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Editorial

Uterus transplantation: Which indications?

Uterine factor infertility (UFI) is defined as an absent or non-functional uterus in a woman of childbearing age. It affects about 20 000 per 100 million women of childbearing age [1]. UFI can result from congenital absence of the uterus (Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome) or from hysterectomy, performed for a non-malignant condition (such as postpartum haemorrhage or adenomyosis) or malignant disease (cervical or uterine cancer). It can also be the result of a non-functional uterus, caused for example by in utero exposure to diethylstilbestrol (DES), pelvic radiotherapy, or severe adhesions such as occur in Asherman's syndrome. Complete androgen insensitivity syndrome (CAIS) is a special case. The only way these women can attain both biological and gestational motherhood is uterus transplantation (UTx). Twelve healthy children have been born worldwide from the 26 UTx procedures that have been published [2]. Most of these patients had MRKH syndrome. Only two had UFI of a different aetiology, namely hysterectomy for cervical cancer [3] and hysterectomy for postpartum haemorrhage [4]. This article discusses the indications for UTx for each UFI aetiology.

MRKH syndrome

MRKH syndrome, characterized by complete agenesis of the uterus and proximal two-thirds of the vagina, affects 1 in 4500 women [5]. Their ovaries and secondary sexual characteristics are normal, and they have a 46XX karyotype. In 50% of cases, MRKH syndrome is associated with urinary tract defects and in particular the presence of a single kidney [5]. During pregnancy, this renal agenesis may lead to preeclampsia. The Swedish team observed 3 cases of preeclampsia among the 4 patients with MRKH syndrome and renal agenesis [6]. Half of MRKH patients have undergone surgical vaginal reconstruction, most frequently using a segment of the ileum or colon [7]. None of the transplant recipients with MRKH syndrome to date had undergone surgical vaginal reconstruction. The German and Turkish teams included patients who had undergone the Vecchietti procedure [8] and ileal colpoplasty [9], respectively. Sigmoid colpoplasty, with the bowel secretions these grafts produce, poses a risk to the uterine graft and embryo implantation. The Turkish team's uterus transplant in a patient who had previously undergone reconstruction through ileoplasty was a technical success, but as she subsequently had two early miscarriages, the possibility that the vaginal reconstruction technique had a negative impact cannot be excluded [9].

As a precaution, UTx would be best avoided in women who have undergone vaginal reconstruction using bowel tissue. The option of UTx for women with UFI should influence the choice of reconstruction procedure used in MRKH patients. The Vecchietti procedure or those using non-bowel tissue (e.g. the Davydov procedure) would be preferable for vaginal reconstruction [9].

Prior hysterectomy for malignant disease

Only one uterus transplant has been performed on a patient who had undergone hysterectomy for cervical cancer, which measured 3 cm [3]. No signs of recurrence were reported despite prolonged exposure to immunosuppressants, as she had two pregnancies following UTx. However, a case of post-UTx cervical dysplasia has been described, which was treated by conization [10]. The main risk for patients with a history of malignancy is reactivation of the cancer by the immunosuppression required after transplantation [11]. The increased risk of cancer associated with immunosuppression is only seen after at least 5 years of treatment however [12].

Ovarian conservation after hysterectomy for cancer is still much debated. If concomitant oophorectomy was performed, UTx would also require the use of donor gametes. No such "double donations" have yet been attempted.

Finally, prior pelvic radiotherapy can cause ovarian and uterine infertility. No uterus transplants have yet been performed after pelvic radiotherapy. There is some uncertainty about the technical aspects of UTx in a woman who has undergone radiotherapy, particularly with regard to vascular suturing.

In summary, UTx after pelvic malignancy remains a very marginal indication, with only one case described to date.

