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Review

Organizing a uterus transplantation programme: The designation of Uterus Transplantation Centres in France

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ABSTRACT

Absolute uterine factor infertility affects several thousand young women in France. The first healthy child delivered to a uterus transplant recipient took place in 2014, and uterus transplantation is developing rapidly in many countries. The French College of Gynaecologists and Obstetricians (CNGOF) formed a uterus transplantation committee (CETUF) in 2015 to advance this technology in France. The CETUF sets out the criteria for the designation of Uterus Transplantation Centres. The objectives, requirements, operation and responsibilities of these centres have been described. Their responsibilities for organizing geographical coverage, continuity of care, communication, training, research and evaluation have been defined. This document will serve as a guide for the authorities concerned, to ensure that the means are provided to adequately manage patients with absolute uterine factor infertility who require uterus transplantation.

Introduction

2014 saw the first birth of a healthy child to a woman who had undergone uterus transplantation (UTx), under the care of Matt Brännström's team in Sweden [1]. Since this first success, at least 38 uterus transplants have been performed worldwide and at least 12 healthy children have already been born to uterus transplant recipients in four countries: Sweden (8 babies since 2014 and UTx were from living donor), the United States (2 babies since 2017 and UTx were from living donor), Brazil (1 baby in 2018 and UTx was from brain dead donor) [2,3] and Italy (1 baby in 2018 and UTx was from monozygotic twin living sister) (unpublished). This complex procedure is therefore developing rapidly worldwide to meet the demand among women with absolute uterine factor infertility (AUFI).

Several teams in France are keen to develop UTx for patients with AUFI. The purpose of this document is to propose a national model for Uterus Transplantation Centres, with the aim of providing a national programme covering every aspect of UTx (clinical practice, training, research) in order to optimize the management of AUFI and to ensure that UTx does not develop in a chaotic fashion in France, given the risks this could pose for patients. It was drafted by the French Uterus Transplantation Committee (CETUF) at the instigation of the French College of Gynaecologists and Obstetricians (CNGOF).

The demand for uterus transplantation in France

Defining absolute uterine factor infertility

Only women with AUFI would be eligible for UTx. Uterine factor infertility is just one of several possible causes of infertility, alongside tubal infertility (tubal blockage), ovarian infertility (ovarian failure), male infertility (the narrowest definition of which is severe oligospermia, i.e. fewer than 5 million sperm/mL) and idiopathic infertility. Uterine infertility can be defined as difficulty becoming pregnant due to a uterine abnormality that

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prevents implantation. In contrast to other, less clear-cut forms of uterine infertility, AUFI is easily defined as it entails complete absence of a uterus. A woman can have difficulty becoming pregnant due to an acquired uterine abnormality such as adenomyosis or uterine leiomyomata that can prevent or hinder implantation. The difficulty with defining uterine factor infertility is that not all adenomyoses or uterine leiomyomata necessarily prevent implantation and that a couple's infertility often results from several factors.

The narrowest definition of AUFI is the absence of a uterus in a woman of childbearing age due to a congenital condition, such as Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, characterized by uterine agenesis, or as an acquired condition (prior hysterectomy). This definition can probably be extended to include women with severe uterine synechiae that completely obliterate the uterine cavity and are uncorrectable by repeated hysteroscopic treatment. The question then arises of whether to extend the definition of AUFI to include patients with chronic acquired uterine abnormalities (such as multiple leiomyomata) that prevent implantation despite at least 2 years of attempting spontaneous pregnancy and several unsuccessful In Vitro Fertilization (IVF) cycles.

Number of patients with absolute uterine factor infertility

It is possible to estimate the number of women with AUFI in France based on its narrowest definition (women with congenital or iatrogenic absence of uterus). To start with congenital causes (absent uterus through a birth defect), it is estimated that between 100 and 200 children are born each year in France with MRKH syndrome, and that up to about 20 000 women between the ages of 18 and 40 years, and who are therefore currently of childbearing age, have congenital AUFI [4]. The true figure is probably slightly higher, because MRKH syndrome does not encompass every syndrome that includes uterine agenesis. Complete androgen insensitivity syndrome (CAIS), which has an incidence of about 1 in 50 000 live births, is one such condition to be taken into account in the prevalence of congenital AUFI [5]. However, CAIS is a marginal indication for UTx for now, as these patients would also require oocyte donation because they lack ovaries. Iatrogenic AUFI applies to women who have undergone hysterectomy, for example for postpartum haemorrhage (affecting an estimated 1 in 800 women although this figure should be lower now) or neoplastic disease. It is estimated that 1 in 800 women of childbearing age have iatrogenic AUFI. In total, an estimated 30 000 women in France have AUFI [6], and some publications report that AUFI affects 3–5% of the female population [7].

