

Uterus Transplant Techniques in Primates: 10 Years' Experience

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Abstract

Preserving and restoring fertility are important quality-of-life outcomes for cancer survivors and others who cannot bear children. Transplantation has advanced sufficiently to allow nonvital organ transplant to become a reality. Together, research on reproductive organs and transplantation has resulted in live human births from ovary transplants used to treat absolute ovary factor infertility. Each year, approximately 5000 women under the age of 25 years undergo a hysterectomy. From various other causes, approximately 9 million women of childbearing age in the United States currently have absolute uterine factor infertility due to the absence of the uterus. Research on uterus transplantation has been reported for decades from multiple institutions around the world. Our group has been involved in the area for more than 10 years. To encourage other investigations in this area, we summarize our results in primates as a proof of concept that uterus transplants can be theoretically done.

Key words: *Reproduction, Organ transplantation, Urogenital system, Primate, Procedure*

Organ replacement is the treatment of choice for end-stage organ failure when other therapies have failed.

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Acknowledgements: Funding was provided in part by the Cancer & Fertility Society, Bild Foundation, NY Downtown Hospital, Andrzej Janczyk Nova Restoration, Margareta De Gea, Anne Zill, Elzbieta and John Zawisny. Technical and equipment support was provided by John Adams, The Montefiore Institute for Minimally Invasive Surgery.

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Experimental and Clinical Transplantation (2008) 1: 87-94

Reproductive organ transplantation is an important area of research for transplant, immunology, perinatal, and infertility medicine. Through more research, we may further enhance quality of life with reproductive organ transplant (1).

We are undertaking research to restore reproductive function through transplant of a human uterus (2). We are also collaborating with transplant, perinatal, immunology, and infertility investigators to maximize the utility of our primate uterus transplant model. We now report our technical experience with primates (*Macaca mulatta*) to encourage other investigators in this field.

Surgical Technique

Background

We have been conducting research on preserving and restoring fertility by transplanting reproductive organs since 1997 (3-10). Since 2002, we have done 27 primate laparotomies to research uterus transplantation. The first 13 were done as part of another research project but included a study of primate pelvic anatomy and sham retrieval and transplant surgery. The next 9 were again part of other ongoing surgery research programs but included dissection of the pelvic and uterine anatomy relevant to transplant. The most-recent 5 surgeries were done in a step-wise manner to achieve progressive landmarks necessary for a successful primate uterus transplant. All procedures were approved by local research ethics and animal care committees.

The basis of our surgical experience and techniques has been previously described in other animal models including our work in rat, rabbit, and pig models (3-7). The surgical skills needed to work with primates are similar to those needed in the aforementioned animal models. However, the primate anatomy is unique, and success in other animal models does not guarantee success in primates.

Surgery in all animal models has a necessary learning curve. Our first attempts at transplant invariably resulted in the loss of the initial subjects in all our models (3, 4). The necessary sacrifice of some animals can be reduced by combining other experiments with the initial transplant attempts. For instance, we gained our initial primate experience by assisting in nontransplant-related primate surgery. We also did postmortem pelvic dissections in animals killed for other research purposes. We encourage other investigators to use postmortem specimens and to assist in other surgeries before beginning independent studies.

For primate transplants, our human clinical experience was directly applicable and perhaps even essential for successful primate transplantation (8, 9, 10). Our human surgeries routinely include radical oncology dissections that gave us the necessary experience with the pelvic vasculature. However, this experience was insufficient for successful transplant retrieval. We also had to work with transplant surgeons to learn the skills of this specialty and apply them together with our knowledge of the pelvis (2, 8, 9). We believe that the optimum uterus transplant team should include transplant surgeons and advanced pelvic surgeon such as experienced gynecologic oncologists.

Details

Donor selection includes several parameters. To minimize rejection issues, we prefer to use a sibling pair whenever possible. Both the donor and recipient should be of proven fertility. If there is a size mismatch, we use the smaller animal as the donor to facilitate the anastomoses of a smaller uterus blood supply into a larger recipient vasculature. Vascular sonograms can ensure normal pelvic anatomy of the uterus and the relevant blood vessels, and can estimate the diameter of the external and internal iliac arteries. We prefer donor and recipient pairs with iliac arteries at least 2 mm in diameter.

