

# Uterus transplants and their ethical implications

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## Abstract

Early experiments in womb transplants have increased interest in the possibility of performing this procedure in women who have no womb, usually for congenital reasons. The present article describes past experiments and summarises the most relevant reference documents before indicating the key ethical implications involved in womb transplants.

## Key words

- assisted reproductive techniques
- bioethics
- obstetrics and gynaecology
- organ transplant

## INTRODUCTION

Clinical and ethical considerations do not apply equally to all the organs that can be transplanted in humans. While some organs are vital for survival (heart, liver, lung), others that are not necessary for survival nonetheless raise ethical, anthropological and emotional issues that involve not only – and in any case to a lesser degree – the physical well-being of the recipient, but also the perception of the self and of one's body.

While a hand or face transplant clearly does not constitute a life-saving procedure, both imply significant problems regarding the patient's self-perception. The present article concerns womb transplants which, because of the particular importance of the womb in female reproductive functions, belongs to the same category. A womb is the place where a new human being settles, is formed and develops, invisible to the world until an ultra-sound reveals it and perceived as growing only by the woman who carries it: a womb transplant – involving only women – is thus the only "gender transplant" performed to date.

We are, therefore, not talking about the usual bioethical problems that accompany new methods of medically assisted procreation (such as the beginning of a person's life or the moral status of the embryo), but rather about the symbolic value attached to the womb. Although the present article addresses the problem from the point of view of the state of the art of the procedure in clinical terms and in regard to the more typically bioethical issues involved in transplants in general, it is nonetheless important to keep in mind the peculiarities of the womb, its functioning and purpose, that are unique characteristics.

Womb transplants were performed in animals as long ago as the 1960s [1]; in humans they have to date been performed in women born without a uterus (Mayer-

Rokitansky-Kunster-Hauser), but could be appropriate for other pathologies that involve the uterus.

The first experimental womb transplant in a woman was performed in 2000 [2]. The uterus was taken from a 46-year old living donor and transplanted into a 26-year old woman. It responded to treatment with oestrogen and progesterone and could thus potentially have been stimulated to achieve endometrial proliferation. However, the development of thrombosis in the anastomosed blood vessels led to necrosis of the graft and it had to be removed.

A second attempt was made in 2011 in Turkey [3]. A 20-year old woman received a uterus taken from a deceased donor of the same age. Twenty days later the patient had her first menstrual cycle, which was followed by two early spontaneous abortions following two embryo transfers.

In 2012-2013 the first clinical trial was conducted, involving eight women with uterine agenesis and one who had had a hysterectomy [4, 5]. The organs were removed from living donors, in most cases the mothers of the recipients. Post-operative complications included: thrombosis in the uterine arteries (1 case in 9) pleural effusion (2/9), intrauterine abscess (1/9) retroperitoneal haematoma (1/9). The only post-operative complication in a donor was one case of urethral-vaginal fistula (1/9). Two of the transplants were unsuccessful: bilateral uterine artery occlusion and persistent endometriosis required hysterectomy. In the remaining cases menstrual cycles were regular after 6 months.

In 2013, at the Sahlgrenska University Hospital in Gothenburg (Sweden), a 35-year old woman suffering from Rokitansky syndrome was given a womb taken from a living 65-year old donor. Prior to the transplant *in vitro* fertilisation had been performed using oocytes from the recipient and spermatozoa from her partner, and 11 em-

bryos had been frozen. Forty-three days after the transplant the recipient had her first menstruation and one year after the first embryo was transplanted. After 31 weeks and 6 days the woman gave birth to a boy of normal weight for his gestational age [6]. Subsequently, the transplants in Sweden resulted in four other births [7, 8].

Table 1 shows a summary of the womb transplants reported to date in the specialised literature.

Although New York's Downtown Hospital had announced plans to perform a womb transplant in January 2007 [9], the first operation was performed on 24<sup>th</sup> February 2016 in Cleveland. The recipient was a 26-year old who had been included in an experimental trial aiming for 10 transplants, and the womb was taken from a deceased 30-year old donor (in contrast to the Swedish trial, which used living donors). On 8<sup>th</sup> March 2016 the transplanted womb had to be removed in an emergency operation, as a result of complications [10].

