in this model (Mihara et al., 2012).

Equally important, UTn would need to satisfy accepted bioethical principles (respect for autonomy, beneficence, non-maleficence and justice) and their applications (informed consent, appropriate assessment of risk and benefit and fair selection of individuals.) Whether seen as innovative surgery or as a medical study, eventually the early decisions to proceed in any venue would depend on approval by a duly constituted ethics review committee, the participating institution, the local transplant team and most importantly, the patient to whom the transplant would be offered (Beauchamp and Childress, 2006).

Clearly, some institutions, and many surgeons, are capable and may proceed with UTn without any further research. However, it must be stated that a defined number of transplants should not be exceeded worldwide without a successful term delivery to minimize proceeding in futility using current techniques. Due to the above-mentioned maternal and fetal complications, 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. Toward this end, a registry should be maintained of all recipients and candidates, much like the transplant waiting list that is updated for other organs.

**Further research**

Even if UTns were to become relatively common, we believe that the following research objectives should be continuously pursued: (i) additional pregnancies in a variety of large animal/primate models (to search for unanticipated consequences), (ii) continuous assessment of women diagnosed with AUFI regarding UTn, (iii) continuous assessment using ‘borrowed’ psychologic tools from transplant centers, adoption agencies and ART centers with potential recipients and (iv) continuous careful ethical reflection, assessment and approval.

Our group will continue to meet annually with the next meeting in London, November 2012, to address these areas and other special challenges that may arise. These challenges will require mature resources from institutions that are experienced in innovation and engaged in UTn. For instance, appropriate ‘guaranteed’ funding levels will be impossible to ensure for the UTn recipient. Much of the expense, pregnancy, delivery and neonatal care will be borne by the traditional payers. As much as possible, every contingency should be considered prior to UTn at any specific institution. Similarly, institutions with UTn capabilities would have to have experience with appropriate pathways for media engagement for the recipient, her partner and eventually, the child.

**Conclusion**

Successful animal models (Díaz-García et al., 2010; Ramirez et al., 2011) resulting in pregnancy together with a second human UTn performed last year mean that UTn may now be a recognized feasible procedure. Pregnancy following organ transplantation is complex, but now commonplace (Coscia et al., 2010). Closing on half a century of experience with pregnancy in solid organ recipients, an abundance of data have accumulated indicating satisfactory maternal and neonatal outcomes. As future UTn candidates are likely to represent a group not burdened by multiple co-morbidities, they may be the beneficiaries of an even better prognosis.

Pregnancy after UTn would be challenging, but cannot be unexpected. As we await news of progress from the Turkish case and of any other human attempts, we believe that UTn has become a matter of ‘when next’ rather than ‘if’.

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**Conflict of interest**

E.M. is a bioethics consultant to Eli Lilly and Company. He holds no stock, nor is he funded to conduct biomedical research of any kind by Eli Lilly. His consulting is limited to provide philosophical and bioethical input on policy issues arising from their Bioethics Program. His consulting arrangement began after the completion and submission of this manuscript.
References


Appendix

The audio of the conference is now available at the Ruth Lilly School of Medicine Library, Indianapolis, USA. The phone number is 00-1-317-274-2272. To access the tapes from the conference go to ‘www.iucat.iu.edu; title search: Uterus Transplant Conference November 2011’.