Steady-state immunosuppression should be achieved preoperatively by frequent blood analyses. We use a semipermanent external jugular catheter to facilitate careful monitoring and frequent blood analyses. In some of our primates, we placed venous access catheters days to weeks before surgery (11). To maintain catheter patency, continuous low-dose heparin is infused to achieve a slightly prolonged activated clotting time. Because of its history of safe

and successful use in human pregnancies, we prefer to use cyclosporine as our primary immunosuppressant (12, 13).

The surgical procedures were all done under sterile conditions, and the animals were given general anesthesia. Monitoring varied from no more than a pulse oximeter to continuous surveillance of blood pressure, urine output, oxygenation, ventilation, electrocardiography, and blood laboratory values. Normal data from our research on the *Homo sapiens* (human) uterus was extrapolated to nonhuman primate surgeries (2, 14).

Intravenous Ringer's solution was given at approximately 10 mL/kg/hour for the first 1 to 2 hours. Since retrieval of the donor uterus can take up to 4 hours, the fluid infusion rate should be adjusted downward and glucose added throughout the surgery. Because it is the most difficult and critical part of the 2 transplant surgeries, retrieval of the donor uterus takes the longest.

Excess intravenous crystalloid fluid causes end-organ damage (15, 16). Most intravenous fluid becomes interstitial water and impairs cellular function through multiple mechanisms. Excess fluid to maintain urine output is misguided. Normal physiologic renal function during surgery is indicated by reduced urine output. Maintaining normal blood pressure, heart rate, and hemoglobin level is the best way to ensure optimal target organ status. Using our minimal crystalloid fluid philosophy, we have not encountered any problems with intraoperative vital signs.

Induction is routine with a restraining device that immobilizes the animal for a parenteral injection. Animals were sedated with ketamine and placed on the operating room table and intubated. Standard inhalation agents (isoflurane) are used to maintain anesthesia.

We place a transurethral catheter preoperatively, or, if this is too difficult, we periodically empty the bladder transperitoneally in the operative field with a sterile needle and syringe.

In primates, no systemic prophylactic antibiotics are used; however, a vaginal antibiotic gel is placed before donor and recipient surgery (2, 17). Using a syringe and a 14-gauge angio-catheter may facilitate placing the antibiotic into the relatively small vagina. A midline incision from the pubic symphysis to the epigastrium was used in all cases. In rabbits and rats, we encountered paraplegia because of spine

positioning. This was not seen in primates using routine operating room tables and the supine position. Using intraoperative lower-extremity pulse oximeters helps assure adequate limb perfusion.

The uterus is inspected for abnormalities that might render the procedure impossible. None were encountered in our experience. Although several of the animals had prior pelvic surgeries, no adhesions were present.

Using 1 or 2 self-retaining retractors and additional handheld retractors is necessary for exposure. Pediatric sizes are needed for subjects less than approximately 12 kg. Operating loupes, 2× to 4×, should be worn by at least 1 operating surgeon. A standard transplant surgery instrument pack will suffice for most surgeries. A complete vascular set is also needed. We prefer smooth forceps, vein retractors, right-angle clamps, and Starzl scissors for most of the dissection. Microvascular clips can speed up the retrieval. Vas deferens reanastomosis clips are also useful to position the donor's and the recipient's vessels for the anastomosis. A bipolar coagulating device is also helpful to eliminate having to tie every vessel. Monopolar coagulators are used as well. Recent innovative sealing techniques are also helpful but not essential.

We start our vascular dissection at the infrarenal aorta and vena cava. This allows us to quickly flush the uterus if needed during the more-difficult pelvic dissection. During the pelvic dissection, large blood loss may be encountered at any time. The most precarious area includes the internal iliac venous system. The retrieval can be salvaged if the previously isolated aorta is quickly cannulated and flushed during an emergency from blood loss. In other organs, non-heart-beating retrievals have an acceptable success rate. The uterus, more so than other organs, appears to be more resistant to warm ischemia, so we are willing to use an organ retrieved in this manner (2, 18).

The vena cava and aorta are dissected from above the level of the inferior mesenteric artery to the bifurcation of the common iliac vessels. This requires ligation of the posterior perforating lumbar vessels. These are highly variable in number, location, and size. The primary surgeon must examine the vessels from every angle before assuming that the dissection is complete. The vena cava and aorta are separated from each other over approximately 2 cm from the bifurcation cephalad. Umbilical tape is placed as far as possible proximal and distal around the aorta

dissection and held for later use when placing the flushing cannula.