The Swedish cases encouraged several surgical teams in various countries to plan womb transplants. Such plans are usually announced in press conferences or through press agencies. For example:

- in France a womb transplant is planned for 2016 in Limoges [11];
- in Italy, the Ethical Committee of the Italian Health Institute has approved a womb transplant protocol at the Umberto I Hospital in Rome, in accordance with the regulations governing the authorisation of such trials [12];
- in the United Kingdom the UK Womb Transplant Research Team led by Richard Smith, consultant gynaecologist at Queen Charlotte's and Chelsea Hospital in London, received authorisation in September 2015 to conduct trials with 10 patients [13].

### INSTITUTIONAL DOCUMENTS

In 2008 a report by the International Federation of Gynecology and Obstetrics (FIGO) found that the lack of sufficient data on the safety and efficacy for the recipient meant that womb transplants were not acceptable from the ethical point of view. The FIGO therefore made the following recommendations:

"1. uterine transplantation, which may reach human clinical experimentation stage, should only occur after significant and adequate research in appropriate large animal models, including primates;

2. the lengths to which some women will go to experience uterine transplantation, even with the availability of such options as adoption and surrogacy in some cultures, can lead to a conflict of interest and pressure on researchers to move prematurely to human application;
3. it is unethical to remove a uterus for transplantation from a young woman who did not complete having the desired number of children or a uterus with a deformed cavity;
4. given the lack of data on safety and the known hazards to live donors, the procedure is considered ethically inappropriate" [14].

In 2012 a working group from McGill University (Montreal, Canada) proposed the "Montreal criteria for the ethical feasibility of uterine transplantation" [15], which were updated the following year [16]. The revised Montreal criteria for the ethical feasibility of uterine transplantation are:

#### 1. The recipient

- a. is a genetic female of reproductive age with no medical contraindications to transplantation,
- b. has documented congenital or acquired UFI that has failed all current gold standard and conservative therapy,
- c. (c1) has a personal or legal contraindication to surrogacy and adoption measures and desires to have a child, or (c2) seeks the UTx solely as a measure to experience gestation, with an understanding of the limitations provided by the UTx in this respect,
- d. has not had her decision to undergo UTx deemed as irrational by expert psychological evaluation, and has no psychological comorbidity that interferes with diagnostic workup or treatment,
- e. does not exhibit frank unsuitability for motherhood,
- f. is likely to take antirejection medication and follow up with the treating team in a responsible manner, and
- g. is responsible enough to consent, informed enough to make a responsible decision.

#### 2. The donor

- a. is a female of reproductive age with no medical contraindications to donation,
- b. (b1) has repeatedly attested to her conclusion of parity, or (b2) has signed an advanced directive for post mortem organ donation,

**Table 1**

Summary of the womb transplants reported to date in the specialised literature

Author	N. patients	Age	Donor/s	Outcome
Fageeh <i>et al.</i> [2]	1	26	living	Hysterectomy for vascular occlusion 3 months after transplant
Ozkan <i>et al.</i> [3]	1	21	deceased	Pregnancy and abortion
Brännström <i>et al.</i> [4] Johannesson <i>et al.</i> [5] Brännström <i>et al.</i> [6] Dahm-Kähler <i>et al.</i> [7] Brännström <i>et al.</i> [8]	10	31.5 (average)	living	7 cases: viable uterus (of which 3 with sub-clinical rejection treated effectively with corticosteroids) 2 cases: serious rejection with bilateral occlusion of arteries 5 live births
Cleveland Clinic [10]	1	26	deceased	Hysterectomy 12 days after transplant for complications

- c. has no history of uterine damage or disease, and
- d. is responsible enough to consent, informed enough to make a responsible decision, and not under coercion.

### 3. *The health care team*

- a. is part of an institution that meets Moore's third criterion as it pertains to institutional stability,
- b. has provided adequate informed consent to both parties regarding risks, potential sequelae, and chances of success and failure,
- c. has no conflict of interest independently or with either party, and
- d. has the duty to preserve anonymity if the donor or recipient do not explicitly waive this right".