A potential demand for UTx therefore exists in France.

Uterus transplantation, gestational surrogacy and adoption

Three paths to motherhood are available to women with AUFI: adoption, gestational surrogacy (GS) and UTx. Adoption provides adoptive parents with legal parenthood of the adopted child. However, both national and international adoption are becoming increasingly difficult. In France, although about 25 000 requests for adoption are lodged by heterosexual couples each year, only 600–700 children are adopted. Adoption opportunities will shrink still further if France abolishes anonymous birth. International legislation is reducing the potential to adopt children from other countries, so the availability of this pathway is also declining, with a high risk of adopting children with "special needs".

GS is another option for women with AUFI to achieve parenthood while also enabling them to be the child's genetic mother through IVF using the patient's own oocytes. GS is not permitted in France and is unlikely to be legalized as part of 2018's revision of national bioethics law. In the 28 countries of European Community, only 9 countries do not forbid GS: Belgium, Netherlands, Poland, Slovakia, Romania, Ireland, United Kingdom, Portugal and Greece. Some French couples use a gestational surrogate from another country but the recognition of children born abroad in this way can be problematic. Until recently, the existence of these children was "unlawful" in the eyes of French law, but case-law has now evolved to allow legal recognition of children born though this route. Even in countries where GS is permitted, it poses ethical problems concerning the commodification of the human body as well as the child's fate. Biological parents have been known to refuse to take a child born with a defect (e.g. Down's syndrome) through GS, creating a terrible human dilemma in which the status of the child and the gestational surrogate is legally insoluble.

Finally, only UTx offers women with AUFI the triple status of genetic, legal and gestational mother.

The three options of adoption, GS and UTx are probably different life choices that will suit different couples. As women with AUFI can attain motherhood through other routes, and since some do not want to have children, the demand for UTx is necessarily smaller than the number of patients with AUFI. In a survey of patients with MRKH syndrome conducted in 2015 by a team from Limoges, about 60% of respondents reported being willing to undergo UTx to have a child [4]. In summary, in routine practice, it can be estimated that about 500–1000 uterine transplants per year would be necessary to meet the demand among patients with AUFI. If this estimate is accurate, 10–15 Uterus Transplantation Centres would be needed, ideally distributed across the country to provide full geographical coverage, given that these patients will require long-term management and multiple consultations with the UTx team, the IVF team and the obstetric team.

Uterus Transplantation Centres

Objectives

The objective of the programme is to improve the management of AUFI by offering UTx in France, bringing together health professionals from different specialties in Uterus Transplantation Centres, ideally distributed across the entire country.

Improved management of AUFI will require:

- Education and training in UTx for health professionals through conferences, seminars, the sharing of experience, international dialogue, etc.
- Development of an animal model;
- Development of clinical and experimental research on UTx;
- Coordination of health professionals around transplant recipients and their unborn child (including immunosuppression specialists, gynaecological and transplant surgeons, obstetricians, human reproduction specialists, paediatricians and psychologists);
- Dissemination of information to the general public;
- Facilitated access to UTx for patients with AUFI;
- Follow-up of children born through UTx;
- Establishment of a UTx registry;
- Establishment of a national UTx waiting list;
- Integration into the national organ transplant network, with centralization;
- Organization of a 24-hour organ retrieval on-call service for UTx, based on the model used for liver, kidney and heart grafts.

Uterus Transplantation Centres will need to be distributed geographically in such a way as to provide access to UTx to the entire population of France. However, the number and locations of these centres will need to be determined on the basis of patients' travelling distance.

