Might uterus transplantation be an option for uterine factor infertility?

Münire Erman Akar

Department of Obstetrics and Gynecology, Akdeniz University Faculty of Medicine, Antalya, Turkey

Abstract

Current data on uterus allotransplantation research has been reviewed and summarized. Over the past 15 years, progress in uterus transplantation research has increased dramatically. As a consequence, the first pregnancy and delivery following uterus allotransplantation in rats have been reported. The technique has been better defined. Although clinical pregnancy and delivery following uterus allotransplantation has been reported in humans, there are still many questions to be answered before clinical application. Gestational surrogacy still remains an important option for being a genetic parent in selected cases with uterine factor infertility. (J Turk Ger Gynecol Assoc 2015; 16: 45-8)

Keywords: Uterus transplantation, uterine factor infertility, gestational surrogacy

Received: 28 May, 2014 **Accepted:** 07 January, 2015

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

Address for Correspondence: *Münire Erman Akar, Department of Obstetrics and Gynecology, Akdeniz University Faculty of Medicine, Antalya, Turkey.*
Phone: +90 546 840 76 73 e.mail: ermanmunire@gmail.com

DOI:10.5152/jtgga.2015.15107

Table 1. Uterus transplantation studies in animals

Reference	Species	Vascular supply	Transplanted organ	Immuno-suppression regimen	Study population	Viable grafts	Pregnancy/ delivery
Knauer 1896	Rabbit(a)*	-	Ovaries	-	1	yes	
Zhordonia 1964	Sheep(a)	Omentopexy	Uterus &	- Ovaries		yes	20/12
Eraslan 1966	Dog(a)	Anastomosis	Uterus & Ovaries	-	18	10 normal function	Not tested
Yonemoto 1969	Dog(h)**	Anastomosis	Uterus & Ovaries	Azathioprine& prednisolone	14	7 rejection by 17-45 days	
Oleary 1969	Dog(a)	Omentopexy	Uterus & Ovaries	-	32		
Mattingly 1970	Dog(a/h)	Anastomosis	Uterus & Ovaries	Azathioprine	7 a 50 h	6a normal function 13h rejection by 6-21 days	2(autot)/1
Scott 1970	Dog(a/h)	Omentopexy	Segmented Uterus	Azat&pred (5 homot)	10 a	7a normal function	Not tested
Scott 1971	Primate (a/h)	Omentopexy	Uterus & tubes	-	10 h 4 a	10h rejection 4a normal function	Normal menst and mating
Barzilai 1973	Dog(a)	Omentopexy Anastomoses	Uterus & Ovaries	-	13 oment 12 anast	9 total necrosis 10 Normal function By 40 days	1(anast)/1
Confino 1986	Rabbit (a/h)	Sutured to the broad lig	Unilat uterus & Ovary	Cyclosporine	8 autot 10 homot	3a 3h preserved by 30 days	Not tested
Lee 1995	Rat& (h)	Anastomosis	Uterus & Ovaries	-	24	Normal function From 1-180 days	Not tested
Diaz Garcia 2010	Rat(allo)	Anastomosis	Uterus	- Tacrolimus	10	Normal function	Delivery
Ramirez 2011	Sheep (allo)	Anastomosis	Uterus		1 allo-transplant	Normal function	Delivery
Mihara M 2012	Monkey (h)	Anastomosis	Uterus	-	2 syngeneic	2 viable graft	1 spontan pregnancy
Diaz Garcia 2014	Rat	Anastomosis	Uterus	Tacrolimus	10 allo-transplant	6 viable graft	5 delivery

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

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

Table 2. Uterus transplantation studies in humans

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

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 transplantations 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.

Peer-review: *Externally peer-reviewed.*

Conflict of Interest: *No conflict of interest was declared by the authors.*

Financial Disclosure: *The authors declared that this study has received no financial support.*

References

1. Milliez J. Uterine transplantation FIGO Committee for the ethical aspects of human reproduction and women's health. Int J Gynaecol Obstet 2009; 106: 270. [CrossRef]
2. Saravelos Saravelos SH, Cocksedge KA, Li TC. Prevalence and diagnosis of congenital uterine anomalies in women with reproductive failure: a critical appraisal. Hum Reprod Update 2008; 14: 415-29. [CrossRef]
3. Kwee A, Bots ML, Visser GH, Bruinse HW. Emergency peripartum hysterectomy: a prospective study in The Netherlands. Eur J Obstet Gynecol Reprod Biol 2006; 124: 187-92. [CrossRef]
4. Erman Akar M, Saygili Yilmaz E, Yuksel B, Yilmaz Z. Emergency peripartum hysterectomy. Eur J Obstet Gynecol Reprod Biol 2004; 113: 178-81. [CrossRef]
5. Farquhar CM, Steiner CA. Hysterectomy rates in the United States 1990–1997. Obstet Gynecol 2002; 99: 229-34. [CrossRef]
6. Quinn MA, Benedet JL, Odicino F, Maisonneuve P, Beller U, Creasman WT, et al. Carcinoma of the cervix uteri. FIGO 26th annual report on the results of treatment in gynecological cancer. Int J Gynaecol Obstet 2006; 95: 43-103. [CrossRef]
7. Del Priore G, Saso S, Meslin EM, Tzakis A, Brannstrom M, Clarke A, et al. Uterine transplantation-a real possibility? The Indianapolis consensus. Hum Reprod 2013; 28: 288-91. [CrossRef]
8. Brännström M, Diaz-Garcia C, Hanafy A, Olausson M, Tzakis A. Uterus transplantation: animal research and human possibilities. Fertil Steril 2012; 97: 1269-76. [CrossRef]
9. Del Priore G, Schlatt S, Malanowska-Stega J. Uterus transplant techniques in primates: 10 years' experience. Exp Clin Transplant 2008; 6: 87-94.
10. Parkinson J, Tran C, Tan T, Nelson J, Batzofin J, Serafini P. Perinatal outcome after in-vitro fertilization-surrogacy. Hum Reprod 1999; 14: 671-6. [CrossRef]
11. Beski S, Gorgy A, Venkat G, Craft IL, Edmonds K. Gestational surrogacy: a feasible option for patients with Rokitansky syndrome. Hum Reprod 2000; 15: 2326-8. [CrossRef]
12. Raziel A, Schachter M, Strassburger D, Komarovsky D, Ron-El R, Friedler S. Eight years' experience with an IVF surrogate gestational pregnancy programme. Reprod Biomed Online 2005; 11: 254-8. [CrossRef]
13. Brinsden PR. Gestational surrogacy. Hum Reprod Update 2003; 9: 483-91. [CrossRef]
14. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Long

