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Review

Uterus transplantation: An update and the Middle East perspective

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ABSTRACT

Uterus transplantation (UTx) is the only available treatment for absolute uterine factor infertility (AUFI), which is caused by either absence (congenital or after hysterectomy) or presence of a non-functioning uterus. Uterus transplantation became a clinical reality after more than 10 years of structured animal-based research. Aside from gestational surrogacy, this procedure is the only alternative for women with AUFI to attain genetic motherhood. In the Middle East, North Africa and Turkey (MENAT) region, out of a population of around 470 million, more than 100,000 women of fertile age are estimated to suffer from AUFI. Introduction of UTx as an infertility treatment in this region will certainly differ in specific countries from ethical, religious and legal standpoints depending on culture and religion. The MENAT region is the cradle of three religions and the geographic area encompasses a variety of cultures and religions with different views on assisted reproduction. In light of these issues, the aim of this article is to give an overview of the research-based development of UTx and its clinical results up until today as well as to explore how UTx would fit into current infertility treatments in the MENAT region, with its existing multifaceted religious perspectives.

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1. Introduction

Absolute uterine factor infertility (AUFI) has for many years been regarded as untreatable. We reported the first live birth after UTx in 2014 [1] and this has been followed by more births [2]. Thus, UTx is now established as the first treatment for AUFI. Historically, there were early attempts to develop UTx with the hope of reaching clinical application. These experiments included transplantation of grafts including the uterus and the oviducts in dogs [3] and nonhuman primates during the 1960s and 1970s [4]. The primary aim was to develop treatment for tubal factor infertility (TFI) and the uterus was included in the graft to simplify surgery. However, the lack of effective immunosuppression (IS) drugs at that time was central in the failure of these pioneering experiments.

After worldwide spread of IVF in the 1980s, TFI became treatable and the interest in UTx-research ceased. Introduction of the first effective IS, cyclosporine, in the mid-1980s, gave rise to a substantial expansion of the clinical field of transplantation surgery. Today even highly immunogenic tissues such as intestines and vascularized composite tissues (hand and face) are transplantable. All existing types of transplants are intended for lifelong use and with continued IS. In this regard, UTx is unique as an ephemeral type of transplantation. Thus, the allograft would just be in the recipient for a restricted time. After the recipient has delivered the number of children desired, hysterectomy should be performed. The recipient can then discontinue IS medications and thereby avoid the IS-related long-term side effects, such as nephrotoxicity [5], as well as increased risks for serious viral, fungal and bacterial infections and certain malignancies [6,7]. The two first UTx attempts in the world were performed in 2000 and 2011 and both took place in the MENAT region [8,9]. Although, these attempts did not result in any births, they paved the way for our clinical trial in Gothenburg, Sweden which included nine patients undergoing UTx in 2013 [10]. The results of all these attempts will be discussed in detail below.

1.1. Potential patient groups for UTx

The causes of permanent AUFI [11] are listed in Table 1. It is estimated that around 15,000 AUFI patients exist in the UK [12] and this would, on a population-basis, correspond to around 100,000 in the MENAT region.

1.2. Guidelines for research and development towards human UTx

The modern research preparations in UTx span over more than a decade [13,14] and follow the IDEAL (Innovation, Development, Exploration, Assessment, Long-term follow up) concept [15], which emphasizes a structured and research-based introduction of any novel, major surgical procedure. This approach minimizes the risks for the patients but also accumulates important scientific data during clinical introduction. Currently, UTx is in the D (Development) phase of the IDEAL concept with our observational study, including nine patients [10]. An International Society for Uterus Transplantation (ISUTx) was recently formed at a meeting in Gothenburg Sweden. This society has initiated the formation of an international registry, to follow all patients (donors, recipients, and children) to accumulate data to also explore the L (Long-term follow-up) phase of the IDEAL concept.

It is necessary that information concerning all ongoing human UTx research and its results reach the public in all countries and societies so that all are informed about this potential new fertility treatment, which also may raise some ethical concerns. It should be mentioned that Federation International Gynecology and Obstetrics (FIGO) launched ethics principles of UTx already in 2009 and these emphasizes that animal experiments is an obligatory component [16].

2. Animal-based UTx research and human UTx

Modern attempts in animal-based UTx research stems from the early 2000s and initially involved smaller rodents, later large domestic species and from around 2005 nonhuman primates [13,14,17]. The key findings of this research are summarized below.

2.1. Rodents

The initial rodent UTx model was the mouse, with the first ever pregnancy after UTx demonstrated already in 2002 [18] and in 2003 we reported the first offsprings [19]. This was in a syngeneic setting (between inbred strains) and consequently IS was not needed. Offspring exhibited normal postnatal growth trajectory and were fertile. The uterus was tolerable to 24 h of cold ischemia, between harvesting from the donor until UTx, since the majority of these cold-preserved and transplanted uteri achieved normal pregnancy and offspring [20]. Additional mouse UTx-studies, characterized rejection after allogeneic transplantation by examining the morphology, blood flow [21], influx of specific subclasses of leukocytes [22,23] as well as influence of immunosuppression by cyclosporine [24].

Table 1
Causes of uterine factor infertility that may be treatable by uterus transplantation.

No uterus
- Congenital uterine absence (Müllerian/Mayer-Rokitansky-Küster-Hauser (MRKH)-syndrome)
- Hysterectomy
  - Cervical/uterine malignancy
  - Leiomyoma
  - Obstetric bleeding
  - Atony
  - Malplacentation (placenta accrete/percreta)
  - Uterine rupture

Uterus present
- Leiomyoma
- Adenomyosis
- Multiple miscarriages/implantation failures
- Radiation damage
- Uterine malformation
  - Fraction of unicornuate uterus
  - Fraction of bicornuate uterus
  - Hypoplastic uterus
- Cervical incompetence with multiple miscarriages
  - Post multiple conisation procedures
  - Post trachelectomy procedure
- Severe intrauterine adhesions, untreatable by hysteroscopy

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