



## Review

## Promise of uterine transplant – Myth or a reality?

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## ABSTRACT

The scientific basis of uterus transplantation has been developing in parallel to other organ transplants throughout the modern period of transplant medicine. Immunosuppression and surgical techniques have been adequate for at least a decade; ethics and society have been less clearly developed. To many observers, it is still unclear if the endeavor is an overall positive or negative. Although scientific and technical challenges have been overcome, the ethical determinations will be a dynamic process while more experience continues to be gained. The most significant experience still lacking is a term gestation. Undoubtedly during a nine-month gestation, unforeseen challenges will test scientific processes and ethical assumptions. Despite dozens of animal experiments and a few animal births, no human birth has occurred to allow any definitive conclusions.

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## 1. Introduction

The first reaction most people have upon hearing the phrase “uterine transplantation” (UTx) is to ask, “Why?” It certainly is not an organ necessary to maintain life. In addition, unlike the case with hands, lower extremities, trachea, abdominal wall, and face for example, (all of which have been transplanted), a recipient woman can function ‘well’ in all aspects of life without a uterus except in one instance: fertility. Does that one purpose justify the serious risks to the mother and the developing fetus associated with major surgery and immunosuppressive therapy? Is the quality of

life impact of absolute uterine factor infertility sufficient to justify UTx risks?

## 2. Needs assessment

The value of UTx to individuals and society varies greatly. It is estimated that approximately 1.2 million women of childbearing age in the US have no uterus, due both to surgical removal and congenital malformations [1]. If you expand the definition to include women up to the age of 40, the number of women affected can be as high as 7 million [2]. Among those women, a significant number still maintain the desire to have children based on normal population fecundity rates.

The most common reason for absolute uterine factor infertility (AUF) is surprisingly hysterectomy for endometriosis. In fact, approximately 5000 women under the age of 25 have a

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hysterectomy each year in the US due to severe endometriosis. By age 30–35, that number is in the tens of thousands of women having hysterectomies for endometriosis each year [2]. Despite that large number, no single factor is the main cause of uterine loss. Multiple factors add up each year to increase the overall number of affected women. Congenital absence as in MMK syndrome is relatively rare with an incidence <1/1000 live births. However since the number of births is large, and the years of reproductive potential long, the total number of affected women from Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is in the hundreds of thousands.

Cancer survivors were a motivating factor in the development of UTX for the treatment of AUI resulting from cancer or its treatment. However cancer is fortunately a relatively unlikely cause of AUI in the US. In our series of UTX candidates, less than a 1/3 of all applicants had a cancer related cause [2]. Elsewhere in the world the ratios will be different, e.g. possibly more cervical cancer causes of AUI in unscreened societies.

Independent of the numbers of affected groups, there is an important individual motivation that is difficult to quantify. The desire to bear children emanates from somewhere deep within our complex human nature and manifests itself as a powerfully felt need. For some women, current choices are not fully satisfactory. Current options are either unavailable through legal, societal or religious restrictions.

Fortunately many do find fulfillment through adoption. For others, in vitro fertilization with a surrogate mother is an option. However, neither choice represents a suitable or available solution for every woman who lacks a functioning uterus. A feeling that nature has deprived them of something they believe is central to their identity; that establishes their sense of worth and purpose, is described by some women who have lost a uterus due to cancer or were born with a congenitally defective one. For them, the experience of pregnancy is the only way in which the urge to be a parent and to achieve a full sense of identity and worth and purpose can be fulfilled [3].

As powerful, valid and eloquent as the argument might be for UTX to “experience carrying a pregnancy” [2,4], this may not be a justifiable indication at this point. For our group, the desire to “bear” children was not considered a sufficient indication for UTX [5]. For instance, if a woman with AUI had an adopted child/family, we felt she was not an ideal initial candidate for UTX. Before this large and deserving group of candidates can be considered as recipients, the risk of UTX must be better known. Once it is known how risky and how effective UTX is, the indication can be expanded. For now, even a temporary transplant, cannot be justified for a woman who already has a family by any other means.

### 3. Ethics

The ethical issues surrounding uterine transplantation are complex, to say the least. Along with the fact that the uterus is not essential to maintaining a woman’s life, there is also the unique problem presented by the one function the uterus serves: to bring new life into the world. Any discussion of the ethical implications of the procedure must by necessity involve the potential harms to both the mother and the child. The risk to the developing child comes from the transplanted organ itself and from the necessary immunosuppressive treatment that prevents its rejection by the recipient mother. In addition, because uterine transplantation is not presently an established surgical procedure, any ethical analysis of it must involve both the traditional criteria we use in patient care and also criteria used to assess the ethics of innovative surgical procedures.

Moore has defined the criteria for ethical analysis of a surgical innovation as involving 3 components: laboratory background,

field strength, and institutional stability [18]. The first, laboratory background, mandates that the research foundation for the procedure is sound. The second, field strength, requires the synthesis of knowledge and expertise from all fields related to the procedure. For uterine transplantation, at a minimum, this would involve the disciplines of surgery, obstetrics, immunology and neonatology. The last criterion, institutional stability, addresses the overall level of expertise in the institution in which the procedure is performed among all the clinical services, how well they function in an inter-disciplinary manner, and the quality of the support services available to patients.

Once the surgical procedure has been successfully performed, immune-suppression will be required adding another point for discussion. Fortunately, modern immune-suppression has a favorable obstetrical record. In fact, in almost all cases, maternal health improves post-organ transplant. The pregnancy outcomes on immunosuppression with a donated organ are typically better than those with end organ insufficiency [6]. This may not be a fair comparison but it is reassuring that pregnancies, in fact over 14,000, have been reported in organ recipients. The first case report of a pregnancy following those early renal transplant recipients happened within a year of the donor receiving the organ [7]. Since then, nearly every transplanted organ has also reported successful pregnancies afterward in the recipients [8]. Even multi-organ recipients have had successful pregnancies [9]. Normal reproductive function is a goal of transplant medicine. The overwhelming consensus is that pregnancy while on immune-suppression is a manageable reality.

In comparison, pregnancy in all developed countries is also complicated by severe life-threatening maternal co-morbidities [10,11]. These include severe cardiac, pulmonary or super morbid obesity. In general, the concept of a “therapeutic” abortion no longer has relevance in the management of any complicated pregnancy. Today it would be considered patronizing for an informed patient to have pregnancy termination presented as the only option. Maternal-fetal-medicine specialists are tackling more complicated pregnancies than ever [12,13]. As our society has fewer children later in life, our concept of ‘normal’ or ‘acceptable risk’ must adapt [14,15].

In the developing world, examples of more extreme risk in pursuit of a family can be even more dramatic. In fact, pregnancy is the most dangerous event in the life of a young woman in the developing world (WHO 2012 report on maternal mortality). Certainly, for a mother to be, accepting the UTX transplant risk is not unprecedented. Mothers at all stages, before and after conception and birth, have assumed greater risk throughout human history than that of UTX.

Some have argued that ethically, more research needs to be done in animals, e.g. primates, before continuing UTX in humans. However, the limitations of extrapolating from research done on animals to the human experience should be obvious. Furthermore, it is impossible to answer the question of how much more research has to be done in animals before another attempt is made in a human, because no objective standards or criteria exist to make that determination. Ultimately, the decision to go forward will depend on the judgment of the researchers, the institutional review board of the participating institution and most importantly, the patient to whom the transplant will be offered [25].

### 4. History

Here, we will address two questions. First, have the technical aspects of the procedure been developed sufficiently to form a basis for continuing the procedure in humans? Secondly, do we also have sufficient knowledge of the effects of immunosuppressive

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