On 23<sup>rd</sup> June 2015 the French Académie Nationale de Médecine published a report on "La transplantation utérine" [17]. The report noted the data published so far, and in particular those relating to the birth in Sweden in 2015; pointed to the uncertainties, risks and problems; noted that transplants from both living and deceased donors raised serious issues; indicated the uncertainties surrounding the long-term health conditions of children born from a transplanted womb, and made the following recommendations:

1. research programmes that are conducted strictly in accordance with regulations laid down in law and by the Agence de la Biomédecine in regard to all innovations in the matter of organ transplantations and medically assisted procreation should continue;
2. clear and detailed information that takes into account the drawbacks and risks associated with womb transplants should be given to living donors and recipients participating in these research programmes, who should be given appropriate assistance before, during and after the procedure;
3. data on research conducted in France and in other countries should be collected with a view to ensuring the validity of womb transplants and, in due course, to assess the possibility of extending the procedure, with respect for the ethical principles that apply in all organ transplantations and medically assisted procreation, in order to avoid deviations".

More recent documents, as we can see, are less wary of the concept of womb transplants. However, the FIGO has still not amended the opinion it published in 2008 [18], notwithstanding the availability of additional results.

## ETHICAL ASPECTS

### *General criteria for experimental surgery*

With very few exceptions new surgical techniques do not enter clinical practice as a result of randomised clinical trials; they evolve gradually from existing techniques or, more rarely, from bold divergences from common practice adopted by a surgical team on the basis of experience [19].

Francis D. Moore has proposed three criteria that should be met in order for innovative surgical procedures to become acceptable, including from the ethical point of view. The first is laboratory experience that optimally should precede a surgical innovation; the second is "field

strength" meaning the intellectual and technical expertise available in the institution where the work is being done; and the third is "institutional stability" based on its resources, support systems, and staff [20, 21]. All three were cited in the "Montreal criteria for the ethical feasibility of uterine transplantation" mentioned above [15, 16].

### *Donation from deceased and living donors*

There are pros and cons for transplants from deceased donors:

#### **Pros:**

- no risk for the donor;
- less time needed for removal;
- technically easier, thanks to longer peduncles and easier anastomosis.

#### **Cons:**

- difficult in making a complete pre-operative appraisal;
- logistic issues: distances, etc.;
- informed consent calls for special attention. When transplanting unusual organs (e.g. face, hands) it is advisable to ask for specific consent in addition to the generic declaration of consent to the donation of organs [21]. This is particularly advisable before removing a womb, given the special significance and symbolic nature of the organ;
- very little clinical experience;
- there are pros and cons for transplants from living donors.

#### **Pros:**

- increased certainty that the organ will function.

#### **Cons:**

- highly complicated procedure for the donor: Brännström reported surgical procedures lasting more than 10 hours, involving considerable risks [6];
- the age of living donors is a further problem. To increase the chance of success the donor should be of childbearing age. It is clearly problematic, to say the least, to remove the womb of a fertile woman, even she has already born children;
- it could be feasible to transplant a womb taken from a living donor with a pathology that does not directly involve the uterus (which therefore continues to function) but prevents her procreating;
- a particular problem arises with transsexual women who wish to have their wombs removed. The Académie Nationale de Médecine has suggested that in these cases a womb transplant could be possible provided two conditions are met: the transplant should be performed in the interest of the transsexual and for the therapeutic benefit of the recipient (i.e. procreation) [17]. On this point it should be noted that some lesbian, gay, bisexual, transsexual (LGBT) associations are campaigning to abolish the need for surgical sterilisation as a requisite for gender reassignment. Clearly, while such cases fall within the category of transplants from living donors, the unusual nature of the donor's personal journey calls for an even more specific form of informed consent;
- current legislation requires that there should be a family connection between the donor and the recipient. Cases of undue influence (such as a mother who feels responsible for her daughter's inability to procreate) and other forms of interference cannot be ruled out.

### **The recipient**

Although womb transplants are seen in some quarters as being relatively simple in comparison with the transplantation of other organs, the procedure is a complex one. The operation described by Brännström lasted 10 hours and 7 minutes for the donor and 4 hours and 55 minutes for the recipient [6].

A womb transplant is not a life-enhancing event for the recipient (in fact, it has the opposite effect), though it does enable her to procreate.

To avoid the need for lifelong immunosuppressive therapy, a womb transplant requires two further operations: a caesarean section for delivery, followed by a hysterectomy.

The possibility of rejection during pregnancy means that an exit strategy is more complicated in a womb transplant than in other organ transplantation procedures.

Issues of distributive justice also arise, given that the high costs of these interventions make them inaccessible to most people.

There is a considerable imbalance between the large number of potential recipients and very few potential donors. The main source should be young, brain-dead donors with healthy wombs, of whom there are very few.

