

A SYSTEMATIC REVIEW OF CASE- CONTROL STUDIES ON UTERINE TRANSPLANTATION

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Obstetrics and Gynecology*

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List of Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine transaminase
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUFI	Absolute uterine factor infertility
CMV	Cytomegalovirus
CRP	C - reactive protein
CsA	Cyclosporines
3D	Three-dimensional
EBV	Epstein-Barr virus
ECG	Electrocardiography
FACS	Fluorescence activated cell sorter
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
IVF	In vitro fertilization
MMF	Mychophenolate mofetil
MRI	Magnetic resonance imaging
MRKH	Mayer-Rokitansky-Kuster-Hauser
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PCR	Polymerase chain reaction
PODs	Postoperative days
PT	Prothrombin time
QALY	Quality-adjusted life year

List of Abbreviations (Cont...)

TPC	Total particle concentration
UA	Uterine artery
UTx	Uterus transplantation
WBC	White blood cells

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ABSTRACT

The present study aimed to explain and clarify of criteria of selection, preparations, investigations, technique and Management of uterine transplantation for donor and recipient, taking in consideration the immune suppressive management before, during and after pregnancy, in addition to discussion of Saudi Arabia case, Turkey case, and the 9 cases of Sweden, we will discuss also the future of this procedure and whatever it will be the standard treatment of absolute uterine factor infertility or other modalities of treatment will replace this procedure. e.g. Artificial uterus or uterus stem cell implantation.

Uterus transplantation had now shown its potential as a highly effective treatment for uterine factor infertility, which was because of absence of the uterus or presence of a nonfunctional uterus. Further prospective observational studies should follow, both with the live and deceased donor concepts. The collective results of the studies will be important to establish sound inclusion and exclusion criteria. Furthermore, the surgical and medical management of the patients will become more efficient and safer when proper scientific results make up the fundament for the uterus transplantation procedure.

INTRODUCTION

Infertility affected over 48 million couples around the world in 2010 (*Mascarenhas et al., 2012*). Many factors lead to a diagnosis of infertility. In approximately one-third of infertility cases, the cause of the infertility is due to a factor involving the male, such as a low sperm count or motility. Additionally, one-third of infertility cases are due to factors surrounding the female whether due to decreased egg quality, difficulties with ovulation, or anatomic abnormalities that impact the normal trajectory of the egg or fertilized embryo from the fallopian tubes to implantation in the uterus. Finally, one-third of infertility cases are due to factors involving both partners and an unidentifiable cause. The specific anatomic abnormality of uterine factor infertility affects approximately 3% of all infertile women, or approximately 9.5 million out of the 62 million women of reproductive age in the United States (*Milliez, 2009*).

UFI can be present due to congenital, disease-related, or iatrogenic causes. For example, a woman can be born without a uterus (Mayer-Rokitansky-Kuster-Hauser syndrome), the uterus may have been removed as a component of surgical staging and treatment for cervical cancer, or an emergency hysterectomy may have been completed during a postpartum hemorrhage after delivery or after a trauma. Organ transplantation had been performed since the early 20th century for a variety of reasons,

including restoring function, saving life, and extending lives. Organ transplantation raised its own ethical considerations, including the use of cadaveric or living donors, allocation of scarce resources, use of medical and other criteria to determine eligibility, and informed consent (*Arora and Blake, 2014*).

Improving the quality of a patient's life, rather than saving life itself, is a more recent goal and achievement of organ transplant (eg, hand, corneal, and face transplants) that presents further ethical considerations (*Olausson et al., 2014*) for example, it is unclear how much risk is justified in the face of interventions aimed at improving quality of life rather than saving life. Uterus transplantation raised these same issues along with novel ones. For example, it is the first organ transplant with the goal being reproduction. Also, uterus transplantation was the first ephemeral organ transplant, or a transplant designed specifically for a short term, rather than the anticipated long-term nature of a transplanted liver or kidney, for example. As a transplant with reproduction as its goal, it necessarily raises ethical questions about technological aid of reproduction, including the rights of any reproductive donors, the interests of the child, co modification of women's bodies, the interests and goals of the mother, and the role of the state in regulating women's bodies and reproduction (*Arora and Blake, 2014*).

To women with uterine factor infertility (UFI) or infertility due to an anatomic issue specifically surrounding the uterus, uterus transplantation offered a novel treatment approach in addition to the currently available options of adoption and gestational surrogacy (*Shah, 2014*).

AIM OF THE WORK

Primary objectives:

- Explanation and Clarification of criteria of selection, preparations, investigations, technique and Management of uterine transplantation for donor and recipient, taking in consideration the immune suppressive management before, during and after pregnancy.
- Discussion of Saudi Arabia case, Turkey case, and the 9 cases of Sweden in details.
- The future of this procedure and whatever it will be the standard treatment of absolute uterine factor infertility or other modalities of treatment will replace this procedure. e.g. Artificial uterus or uterus stem cell implantation.

