Multivisceral (Cluster) Transplants, Their Spinoffs, and Uterine Transplants

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Abstract

In this presentation, we sought to update the information on cluster transplants and their spinoffs. In addition, we explain why we believe that uterine transplantation is a project worth pursuing as an option for women with uterine infertility.

Introduction

Mass homotransplant of abdominal organs was introduced by Dr. T. E. Starzl in 1960 as an experimental model for studying the physiology of the denervated graft. Its presentation, at the Surgical Forum of the American College of Surgeons, was the subject of ridicule, and the birth of the “cluster” concept. The cluster concept is defined as: abdominal organs are 3 clumps of a single cluster used as composite or solitary grafts. The clumps are composed of the liver, stomach (with the pancreaticoduodenal complex), and the gut.

At this point, there are long-term results of the multivisceral transplants and their variants. Our data from the University of Miami are representative of world experience and show that 17 years after transplant, more than one third of the pediatric and one fourth of adults are alive.

In a study presented at the American Surgical Association, Dr. Kareem Abu Elmagd showed that survival improved over time, and that all surviving patients are independent of intravenous treatments except patients who lost, or are losing, their grafts (chronic rejection). Their body mass index improved after transplant and it is normal. Nevertheless, even patients and grafts that survive for 5 years have a high rate of attrition on further follow-up. Dr. Abu Elmagd recognized 2 major risk factors: the absence of the liver from the graft, and the lack of social support. This was the first time that the importance of social support was shown unequivocally. Indeed, the lack of social support had just as much an effect as the lack of the liver from the graft. Additionally, long-term survivors present with many problems including hearing loss, developmental delay, depression, substance abuse, and impaired cognitive functions. Despite these setbacks, most patients completed their education, 84% maintained marital status, and 75% were appropriately employed.

Abdominal wall transplants have been spinoffs of cluster transplants. Initially presented in 2003, the blood supply was through the inferior epigastric arteries, and anastomoses of the iliac vessels of the donor to the lower abdominal vessels of the recipient. This is an adaptable graft and can cover practically any abdominal wall defect. The same, or a different, compatible donor can be used, at the same or subsequent surgical session. Our first abdominal wall graft is in place and surviving after 12 years. In Miami we did 10 such grafts. The original technique has been adopted and modified in other programs.

At the University of Bologna, Dr. Antonio Pinna used microvascular anastomoses to the inferior epigastric or deep iliac circumflex vessels. The main advantage of this modification is that it avoids disturbing the intestinal graft with anastomoses in deep vessels at the expense of the mobility of the graft. Dr. Anil Vaidya, at the University of Oxford introduced remote revascularization to preserve the abdominal wall grafts with the radial artery and venae comitantes of the nondominant arm of the patient. The graft is later transferred to the abdominal wall using microvascular anastomoses.
Other composite abdominal transplants have been spinoffs of the clusters and have 2 main advantages: there are only 2 large vascular anastomoses, the abdominal aorta and inferior vena cava and an immunologic protective effect of the liver. Disadvantages are that one has to consider the 3-dimensional fit of the composite grafts before implantation to avoid technical imperfections. In principle, grafts from donors who are smaller than the recipient are easier to fit.

En block liver/kidney transplants is such a variant. We performed 9 such transplants in Miami with Dr. Akin Tekin. It is a valuable procedure for children. Eight of our patients had congenital hepatic fibrosis and autosomal recessive polycystic kidney disease, 1 from hyperoxaluria. All are alive with functioning grafts except 1 who died of rejection, more than 10 years after transplant because of noncompliance.

A variant of this procedure is the combined liver/pancreas/kidney transplant for Wolcott-Rallison syndrome. This is a genetic disorder caused by mutations in the gene that control protein unfolding. It is the most common cause of neonatal diabetes. Death usually occurs in childhood from fulminant liver and kidney failure. We have performed 1 such successful case which, for the first time, resulted in control of the syndrome. The child is alive and has been well for almost 2 years following the transplant.

One more spinoff is intestinal autotransplants designed to treat otherwise unresectable lesions of the route of the mesentery, as slowly growing tumors and severe vascular malformations. Usually, the head of the pancreas is removed en block with the intestine, the pathology is resected in the bloodless field of the back table, followed by any needed vascular reconstructions, and the graft is reimplanted.

In 1 extreme case of a retroperitoneal sarcoma that we performed with my associate, Dr. Tomoaki Kato, resection included part of the abdominal aorta and cava, reimplantation of the hepatic artery, and superior mesenteric artery was achieved with an interposition graft at the back table, using prosthetic material.