Prior hysterectomy for a non-malignant condition

Hysterectomy is performed to manage major bleeding in 1 in 1000 births [13]. The bleed would usually have required blood transfusion. In such cases, there is a risk of HLA sensitization, a risk also posed by pregnancy itself. In patients undergoing organ transplantation, HLA sensitization is associated with a high risk of graft rejection [7]. Perfect HLA compatibility between the donor and recipient is therefore necessary, greatly reducing the number of potential donors for these patients.

An ethical problem may arise if a patient already has children and underwent hysterectomy for postpartum haemorrhage. The high surgical and medical risk associated with UTx and the risk of recurrence of postpartum haemorrhage for a woman who already has one or more children require further discussion. Finally, it may be difficult psychologically for a patient to undergo hysterectomy twice, as her uterus will be removed "a second time" once the planned child or children have been born.

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Prior hysterectomy for non-malignant disease is a potential indication for UTx, but evaluation is required.

Presence of a non-functional uterus (non-absolute uterine factor infertility)

Many conditions can cause the uterus to become non-functional. Examples include extensive adenomyosis, post-irradiation uterine injury, Asherman's syndrome and diethylstilbestrol syndrome. In these cases, the main difficulty lies in determining whether infertility is entirely due to a uterine problem, with no contribution from other aetiologies. In addition, the presence of a non-functional uterus requires elective hysterectomy before UTx, increasing the surgical risk.

The drug diethylstilbestrol, widely used in France to treat vomiting in pregnancy, was withdrawn from the market in 1977. In utero exposure to diethylstilbestrol has caused uterine malformations that can result in infertility. Given the date of its market withdrawal, the last patients exposed in utero would now be ineligible on age grounds for assisted reproduction and therefore UTx. However, transgenerational effects through epigenetic mechanisms have been described in the literature, causing genital tract malformations in children of women who were exposed in utero to diethylstilbestrol [7].

For women with non-absolute UFI, UTx should only be considered when their uterine anomaly is confirmed as the sole factor underlying their infertility.

CAIS

CAIS affects between 1/20 000 and 1/99 000 women at birth [7]. It is due to a mutation in the gene encoding androgen receptors. These women have an XY karyotype and no uterus or ovaries but have female secondary sexual characteristics. Within society, they are considered women on account of their female phenotype. UTx for these patients poses two problems. First is the anatomical problem, because they lack ovaries and would require donor oocytes. They would not therefore be the child's biological mother. Second, these patients have an XY karyotype, which currently makes them ineligible for assisted reproduction and therefore UTx.

UTx is currently therefore contraindicated in CAIS for two reasons: absence of an ovary and a 46XY karyotype.

Age limit for access to UTx

The age limit for performing UTx remain contentious. The woman's age when her oocytes or embryos were frozen may differ from the age at which she undergoes UTx. As pregnancy rates decline after the age of 35 years, it would be better to freeze eggs or embryos before 38 or even 35 years of age in order to optimize the success of UTx. The uterus transplant could be performed later, although pregnancy after the age of 40 years is associated with greater risk [14].

Typically, the upper age limit for participation in UTx trials has been 36–38 years. The median age of recipients in the Swedish series was 31.9 years (± 3.9 years) [3]. The age range of recipients in the study conducted by Testa et al. was 28 to 34 years [15], while the German team's recipients were aged between 23 and 34 years [8].

It is time for a debate in France about whether women with UFI should undergo early oocyte cryopreservation, before any plans are made to perform a uterus transplant.

Conclusion

UFI has many causes that differ in prevalence but more importantly in their aetiology. Theoretically each of these aetiologies could be treated by UTx, thereby enabling these women to have a child. However, UTx is still at an early stage of development, and candidates must be selected with care. The current restricted indications will be expanded at a later date.

Currently the ideal candidate for UTx in France is a nullipara under the age of 36 years, with absolute UFI and no history of abdominal surgery or pelvic irradiation and no malformations of non-genital organs, who also has functional ovaries and satisfies the country's general eligibility criteria for access to assisted reproduction.

Disclosure of interest

The authors declare that they have no competing interest.

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