Secondary objectives:

- Review the literature of the anatomy and physiology of female human uterus.
- Review the incidence, causes and diagnosis of absolute uterine factor infertility (AUF) and magnitude of problem in Egypt.
- Evaluate current treatments of AUF and from which can be successful and accepted in Egypt.
- Spot on role of uterine transplantation in treatment of AUF, Ethics and its cost taking in consideration the Embryo cryopreservation.

ANATOMY

Anatomy of uterus:

The uterus is a hollow, thick-walled, muscular organ of the female reproductive tract that lies in the lesser pelvis. The uterus has an inverted pear shape. In the adult, it measures about 7.5 cm in length, 5 cm wide at its upper part, and nearly 2.5 cm in thickness. It weighs approximately 30-40g. The uterus is divisible into two portions: body and cervix. About midway between the apex and base, is a slight constriction known as the isthmus. The portion above the isthmus is termed the body and that below, the cervix. The part of the body which lies above a plane passing through the points of entrance of the uterine tubes is known as the fundus.

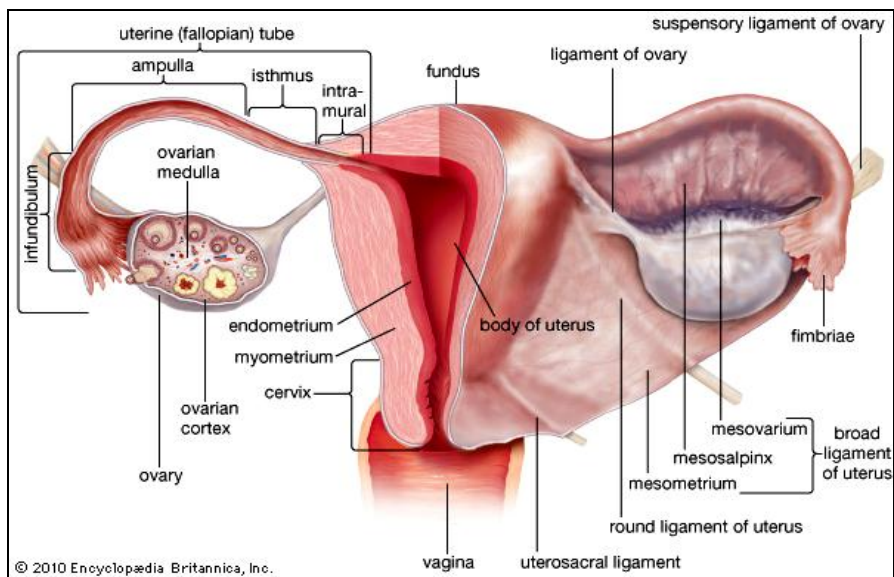


Fig. (1): Anatomy of the uterus (adapted from *Encyclopedia Britannica, 2010*).

The body gradually narrows from the fundus to the isthmus. The cavity of the body is a mere slit, flattened anteroposteriorly. It is triangular in shape:

- The base being formed by the internal surface of the fundus between the orifices of the uterine tubes.
- The apex by the internal orifice of the uterus through which the cavity of the body communicates with the canal of the cervix.

The uterine cervix, although anatomically a part of the uterus, has rather separate function and is associated with separate pathological entities (*Standring and Gray, 2008*).

Uterine supports and ligaments

- Anterior - pubocervical ligament
- Lateral - transverse cervical ligaments (Cardinal or Mackendrodt's)
- Posterior - uterosacral ligaments
- Inferior - puborectalis and pubovaginalis parts of the levatorani muscle

Relations

- Anteriorly - bladder; uterovesical pouch
- Posteriorly - rectum; pouch of Douglas

- Laterally - broad ligament; uterine vessels uterine tubes open into its upper part
- Inferiorly - uterine cavity communicates with that of the vagina

Position

- The most common position of the uterus is anteverted (cervix angles forward) and anteflexed (body is flexed forward). The position of the uterus in the adult is liable to considerable variation, depending chiefly on the condition of the bladder and rectum. When the bladder is empty the entire uterus is directed forward, and is at the same time bent on itself at the junction of the body and cervix, so that the body lies upon the bladder. As the latter fills, the uterus gradually becomes more and more erect, until with a fully distended bladder the fundus may be directed backward toward the sacrum (*Speroff et al., 1999*).

Uterine Corpus (or Body)

The uterine corpus is a thick, pear-shaped organ, somewhat flattened anteroposteriorly. The wall of the body of the uterus is composed of three layers: the endometrium, a glandular mucous membrane; the myometrium or smooth muscle layer; and the serosa. The function of the endometrium is to provide a suitable environment for the implantation and