In our series of 10 patients, 4 children and 6 adults who underwent these procedures in January 1999, seven patients are alive up to 13 years later, 6 with functioning autografts; 1 had to be rescued with an allotransplant. Intestinal autotransplants provide local control for patients who have otherwise untreatable tumors or genetic malformations. Dr. Kato has developed a series of autotransplants in New York City.

Uterine transplant is used to treat uterine infertility. This is a common problem, there are thousands of women who need help, about 50,000, just in the United States. It is because of congenital absence of the uterus (Mayer-Rokitansky syndrome), surgical resection, or damage from abortions or infections. In several parts of the world, there is no realistic option for these women if they wish to have children.

The first 2 clinical uterine transplants were performed in the Middle East where the problem seems to be pressing: the first one in Saudi Arabia by Dr. Wafa Fageeh in 2000, the second one in Antalya, Turkey, by Drs. Omer Ozkan and Munire Erman Akar, 2 years ago. Unfortunately, the first attempt failed. The graft had to be removed 3 months after implantation, because of vascular thrombosis. The second graft, in Antalya, seems to be functioning normally. Apparently, there have been attempts at in vitro fertilization which have not yet succeeded.

In the Western countries, there are 2 options for these women: adoption and surrogacy. They are suitable solutions for many couples but impossible for others. Adoption saves lives, because there are more than 20 million children worldwide who are orphaned and in need of a home. Adoption gives them an opportunity for a new family and new life. The child has no genetic relationship to the parents, a fact which is prohibitive for some families. The process of adoption is lengthy and expensive. In addition there is a relative shortage of available children and as a result, families must adopt children from other countries. These international adoptions have been the subject of diplomatic games between governments.

Surrogacy provides parents with a child genetically related to one or both parents. It is an ancient practice. In the Bible: Sarah could not conceive, so she offered her Egyptian slave, Hagar, to Abraham to bear his children. As soon as Hagar became pregnant, she became intolerable and was asked to leave the house. She left, but an angel told her that her son Ishmael will be a leader of the Jews and that she had to go back, which she did. Sarah, unexpectedly became pregnant and after Isaac was
borne, Hagar was sent away forever to the land of Paran. Problems with surrogacy even in antiquity.

In the present day, several countries and states expressly prohibit surrogacy. In the United States, agreements signed are unenforceable and void simply by crossing state lines. The cost is significant, more than $100,000 in the United States. Most insurance policies do not provide coverage for surrogates; it is unclear who is responsible for complications. There is a risk of exploitation of poor women by attracting them to a career in commercial surrogacy.

These problems are reasons to develop uterine transplant as an option for uterine infertility. A uterine transplant is not a life-saving procedure. Unlike other transplants, it is an ephemeral transplant: a transplant not intended to last for the duration of the patient’s life but only until successful pregnancies are accomplished. Indeed, support with immunosuppression will be discontinued and the uterine graft will be removed or left to atrophy. It offers important benefits: the opportunity for gestation and delivery by the biological mother and normal genetic sharing from the parents. On the other hand, 3 lives are placed at possible risk: the mother’s, the donor’s (in case of living donation) and the offspring’s. Unease about these risks cannot be overemphasized. The anatomy and physiology of gestation and delivery are species specific; consequently, there is no perfect animal model. Despite of this fact, every stage of the procedure has been performed successfully in experimental animals.

A group from the University of Gothenburg led by Professor Brannstrom introduced the technique of vascularized uterine transplant in small animals, studied the effects of ischemia and immunosuppression. They also showed that it can carry normal pregnancies and produce normal offspring’s. They also carried out successfully autotransplants in nonhuman primates.8–12

In Miami, we used a heterotopic model in miniswine provided by Dr. David Sachs and achieved long-term survival in several of these animals.13 We had an opportunity to perform hysteroscopies and studied rejection of the Uterus, its prevention and treatment. We also worked with the Swedish group and performed successfully autotransplants and allotransplants in baboons.

Other groups performed successful allotransplants and achieved term pregnancy and delivery of normal sheep14 and cynomolgus monkey.15 The work of the Gothenburg group has culminated in a clinical trial led by Drs. Brannstrom and Olausson. Nine transplants have been performed in this trial. We all await their outcomes.

In summary, we believe that uterine transplant is a project worth pursuing, because if successful, it will be a valuable option for women with uterine infertility.

References

7. Genesis 16: 1–16