The procedure continues inferiorly until the external iliac vessels are dissected to the inguinal ligament. The external iliac vessels are moved medially using a vein retractor. Again, careful inspection of the entire vasculature must be made 360° completely around each vessel to identify any variations in their normal vascular anatomy.

In general, the vessels of the primate parallel those of the human anatomy with notable exceptions (see Figure 1). First, the aortic bifurcation in primates occurs much further cephalad than it does in humans. As measured from the xiphisternum to the pubic symphysis, the bifurcation is found nearly half way between these 2 landmarks with only a slightly smaller distance from the bifurcation to the pubis than from the bifurcation to the xiphisternum. Consistent with this difference, the length of the common iliac vessels is equal to the external iliac vessels and relatively straight. In humans, the common iliac vessel may be relatively shorter and curves along the pelvic brim. In addition, the ratio of the aorta:vena cava diameter in humans is never more than 1:2. In other primates, it may be as great as 1:5. Finally, in primates, the middle sacral vessels can be larger than the internal iliac.

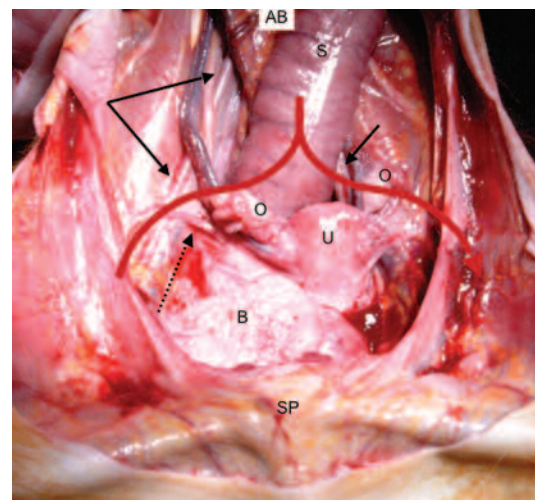


Figure 1. Primate anatomy superimposed on a human. Vessels parallel the human anatomy with notable exceptions. Solid black arrow, common iliac vessels; dashed black arrow, iliac vessel may be the primary blood supply to the uterus through an anastomosing circumflex vessel.

Abbreviations: AB, aortic bifurcation; B, bladder; O, ovary; S, sigmoid colon; SP, symphysis pubis; U, uterus.

The pelvic vessels are more variable in primates. For instance, the external iliac arteries may be the primary blood supply to the uterus through an

anastomosing circumflex iliac artery or ascending obturator. A substantial (1-2 mm) draining uterine vein may lead to the inferior vesicle while the "uterine" vein may be barely visible going directly to the internal iliac vein. Developing potential spaces (eg, perivesical and vesicovaginal spaces) helps identify these variable patterns.

After adequate exposure of the pelvis, the round ligaments are divided and ligated close to the pelvic sidewall. They eventually may be used in the recipient to stabilize the uterus. The broad ligament is further opened to allow greater exposure of the retroperitoneal structures, including the ureter attached at the medial aspect. The ureters are transected as late as possible to allow urine production throughout the case.

The paravesical space is then opened with blunt dissection. The dissection of the spaces around the uterus will commence medial and slightly inferior to the internal iliac vein. The paravesical space is bounded medially by the bladder and the hypogastric artery and posteriorly by the ventral aspect of the cardinal ligament. The pararectal space is then opened using a similar technique. This space is bounded by the rectum medially, the sacrum ventrally, the pelvic sidewall, the internal iliac vessels laterally, and the cardinal ligament anteriorly. The spaces must be opened more extensively than typical for radical cancer surgery but certainly within the capabilities of experienced pelvic surgeons.

Sharp dissection is used to expose the vesicovaginal and rectovaginal spaces by freeing the bladder and rectum from the uterus down to the level well beyond the vaginal fornix. The ureters are not dissected extensively from the peritoneum.

No attempt is made to dissect an individual uterine artery and vein. Instead, a right angle clamp is passed as inferiorly as possible from the pararectal to the paravesical space well below the cardinal ligament. This is most easily done by dissecting to the endopelvic fascia directly on the vaginal wall anteriorly and posteriorly (see Figure 2). The easiest place to identify the endopelvic fascia on the vaginal wall is to start anteriorly from the vesico-vaginal space. Simultaneously starting posteriorly from the recto-vaginal space is also helpful. From these anterior and posterior landmarks, we move laterally toward and inferior to the cardinal ligament. This inferior border defines the place of vaginal transection later on.