term management of the transplant recipient. Pregnancy in renal transplant recipients Nephrol Dial Transplant 2002; (17 Suppl) 4: 50-5.
15. Baykal B, Korkmaz C, Ceyhan ST, Goktolga U, Baser I. Opinions of infertile Turkish women on gamete donation and gestational surrogacy. Fertil Steril 2008; 89: 817-22. [CrossRef]
16. James S, Chilvers R, Havemann D,Phelps JY. Avoiding legal pitfalls in surrogacy arrengements. Reprod Biomed Online 2010; 21: 862-7. [CrossRef]
17. J. Cohen, H.W. Jones Jr. Worldwide legislation. In: D. Gardner, A. Weissman, C. Howless, Z. Shoham, editors. Textbook of assisted reproductive techniques. London: Taylor & Francis; 2004. p. 934.
18. Ethics Committee of the American Society for Reproductive Medicine. Consideration of the gestational carrier: a committee opinion. Fertil Steril 2013; 99: 1838-41. [CrossRef]
19. Fasouliotis SJ, Schenker JG. Social aspects in assisted reproduction. Hum Reprod Update 1999; 5: 26-39. [CrossRef]
20. Ramirez ER, Ramirez DK, Pillari VT, Vasquez H, Ramirez HA. Modified uterine transplant procedure in the sheep model. J Minim Invasive Gynecol 2008; 15: 311-4. [CrossRef]
21. Gauthier T, Bertin F, Fourcade L, Maubon A, Saint Marcoux F, Piver P, et al. Uterine allotransplantation in ewes using an aortocava patch. Hum Reprod 2011; 26: 3028-36. [CrossRef]
22. Siemionow MZ, Kulahci Y, Bozkurt M. Composite tissue allotransplantation. Plast Reconstr Surg 2009; 124 (6 Suppl): e327-39. [CrossRef]
23. Fageeh W, Raffa H, Jabbad H, Marzouki A. Transplantation of the human uterus. Int J Gynecol Obstet 2002; 76: 245-51. [CrossRef]
24. Milliez J. Uterine transplantation FIGO Committee for the Ethical Aspects of Human Reproduction and Women's Health Int J Gynaecol Obstet 2009; 106: 270.
25. Hanafy A, Diaz-Garcia C, Olausson M, Brännström M. Uterine transplantation: one human case followed by a decade of experimental research in animal models. Aust N Z J Obstet Gynaecol 2011; 51: 199-203. [CrossRef]
26. Ozkan O, Demirkan F, Ozkan O, Dinckan A, Hadimoglu N, Tuzuner S, et al. The first double hand transplantation in Turkey. Transplant Proc 2011; 43: 3557-60. [CrossRef]
27. Akar ME, Ozkan O, Ozekinci M, Sindel M, Yildirim F, Oguz N. Uterus retrieval in cadaver:technical aspects. Clin Exp Obstet Gynecol 2014; 41: 293-5.
28. Ozkan O, Akar ME, Ozkan O, Erdogan O, Hadimioglu N, Yilmaz M, et al. Preliminary results of the first human uterus transplantation from a multiorgan donor. Fert Stert 2013; 99: 470-6. [CrossRef]
29. Erman Akar M, Ozkan O, Aydinuraz B, Dirican K, Cincik M, Mendilcioglu I, et al. Clinical pregnancy following uterus transplantation. Fertil Steril 2013; 100: 1358-63. [CrossRef]
30. Akar ME. Pregnancy following transplantation. Transplantation 2013; 96: e77. [CrossRef]
31. Johannesson L, Kvarnström N, Mölne J, Dahm-Kähler P, Enskog A, Diaz-Garcia C, et al. First clinical uterus transplantation trial: a six-month report. Fertil Steril 2014; 101: 1228-36. [CrossRef]
32. Brännström M, Johannesson L, Bokström H, Kvarnström N, Mölne J, Dahm-Kähler P, et al. Livebirth after uterus transplantation. Lancet 2014; pii: S0140-6736(14)61728-1.
33. Kisu I, Mihara M, Banno K, Umene K, Araki J, Hara H, et al. Risks for donors in uterus transplantation. Reprod Sci 2013; 20: 1406-15. [CrossRef]
34. Yalcinkaya TM, Sittadjody S, Opara EC. Scientific principles of regenerative medicine and their application in the female reproductive system. Maturitas 2014; 77: 12-9. [CrossRef]