Recipients should receive detailed information regarding: the surgical risks, probable need to remove the transplanted uterus, complex preparation process (pre-operative hormone therapy), possible failure to procreate and the effects of immunosuppressive therapy.

### **Womb transplants and medically-assisted procreation**

The two are linked because to date post-transplant pregnancies have been initiated only after *in vitro* fertilisation.

Womb transplants pose many problems similar to those posed by other assisted procreation procedures: rights of the donor, health consequences for the foetus and child, interventions on a woman's body, the role of the state in regulating procreation, etc.

There are considerable regulatory problems. Current regulations in most states do not mention womb transplants either in the context of assisted procreation or among types of transplants performed to date.

Womb transplants could be considered as a means to counter the perverse phenomenon of surrogacy, though in the current circumstances it is too experimental a procedure to be an alternative: this could change if and when womb transplants become a part of consolidated clinical practice. For the sake of clarity, the lack of a "medical" alternative to surrogacy does not make this phenomenon ethically legitimate; it remains an unacceptable exploitation of women and a violation of the rights of the child. In the current state of knowledge the requisite cited in the "Montreal criteria for the ethical feasibility of uterine transplantation" – that the recipient should have "a personal or legal contraindication to surrogacy" – is ethically highly controversial and, in the authors' opinion, quite unacceptable.

There could be a higher risk of trade in wombs than in other organs. This risk is heightened by the fact that

while there exist international conventions against the trade in organs for transplantation [22] (which unfortunately is nonetheless present in some states), some countries allow the legal sale of gametes. This, combined with the current legalisation or, in some states, mild acceptance of surrogacy, could lead to the treatment of the womb as a "separate" case associated with female reproduction, an area that is already more susceptible to market criteria and less protected.

### **Pregnancy**

Because the objective of womb transplants is conception, these procedures pose highly specific problems linked to the wellbeing of the product of conception, that are not associated with the transplantation of other organs. In ethical terms the risks are of primary concern.

Currently available figures do not point to short-term risks for the child as a consequence of immunosuppression, but risks associated with premature birth cannot be excluded, nor can long-term risks such as haemophilia, cancer, retarded growth or other pathologies.

There is the possibility of psychological risks for children on learning they were born from a transplanted womb.

### **CONCLUSIONS**

The transplantation of a womb is the first all-female "gender transplant" performed to date: it stands alone in the world of transplants, also because of the emotional and symbolic importance attached to the functioning and purpose of the womb. In ethical and clinical terms, it is the opinion of the authors that in the current state of knowledge womb transplants are still a highly experimental procedure and should be subject to all the risk/benefit assessments normally applied in similar circumstances. It should also be recalled that this is not a life-saving procedure and that the womb should in any case be removed after any pregnancy in order to permit the interruption of immunosuppressive therapy: the risk/benefit assessment should be performed in this light. The state of the art for the moment excludes the possibility that womb transplants can be considered as an alternative to other forms of pregnancy, which in any case are highly controversial in ethical, social and psychological terms (and unacceptable in the authors' opinion), such as surrogacy, or even as an alternative to legitimate means of achieving parenthood such as adoption. In brief, in ethical terms womb transplants from a deceased donor, in specific, carefully controlled and clinically assessed circumstances and bearing in mind that such procedures are currently highly experimental, could be acceptable, while the removal and transplantation of a womb from a living donor presents for now such major issues and contra-indications as to render it unacceptable.

### **Conflict of interest statement**

None.