After this exposure, dissection of the common and

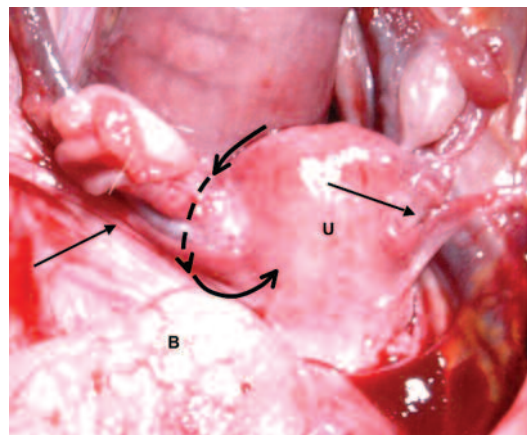


Figure 2. Cardinal ligament containing uterine veins. A right angle clamp can be passed as inferiorly as possible from the pararectal to the paravesical space well below the cardinal ligament, as indicated by the dashed line.

external iliac vessels is continued from the bifurcation of the iliac vessels in a caudal direction to the external iliac vessels and cephalad to the point of the previous aorta-caval dissection. Care must be taken to avoid damage to any other useful anastomoses.

The superior vesicle and all collateral vessels of the internal iliac system will be ligated except for the uterine branches and any anomalous useful vessels. Silk ties are placed but not tied proximal to the inguinal ligament but distal to any useful anastomoses. These are held until just before flushing (see Figure 3). When the aorta is cross-clamped, they are tied to concentrate flushing in the target organ (ie, the uterus). The same is done to the inferior vesicle vessels. Vascular clips also

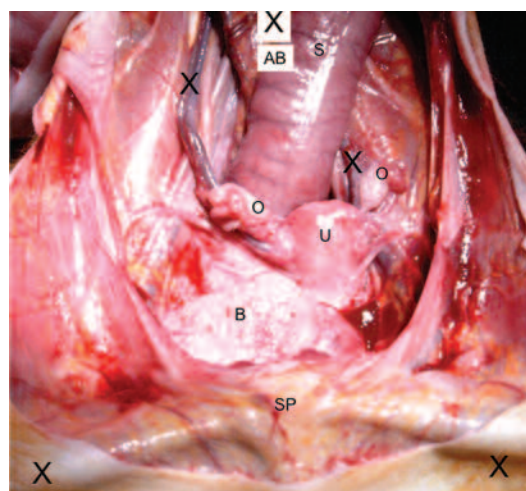


Figure 3. Preflush ligated vessels. The femoral and all collateral vessels of the internal iliac system will be ligated except for the uterine branches and any anomalous useful vessels as indicated by large black X.
Abbreviations: AB, aortic bifurcation; B, bladder; O, ovary; S, sigmoid colon; SP, symphysis pubis; U, uterus.

are acceptable for ligating these vessels to concentrate the flushing. We prefer to tie the proximal ends of all of these vessels that will remain part of the uterus vasculature in the recipient.

When the uterus is satisfactorily dissected, a heparin bolus (approximately 500 units/kg) is given to the primate at least 5 minutes before cannulating the aorta. The previously placed umbilical tapes are used to control the vessel. A proximal then distal vascular clamp is placed to occlude blood flow. The time is noted. An incision is made in the aorta. We prefer a No. 11 blade and Potts scissors. The largest cannula possible is inserted into the distal aorta and secured using the umbilical tape. Some specimens can only accommodate a 14-gauge angiocatheter. Care must be taken not to pass the device too far into the aorta past the bifurcation, and thus exclude 1 iliac artery from receiving the flush.

Simultaneous with the aorta flush, the bilateral distal external iliac vessels are occluded to concentrate the flush in the target organ. Cold preservation fluid is rapidly instilled by gravity through the artery catheter in the usual manner. Sterile slush is placed on the organ and in the pelvis. A vena cava venotomy is made. Flush solution with heparin is infused into the aorta until clear fluid returns from the vena cava incision.