Current organization in France

The CNGOF formed the CETUF, led by Prof. Tristan Gauthier of Limoges University Hospital, in 2016. The other members of the committee are Dr Olivier Garbin and Prof. Israel Nisand from Strasbourg University Hospital, Prof. Pierre Collinet from Lille University Hospital, Prof. Aubert Agostini from Greater Marseille University Hospitals (AP-HM), Prof. Jean-Marc Ayoubi from Centre Hospitalier Foch, and Prof. Vincent Lavoué from Rennes University Hospital. The CETUF's aim is to foster the development of UTx in France, in terms of both organizational logistics at the clinical level, and its research and development. It also has a role in liaising with the relevant national authorities, such as the French Biomedicine Agency (ABM), the National Authority for Health (HAS), the French National Agency for Medicines and Health Products Safety (ANSM), and France's national health insurance system.

A number of centres have already made progress towards offering UTx in France. The Limoges team obtained funding through the Hospital Clinical Research Programme (PHRC) in 2015 and authorization from the ANSM in 2016 to perform 10 uterus transplants using brain-dead donors. These were obtained after several years of research on an ovine animal model and a clinical feasibility study of uterus retrieval from brain-dead donors [8–10]. Hôpital Foch obtained authorization from the ANSM in March 2017 to perform uterus transplants and is currently seeking funding. Other centres are developing animal models to acquire surgical and organizational experience in UTx. There are several potential animal models: Limoges and Foch chose an ovine model [9], and Rennes has developed a porcine (Yucatan) model (submitted) [11]. Ways of improving graft quality during cold ischaemia [12] (submitted) and postoperative monitoring using MRI (submitted) are bring sought and tested [13]. The Limoges and Rennes teams obtained grants from the ABM to undertake these developments.

What facilities does a Uterus Transplantation Centre require?

UTx is a multi-step process:

Step 1: Frozen embryos are created by IVF, using gametes from the couple requesting UTx. Alternatively, oocytes are frozen in order to transfer a fresh embryo after UTx.
Step 2: The uterus of a live or deceased donor is transplanted into the recipient
Step 3: Frozen or fresh embryos are transferred 6–12 months after UTx.
Step 4: The baby is delivered by caesarean section.
Step 5: The transplanted uterus is explanted (ephemeral transplantation), possibly after two pregnancies, as the Swedish team has done.

A Uterus Transplantation Centre must be able to offer pre-UTx assessments to screen candidate UTx recipients and potential living or brain-dead uterus donors. UTx surgery must be as safe as possible for both donor and recipient, and be performed by multidisciplinary teams. Psychological support must be available. As UTx requires IVF, the centre must also have an assisted reproduction centre. The centre must be able to monitor the pregnancies of transplant recipients and have a maternity unit with facilities to care for high-risk pregnancies and premature neonates. Finally, given that patients may live a long way from the centre and will have to attend multiple consultations, the Uterus Transplantation Centre must be in a position to delegate part of the patient's care to a hospital near her home. Given the risk of complications requiring urgent action, especially during a post-UTx pregnancy, the centre must have a telephone hotline to answer questions and suggest the appropriate course of action at every stage of the UTx process, up to and beyond the birth of the child.

Uterus Transplantation Centres must therefore have:

