Introduction

Uterine-related infertility is one of the main unresolved causes of infertility, and it affects around 3-5% of the general population (1-7). It might be congenital (agenesis or malformation) or acquired (Asherman syndrome, myoma uteri, adenomyosis, or hysterectomy). Research on uterus transplantation started in rabbits and dogs in 1896 (8, 9). Clues on the transplantation technique and improvements in immunosuppressive agents have enabled progression to the clinical research phase in the last two decades (8, 9). Currently, uterine factor infertility patients can conceive through gestational surrogacy (10). Other indications of gestational surrogacy are history of recurrent miscarriage and implantation failure and deteriorating maternal diseases such as severe systemic lupus erythematosus, cardiac disorders, Takayasu’s arteritis, history of breast cancer, hematological condition, pulmonary hypertension, residual pituitary macroadenoma, and brain tumor (10, 11). Results of many studies have shown that children born through vital organ tissue transplantation and immunosuppression or gestational surrogacy are healthy (12-14). Attitudes toward gestational surrogacy can be affected by religious, cultural, ethical, and legal factors (15, 16). Gestational surrogacy is not allowed in Australia (South and West), Austria, the Czech Republic, Denmark, Egypt, France, Germany, Ireland, Italy, Japan, Jordan, Norway, Poland, Saudi Arabia, Singapore, Spain, Sweden, Switzerland, Taiwan, and Turkey (17). Solving the legal and ethical issues and increasing public awareness regarding gestational surrogacy may increase the acceptance rate (18, 19).

Uterus transplantation research

Uterus transplantation research has been conducted in several animal models (mouse, rat, sheep, pig, baboon, and macaque) (Table 1) (8, 9). The allogeneic uterus transplantation technique has been better defined with either end-to-end anastomosis of the uterine arteries and veins or anastomosis of an aortacaval patch to the external iliacs (20, 21). Progress in composite tissue transplantation has been achieved with the development of new immunosuppressive therapy regimens (22). The first attempt in human uterus transplantation was performed by Fageeh et al in 2000 (23). The graft has to be removed on 99th day due to thromboses in the anastomosis site. International Federation of Gynecology and Obstetrics (FIGO) advised that the human clinical experimentation stage should take place only after significant and adequate research in appropriate, large animal models, including primates (24). Since FIGO’s statement in 2009, numerous animal studies, including studies using primates, have been performed (25). Akdeniz University is a well-known transplantation center that has also performed the first double hand and face transplantations in Turkey (26). A transplantation center’s experience with microsurgery, immunosuppression, and infection control should be the most important factors determining success when attempting a new composite tissue transplantation procedure. Following surgical uterus retrieval experience with cadavers for checking the feasibility of this surgical procedure, and taking institutional review board approval and discussing the procedure with the organ transplantation team and the recipient candidates, our team performed the first uterus transplantation from a multiple organ donor (27). The anonymous details of the...
patient, her condition, the rationale and background for the use of this procedure, exactly what was performed, and adequate details regarding the relevant outcomes have been reported automatically as advised (personal communication with Dr Mats Brännström, October 2011). The better recording of surgical training and the experience of participating surgeons have also been defined by our group (28). Full and clear informed consent had also been obtained from the recipient following long-term consultation. We reported the first clinical pregnancy 18 months after uterus transplantation (29). Unfortunately, this pregnancy resulted in miscarriage (30). Brännström’s team has performed nine uterus transplantation surgeries from live donors (31). They have recently reported the first live birth after uterus transplantation, which is a very important step forward (32). The outcomes of their seven cases, as well as our case, will provide very important information for the future of uterus transplantation (Table 2).

Safety concerns associated with uterus transplantation
Following the first live donor uterus transplantation attempt, FIGO stated that the harvesting of the donated uterus, if removed from a living donor, necessitates relatively major surgery with its own risk of complications (33). They further considered the procedure ethically inappropriate and advised surgeons to not perform the procedure using organs from live donors, given the lack of data on the safety and hazards for live donors.