The rectum and bladder are further dissected away from the uterus, thus freeing it of its final attachments. The uterus is carefully placed on traction and removed with as much vaginal tissue as possible to facilitate later attachment into the recipient. The sigmoid colon must be transected to remove the entire intact vasculature from bifurcation to the external iliac vessels. We prefer using an automatic stapling-dividing device across the sigmoid that simultaneously seals and cuts the colon. In some cases, we do not retrieve the pelvic vessels above the bifurcation. In these cases, the common iliac vessels are transected bilaterally obviating the need to transect the colon.

The gonadal vessels have remained intact until this point. They can be used with an aorta-cava patch to anastomose the uterus into the recipient if the pelvic vessels are not salvaged. However, the gonadal vessels may be inadequate for flushing and perfusing the uterus.

Our initial radical trachelectomy experience in humans suggested that the gonadal vessels would not be sufficient to perfuse the reapproximated uterus (19). However, now, after more than 100 trachelectomies (20), it is clear that the gonadal vessels can easily

perfuse the uterus with an adequate blood supply. Still, they are not always of sufficient size to flush the uterus adequately during retrieval (2). In the end, to rescue an otherwise failing experiment, they should be retained until the last possible moment.

Once the pelvic supply is confirmed, the gonadal vessels should be ligated just distal or proximal to the ovaries depending on the experimental needs. Because most experimental recipient animals will need a hysterectomy before receiving the transplant, a different hysterectomy technique will be described later for this purpose.

On a table separate from the main operation, the gonadal vessels, ovary, and adjacent fallopian tubes are separated from the uterus by ligating the utero-ovarian ligament. The ovaries are thus available for other research purposes. The uterus is reperfused with the appropriate preservative solution. Until enough experience is obtained to ensure them without testing, flow rate, pressure, and volume are all assessed to ensure a well-flushed organ. The uterus is then packaged in a double sterile intestinal retention bag in a sterile ice bath until needed for the transplant. It appears that the uterus on ice is usable for up to 24 hours (2, 18).

Uterus transplant surgery

The surgical procedure is done under sterile conditions, with the animal in the supine position under general anesthesia. We prefer chlorhexidine or any other non-Betadine solution to prepare the skin. Only vaginal antibiotics are used after vaginal preparation. Induction is as described previously.

A midline incision is made from the umbilicus to the pubis. A self-retaining retractor is positioned first over the pelvis for the recipient's hysterectomy. The abdomen is explored for contraindications. We have found none.

The donor hysterectomy starts with division of the round ligaments using cautery. The broad ligament is opened and the ureters identified. The utero-ovarian ligament is clamped, cut, and tied bilaterally to preserve the recipient's ovaries and tubes. The ovaries are placed in the retroperitoneum temporarily until the end of the surgery. At that time, they can either be placed in the pelvis and left to assume a natural position by gravity, or an oophoropexy can be done (21). In either case, spontaneous pregnancies are unlikely. For this reason, we require that cryopreserved embryos be available before the uterus is transplanted.

An oophoropexy may prevent retroperitoneal ovary syndrome whereby adhesions and inclusion cysts form over the ovary making assisted reproductive techniques more difficult but not impossible. Unfortunately, oophoropexy also may further prevent spontaneous conception as the ovaries will be further from the uterus. If spontaneous conception is considered for a particular experimental design, the donor fallopian tubes can be retained at their natural attachment to the donor uterus. The recipient ovaries should then be approximated to the ovarian fossa with radio-opaque clips.

In most cases, we prefer to do the oophoropexy by incising the paracolic gutter white line of Toldt. This is done only enough to allow passing of the retroperitoneal ovaries into the paracolic space with minimum traction. The now intraperitoneal ovaries are fixed to the surrounding peritoneum and marked with radio-opaque clips. Care must be taken not to occlude the lateral end of the retained fallopian tube as a sterile hydrosalpinx will form. This technique makes access to the ovaries easy for follicle aspiration since they end up close to the anterior abdominal wall just above the anterior iliac crest. When this procedure has been used, spontaneous conception has occurred in humans. Adhesive barrier materials may be wrapped around the ovaries and fallopian tubes as well.

The donor hysterectomy is continued by clamping, cutting, and tying the cardinal ligaments using an extra-fascial hysterectomy technique. This will eliminate ureteral injury here and provide the best pelvic floor support for the donor organ. This is best accomplished using a clamp with a distal tooth that can be set into the stroma of the paracolpos. Once the angle of the vagina (ie, the vaginal fornix) is reached, traction is forcibly placed on the fundus to extend the vaginal canal. The bladder and rectum are sharply dissected inferiorly at least 1 cm below the eventual vaginal cuff.