An assisted reproduction centre. Since the fallopian tubes are not currently conserved in UTx, IVF is necessarily required. Women cannot undergo living donor or brain-dead donor UTx until a certain number of frozen embryos has been obtained through IVF (at least 8 or 12 frozen embryos, depending on the protocol). If her ovarian reserve is insufficient to successfully generate embryos through IVF, there is no point performing UTx.
An animal research centre and preparation on an animal model. In countries in which UTx has been performed, the graft survival rate was 82% (9/11) in surgeries performed by teams who prepared with animal experiments before clinical application and 55.6% (15/27) in those performed by teams without prior animal experience [14]. This suggests the need for preparation for clinical application using basic experiments and repeated animal model surgical training. The ANSM and the ABM rightly asked that centres prepare in this way before they can be granted approval to perform UTx.
A solid organ transplantation centre. Given that UTx is a new branch of obstetrics and gynaecology, the gynaecological surgery teams who perform it will have to liaise with transplantation specialists to benefit from their expertise. The Uterus Transplantation Centre must therefore also be a centre for the transplantation of other solid organs, such as liver, kidney or heart. Solid organ transplantation centres already have the facilities required to monitor transplant recipients and experience with immunosuppressive therapy. They also already have a local infrastructure in place to coordinate with the national infrastructure to gain access to the multi-organ procurement "circuit". This logistical aspect is necessary for the development of UTx from brain-dead donors.
A robotic surgery centre. One of the technical advances that has been made in UTx is the use by some teams of robot-assisted minimally invasive surgery rather than an open abdominal approach to retrieve the uterus from a living donor [15–17]. Two teams have proposed a non-robotic laparoscopic approach, but none of the 4 uterus transplants was successful [14]. The robot-assisted minimally invasive approach enables safer, finer dissection through magnification and the dexterity of the instruments, and improved postoperative recovery for the living donor. The Chinese teams reported that living-donor surgery lasted about 6 h, versus 11 h for the Swedish team using an open approach [15,18]. Brännström's team is just starting a new clinical trial at the Karolinska Institute, with robot-assisted laparoscopic uterus retrieval from living donors.
A maternity unit with facilities for high-risk pregnancies. A Uterus Transplantation Centre must also have a maternity unit with the facilities to monitor and manage pregnant transplant recipients and to care for premature neonates due to the risk of preterm delivery. For example, the first livebirth following UTx, performed by the Swedish team, was delivered by emergency caesarean section at 32 weeks' gestation due to pre-eclampsia [1].

Psychologists. Psychologists must be available to provide psychological evaluation and counselling for UTx recipients and live donors.

Uterus transplantation research. UTx must be combined with clinical and experimental research. Clinical research and the establishment of a national and international registry are necessary to develop scores predictive of success, to assess complication rates, and to monitor outcomes in children born following UTx. Likewise, continued experimental research on animal models is necessary to improve transplantation protocols, immunosuppressive regimens and surgical protocols.

Multidisciplinary team meetings. These meetings, to include a surgeon, fertility specialist, obstetrician, transplant specialist, psychologists, etc., must be organized to analyze the eligibility of candidates for UTx.

The responsibilities of a Uterus Transplantation Centre

Responsibility for organizing geographical coverage

The Uterus Transplantation Centre must organize continuity of care for uterus transplant recipients before, during and after pregnancy. To achieve this, care and follow-up should be arranged as close to the patient's home as possible by creating a network of professionals capable of monitoring such patients and who will discuss her management with the centre responsible for her uterus transplant, based on the results of this follow-up.

Responsibility for communication

If the care network is to function properly at "regional" level (i.e. around the transplantation centre), the centre must organize a system of communication between all the professionals within and outside the centre who are involved in these patients' management. Digital technology such as smartphones should facilitate the exchange of information between health professionals and the patient.

Responsibility for education and training

The first Uterus Transplantation Centres created will have to develop education and training in UTx to enable professionals to share their experiences and establish other Uterus Transplantation Centres to satisfy the demand among women with AUFI nationwide.

Responsibility for research

Uterus Transplantation Centres will need to organize a UTx registry to collate complications, successes and failures, and the outcomes of transplant recipients and children born through UTx, probably in conjunction with the relevant national authorities. The centre will also need an animal research centre to develop research initiated by the team, and which can also be used for training.

Responsibility for evaluating quality of care

Centres must produce a report on the UTx surgeries performed each year and an annual overview of the multidisciplinary team meetings held.

Funding Uterus Transplantation Centres

UTx is a new technology that requires specific long-term funding for the transplantation centre, as is the case for the transplantation of other solid organs, such as liver, heart and kidney. This operational funding must cover medical and non-medical staff costs (such as a uterus transplant coordinator nurse) and secretarial and office support.

Funding for training will also be required. Research could be funded through a combination of long-term finance, to operate registries for example, and one-off grants for specific animal and translational research projects.

Similarly, agreement should be obtained from the French national health insurance system to cover the full cost of UTx for patients. The estimated societal cost of a uterus transplant followed by pregnancy is around €100 000.

Conclusion

UTx is a major advance for patients with congenital, iatrogenic or acquired AUFI. Since proof of concept for UTx was provided by the birth of a healthy child in Sweden in 2014, this technique has rapidly developed in many countries and has already undergone a number of technical simplifications and produced other healthy children. France must be able to offer these developments in an organized, lasting and above all safe fashion to its population of women with AUFI.

Disclosure of interest

The authors declare that they have no competing interest.

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