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## REFERENCES

1. Eraslan S, Hamernik RJ, Hardy JD. Replantation of uterus and ovaries in dogs, with successful pregnancy. *Arch Surg* 1966;92(1):9-12.
2. Fageeh, W, Raffa H, Jabbad H, Marzouki A. Transplantation of the human uterus. *Int J Gynaecol Obstet* 2002;76(3):245-51.
3. Ozkan O, Akar ME, Erdogan O, Ozkan O, Hadimioglu N. Uterus transplantation from a deceased donor. *Fertil Steril* 2013;100(6):e41.
4. Brännström M, Johannesson L, Dahm-Kähler P, Enskog A, Mölne J, Kvarnström N, Diaz-Garcia C, Hanafy A, Lundmark C, Marcickiewicz J, Gäbel M, Groth K, Akouri R, Eklind S, Holgersson J, Tzakis A, Olausson M. First clinical uterus transplantation trial: a six-month report. *Fertil Steril* 2014;101(5):1228-36.
5. Johannesson L, Kvarnström N, Mölne J, Dahm-Kähler P, Enskog A, Diaz-Garcia C, Olausson M, Brännström M. Uterus transplantation trial: 1-year outcome. *Fertil Steril* 2015;103(1):199-204.
6. Brännström M, Johannesson L, Bokström H, Kvarnström N, Mölne J, Dahm-Kähler P, Enskog A, Milenkovic M, Ekberg J, Diaz-Garcia C, Gäbel M, Hanafy A, Hagberg H, Olausson M, Nilsson. Livebirth after uterus transplantation. *Lancet* 2015;385(9968):607-16.
7. Brännström M. Uterus transplantation. *Curr Opin Organ Transplant* 2015;20(6):621-8.
8. Dahm-Kähler P, Diaz-Garcia C, Brännström M. Human uterus transplantation in focus. *Br Med Bull* 2016;117(1):6-78.
9. Stein R. First US uterus transplant planned. Some experts say risk isn't justified. *The Washington Post* 15 January 2007.
10. Cleveland Clinic. *Statement from Cleveland Clinic. Update on 1st uterus transplant*. March 2016. Available from: <http://my.clevelandclinic.org/about-cleveland-clinic/newsroom/releases-videos-newsletters/2016-2-16-update-on-first-uterus-transplant>.
11. Génétique. *Greffe d'utérus: un premier essai clinique autorisé en France*. 9 Novembre 2015. Available from: [www.genetique.org/fr/greffe-duterus-un-premier-essai-clinique-autorise-en-france-64392.html](http://www.genetique.org/fr/greffe-duterus-un-premier-essai-clinique-autorise-en-france-64392.html).
12. Conferenza permanente per i rapporti tra lo Stato, le Regioni e le Province autonome di Trento e di Bolzano. Accordo tra il Ministro della Salute, le Regioni e le Province autonome di Trento e Bolzano 14 febbraio 2002. Repertorio atti n. 1388 del 14 febbraio 2002. *Gazzetta Ufficiale della Repubblica Italiana - Serie generale* 3 ottobre 2002;143(232):34-5.
13. UK Womb Transplant. *UK Womb Transplant Research Team receives go-ahead to begin operations*. 29 September 2015. Available from: <http://wombtransplantuk.org/uk-womb-transplant-research-team-receives-go-ahead-to-begin-operations>.
14. Milliez J. Uterine transplantation FIGO Committee for the Ethical Aspects of Human Reproduction and Women's Health. *Int J Gynaecol Obst* 2009;106:270.
15. Lefkowitz A, Edwards M, Balayla J. The Montreal criteria for the ethical feasibility of uterine transplantation. *Transpl Int* 2012;25(4):439-47.
16. Lefkowitz A, Edwards M, Balayla J. Ethical considerations in the era of the uterine transplant: an update of the Montreal criteria for the ethical feasibility of uterine transplantation. *Fertil Steril* 2013;100(4):924-6.
17. Henrion R, Milliez J (Eds). *La transplantation utérine. Rapport*. Académie Nationale de Médecine; 23 Juin 2015. Available from: [www.academie-medecine.fr/wp-content/uploads/2015/06/Transpl-uterus-C.pdf](http://www.academie-medecine.fr/wp-content/uploads/2015/06/Transpl-uterus-C.pdf).
18. Petrini C. Surgical experimentation and clinical trials: differences and related ethical problems. *Ann Ist Super Sanita* 2013;49(2):230-3.
19. Moore FD. Ethical problems special to surgery: surgical teaching, surgical innovation, and the surgeon in managed care. *Arch Surg* 2000;135(1):14-6.
20. Morgenstern L. Innovative surgery's dilemma. *Surg Innov* 2006;13(2):73-4.
21. Agich GJ. Extension of organ transplantation: some ethical considerations. *Mt Sinai J Med* 2003;70(3):141-7.
22. Council of Europe. *Convention against trafficking in human organs (Adopted by the Committee of Ministers on 9 July 2014 at the 1205th meeting of the Ministers' Deputies. Signed in Santiago de Compostela 25 March 2015)*. 9 July 2014. Available from: <https://wcd.coe.int/ViewDoc.jsp?Ref=CM/Del/>