Using coagulating monopolar cautery, the cervix is cored from the cardinal ligament, and the vaginal length is maximized. This is an essential step to facilitate suturing the donor uterus to this extended recipient vaginal cuff.

Before placing the donor uterus in the recipient, the organ is flushed with iced lactated Ringer's solution and then placed for orientation in the recipient's pelvis. The recipient vagina is grasped at either lateral apex, and a suture of 0 Vicryl is placed posterior to anterior. It is continued into the donor uterus vaginal cuff inside

to out and tied. A running locking stitch is preferred and continued circumferentially around until the origin is reached. Alternatively, multiple circumferential interrupted sutures can be held and then tied in a parachute technique. A comprehensive up-to-date surgical atlas should have a description of these basic techniques including the abdominal radical trachelectomy, which is the inspiration and foundation for much of this transplant surgery (22).

In situations with a previous hysterectomy or congenital uterine absence, the peritoneum overlying the vaginal apex is incised to expose the vaginal mucosa. This is facilitated by distending the vaginal apex with a small (approximately 1 cm) sponge stick. A probe also may be used to perforate the apex from the vagina to identify the point of incision. The vaginal mucosa is opened further to a length that would accommodate the donor vaginal cuff circumference.

The retroperitoneum is incised over the bifurcation and extended cephalad and caudad to the inferior mesenteric artery and the iliac bifurcation, respectively. The exact anastomosis site is chosen depending on donor organ vascular length and the recipient's anatomy. The preferred hierarchy of sites is as follows: the internal iliac vessels a short distance distal to the bifurcation of the iliac vessels, the external iliac vessels, the common iliac vessels, and the aorta and vena cava. Proximal and distal control of the recipient vessels is obtained with short, "bulldog" atraumatic vascular clamps.

An incision into the recipient vein is made using a size 11 blade. Using 6-0 to 8-0 nonabsorbable monofilament suture, the donor vein will be encircled and sutured to the recipient location. The exact technique depends on the actual anatomy, but standard microvascular techniques are sufficient. For instance, we nearly always use lateral stay sutures. The arterial anastomosis is done in a similar fashion. Testing of the anastomosis is done after isolating the transplant organ from the anastomosis site. Only after both vessels are adequately assessed for patency is the entire organ perfused.

Arterial clamps are removed and the organ is observed for signs of reperfusion including color and bleeding at the venous site. Appropriate oxygen saturation and pulsatile index, as determined in our previous studies, must be obtained (14, 23). Intraoperative color Doppler ultrasound imaging of the anastomosed vessels also may be done but are not

essential. The organ is warmed with peritoneal lavage.

The abdomen is closed in the usual fashion. After the surgery, animals receive appropriate analgesic treatment and comprehensive veterinary services.

Conclusions

Reproductive organ transplants have been done verifiably for approximately 100 years. During the 1970s, detailed reproductive organ transplant experiments including those of the fallopian tube, ovary, and uterus were reported in animal models. These studies have culminated in recent successful pregnancies in animals after uterine transplant, confirming earlier successes. Successful human ovary transplants have been reported in a variety of settings. These include donor-to-recipient transplants, but more commonly involve a cryopreserved autologous transplant. Despite only 2 successful deliveries before 2006 from transplanted ovaries after nearly 100 years of attempts, patients continued to undergo this surgery in 2007 in the hope of its eventual success. As of this writing, the number of deliveries from transplanted ovaries has increased to more than 7.

Transplant of reproductive organs has been considered in reproductive medicine for both research and clinical purposes. Among female reproductive organs, the majority of studies have been done involving ovarian transplants, first attempted as a potential treatment for menopause. The animal models used for ovarian transplants were generally autotransplant models, with only the ovary replanted or the ovary replanted together with the oviduct within the same animal.

There are fewer reports in the literature concerning transplants of the uterus. A uterus has been transplanted together with the oviduct and ovary in a ewe (24) a dog (25), and a macaque monkey (26). The technique for uterine transplant is either by direct vascular anastomosis or by omentopexy to obtain revascularization.

We believe that our experiences in primates, including humans, may provide other investigators enough information to begin additional studies on uterus transplantation. Through collaborative efforts, we hope progress will be made using this model in transplant, immunology, perinatal, and infertility investigations. Eventually, we hope to continue our

fertility preservation work and in a few rare cases, restore fertility through human uterus transplants.

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