Table 1. Uterus transplantation studies in animals

<table>
<thead>
<tr>
<th>Reference</th>
<th>Species</th>
<th>Vascular supply</th>
<th>Transplanted organ</th>
<th>Immuno-suppression regimen</th>
<th>Study population</th>
<th>Viable grafts</th>
<th>Pregnancy/delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knauer 1896</td>
<td>Rabbit(a)*</td>
<td>-</td>
<td>Ovaries</td>
<td>-</td>
<td>1</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Zhordonia 1964</td>
<td>Sheep(a)</td>
<td>Omentopexy</td>
<td>Uterus &amp; Ovaries</td>
<td>-</td>
<td>18</td>
<td>10 normal function</td>
<td>Not tested</td>
</tr>
<tr>
<td>Eraslan 1966</td>
<td>Dog(a)</td>
<td>Anastomosis</td>
<td>Uterus &amp; Ovaries</td>
<td>-</td>
<td>14</td>
<td>7 rejection by 17-45 days</td>
<td></td>
</tr>
<tr>
<td>Yonemoto 1969</td>
<td>Dog(h)**</td>
<td>Anastomosis</td>
<td>Uterus &amp; Ovaries</td>
<td>Azathioprine &amp; prednisolone</td>
<td>7 a 50 h</td>
<td>6a normal function</td>
<td>2(autot)/1</td>
</tr>
<tr>
<td>Oltary 1969</td>
<td>Dog(a)</td>
<td>Omentopexy</td>
<td>Uterus &amp; Ovaries</td>
<td>-</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mattingly 1970</td>
<td>Dog(a/h)</td>
<td>Anastomosis</td>
<td>Uterus &amp; Ovaries</td>
<td>Azathiopine</td>
<td>7 a 50 h</td>
<td>6a normal function</td>
<td>2(autot)/1</td>
</tr>
<tr>
<td>Scott 1970</td>
<td>Dog(a/h)</td>
<td>Omentopexy</td>
<td>Segmented Uterus</td>
<td>Azat&amp;pred (5 hormot)</td>
<td>10 a</td>
<td>7a normal function</td>
<td>Not tested</td>
</tr>
<tr>
<td>Scott 1971</td>
<td>Primate (a/h)</td>
<td>Omentopexy</td>
<td>Uterus &amp; tubes</td>
<td>-</td>
<td>10 h 4 a</td>
<td>10h rejection 4a normal function</td>
<td>Normal menst and mating</td>
</tr>
<tr>
<td>Barzilai 1973</td>
<td>Dog(a)</td>
<td>Anastomosis</td>
<td>Uterus &amp; Ovaries</td>
<td>-</td>
<td>13 oment 12 anast</td>
<td>9 total necrosis</td>
<td>1(ananst)/1</td>
</tr>
<tr>
<td>Confinio 1986</td>
<td>Rabbit (a/h)</td>
<td>Sutured to the broad lig</td>
<td>Unilat uterus &amp; Ovary</td>
<td>Cyclosporine</td>
<td>8 autot 10 hormot</td>
<td>3a 3h preserved by 30 days</td>
<td>Not tested</td>
</tr>
<tr>
<td>Lee 1995</td>
<td>Rat&amp; (h)</td>
<td>Anastomosis</td>
<td>Uterus &amp; Ovaries</td>
<td>-</td>
<td>24</td>
<td>Normal function From 1-180 days</td>
<td>Not tested</td>
</tr>
<tr>
<td>Diaz Garcia 2010</td>
<td>Rat(allo)</td>
<td>Anastomosis</td>
<td>Uterus</td>
<td>- Tacrolimus</td>
<td>10</td>
<td>Normal function</td>
<td>Delivery</td>
</tr>
<tr>
<td>Ramirez 2011</td>
<td>Sheep (allo)</td>
<td>Anastomosis</td>
<td>Uterus</td>
<td>-</td>
<td>1 allo-transplant</td>
<td>Normal function</td>
<td>Delivery</td>
</tr>
<tr>
<td>Miñaur M 2012</td>
<td>Monkey (h)</td>
<td>Anastomosis</td>
<td>Uterus</td>
<td>-</td>
<td>2 syngeneic</td>
<td>2 viable graft</td>
<td>1 spontan pregnancy</td>
</tr>
<tr>
<td>Diaz Garcia 2014</td>
<td>Rat</td>
<td>Anastomosis</td>
<td>Uterus</td>
<td>Tacrolimus</td>
<td>10 allo-transplant</td>
<td>6 viable graft</td>
<td>5 delivery</td>
</tr>
</tbody>
</table>

a* autotransplantation
h** homotransplantation
ATG***antithymocyte globulin

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Table 2. Uterus transplantation studies in humans

<table>
<thead>
<tr>
<th>Reference</th>
<th>Species</th>
<th>Vascular supply</th>
<th>Transplanted organ</th>
<th>Immunosuppression regimen</th>
<th>Study population</th>
<th>Viable grafts</th>
<th>Pregnancy/delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fageeh W 2000</td>
<td>Human</td>
<td>Anastomosis</td>
<td>Uterus</td>
<td>Cyclosporine Azathioprine Prednisolone Antithymocyte globulin</td>
<td>1 allotransplant</td>
<td>Normal function for 3 months</td>
<td>Not tested</td>
</tr>
<tr>
<td>Ozkan and Akar M 2013</td>
<td>Human</td>
<td>Anastomosis</td>
<td>Uterus (multiple organ donor)</td>
<td>ATG*** Tacrolimus Mycophenolate mofetil Azathioprine Prednisolone</td>
<td>1 allotransplant</td>
<td>1 viable graft</td>
<td>Spontaneous abortion</td>
</tr>
<tr>
<td>Brannstrom M 2014</td>
<td>Human</td>
<td>Anastomosis</td>
<td>Uterus</td>
<td>ATG Tacrolimus Mycophenolate mofetil Azathioprine Prednisolone</td>
<td>9 allotransplant</td>
<td>7 viable graft</td>
<td>1 delivery</td>
</tr>
</tbody>
</table>

donors. Risks for the live donor and recipient are defined as the complications of hysterectomy, sequelae associated with the removal of vascular pedicles, probable ovarian dysfunction, and decreased quality of life (34).

Conclusion

Uterus transplantation should be performed by a team comprising transplant surgeons, gynecologists, plastic surgeons, transplant internists, infection specialists, and transplant psychiatrists. Any team planning to perform human uterus transplantsations in the future should undergo extensive training and methodological development with the use of large animal models or cadavers. In addition, all aspects of transplantation, including immunosuppression protocols and the follow-up of transplant patients and pregnancies, are fundamental parts of the training process, because the procedure carries major surgical risks to the live donor and recipient, and no definitive conclusions can be made regarding uterus transplantation. Regenerative medicine also holds significant promise for transplantation in the future (35). Concerning the surgery and immunosuppression-related risks, congenital anatomical variations in the genitourinary system of the recipient, such as solitary pelvic kidney, gestational surrogacy policies should be established in parallel with clinical and experimental uterus transplantation studies.

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