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# ORTHOTOPIC UTERUS TRANSPLANTATION. SHEEP MODEL EXPERIMENT, CALI (COLOMBIA)

## Trasplante ortotópico de útero. Experimento en modelo ovino, Cali (Colombia)

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## ABSTRACT

**Objective:** It has been recommended that professionals who are planning to perform uterine transplantation should first carry out animal experiments. This paper describes the procedure for uterine transplant in sheep, as well as short and medium-term results.

**Materials and methods:** Experimental surgery study in sheep subjected to uterine explantation and transplant. Four 40-50 kg sheep received uteri transplantation (orthotopic) from four live donors. End-to-side vascular anastomosis was used, the vagina was sutured on one plane and the uterus was fixed to the pelvic wall. Complications and 180-day evolution are described.

**Results:** Transplant surgery was accomplished in the 4 sheep. Surgical time in the first procedure was 240 minutes, while the last procedure lasted 185 minutes. Warm ischemia time was reduced from 42 to 22 minutes. One sheep died on the seventh postoperative day due to an intraoperative complication unrelated to the vascular anastomosis. A second sheep developed local vaginal infection which was treated with metronidazole, and evolved satisfactorily. No transplant rejection had occurred in the remaining 3 sheep after 6 months.

**Conclusions:** The ovine model allowed surgical training in experimental uterine transplant surgery. For the authors, it offered an opportunity to gain knowledge and make progress towards future uterus transplantation in women with uterine factor infertility in Colombia.

**Key words:** Transplant; uterus; infertility

## RESUMEN

**Objetivo**: se ha recomendado a los profesionales que tengan como proyecto realizar trasplante uterino, hacer previamente trabajos experimentales en animales. Este trabajo describe el procedimiento del trasplante uterino en ovejas y los resultados a corto y mediano plazo.

**Materiales y métodos**: estudio de cirugía experimental en ovejas sometidas a explante y trasplante uterino. A cuatro ovejas de 40-50 kg de peso les fue trasplantado el útero (ortotópico) de cuatro ovejas

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vivas donantes. Se utilizó técnica de anastomosis vascular término-lateral, la vagina se suturó en un plano y el útero se fijó a la pared pélvica. Se describen las complicaciones y la evolución a 180 días.
**Resultados**: se realizó la cirugía de trasplante en las cuatro ovejas. El tiempo quirúrgico fue de 240 minutos (min) en el primer procedimiento y de 185 min en el último, y el tiempo de isquemia caliente se redujo de 42 a 22 min. Una oveja murió al séptimo día posoperatorio por una complicación intraoperatoria ajena a las anastomosis vasculares. Otra oveja que fue trasplantada desarrolló infección-local vaginal manejada con metronidazol, con evolución satisfactoria. Las tres ovejas no habían presentado rechazo al trasplante a los 6 meses.
**Conclusiones**: el modelo ovino permite entrenamiento quirúrgico en cirugía experimental de trasplante uterino. Para los autores constituyó adquisición de conocimiento y avanzar hacia la realización futura del trasplante uterino en mujeres con infertilidad absoluta por factor uterino en Colombia.
**Palabras clave:** trasplante; útero; infertilidad.

## INTRODUCTION

Infertility is defined as the inability to achieve clinical pregnancy after 12 months or more of regular unprotected intercourse (1). In Colombia, according to the 2015 National Health Demographics Survey (ENDS), 10.2% of women between 13 and 49 years of age who want one or more children have experienced fertility problems. The highest percentage of infertility problems of 25.4% is found in women between 40 and 44 years of age (2). Reports in the literature cite a global infertility rate of 10.5% of the population (3).

Infertility is explained in part by uterine abnormalities. In the reproductive process, the uterus participates in important events such as sperm transport, embryo implantation, and embryo and fetus nourishment. For this reason, uterine abnormalities, either congenital or acquired, may play a negative role in infertility (4). In a narrative review of the literature, Acién reports a frequency of uterine abnormalities in the general population that ranges between 2 and 4% and can be as high as 16% in women with a history of infertility (5). Uterine abnormalities have been described to be as high as 27% in women undergoing in vitro fertilization (6). The frequency of infertility in women with congenital uterine abnormalities ranges between 3 and 6% (4,7).

According to theAmerican Fertility Society (1988), there are seven types of congenital uterine abnormalities: uterine hypoplasia or agenesis, unicornuate uterus, didelphys uterus, bicornuate uterus, septate uterus, arcuate uterus and uterus exposed to diethylstilbestrol (8). Some of these uterine malformations lead to absolute uterine-factor infertility (AUFI) or untreatable female infertility (9). The main causes of untreatable infertility are uterine hypoplasia, unicornuate or bicornuate uterus, and the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome. Other causes of untreatable infertility include: severe endometrial synechiae, absent uterus after surgical removal due to giant uterine fibroids or malignant tumors (9). Options available to women with AUFI are adoption, surrogacy and uterine transplantation. In Colombia, the only option currently available is adoption (10), given the lack of clarity in the legislation regarding surrogacy; although there is no outright ban, it has been suggested that a regulatory legal framework is required (11). On the other hand, there are no centers in the country working on uterine transplantation.

The first attempt at uterine transplantation was carried out in Saudi Arabia in 2000, using a live donor, but the graft was lost on postoperative day 99 due to vascular thrombosis secondary to graft prolapse (12). The first baby from a live donor uterine transplantation was born in 2014 as part of a group

of women who underwent transplantation in Gothenburg, Sweden (13); later, in 2017, the first baby born from deceased donor uterine transplantation was born in São Paulo, Brazil (14). Human uterine transplantation is still in its experimental phase (9) and there are multiple ethical considerations yet to be resolved (15).

In 2009, the International Federation of Obstetrics and Gynecology (FIGO) recommended that all practitioners who are considering a project of uterine transplantation should carry out experimental work in animals first (16). Multiple animal models have been used, including rats, rabbits, pigs, sheep and primates as part of the technical training in transplantation of female reproductive organs, with pregnancies having been achieved in some of them (17-19). Because of its vascular anatomic similarities with humans, the sheep model is one of the most widely used for training in uterine transplantation (20). The teams with the longest experience in Sweden, Brazil, United States and Czech Republic did their training in sheep (21).

The objective of this study is, first, to present the training experience of a team of surgeons in Colombia working with sheep, emphasizing the description of the preoperative preparation, the surgical procedure, donor organ management and postoperative follow-up; and then to present the results of the surgery in sheep in order to consolidate the initial phase of the surgical procedure that can serve as a basis for future developments that may eventually lead to the creation of a uterine transplantation program in women in our country, and to the promotion of training centers driven by the possibilities offered by this complex surgery in the future.

## MATERIALS AND METHODS

*Design and population.* Experimental study in sheep, with no control group. Sheep over 1.5 years and under 5 years of age, weighing more than 40 kg, with a history of at least one pregnancy resulting in live offspring were included. Sheep with any infectious disease diagnosed and still present at the time of preoperative selection were excluded. All the interventions were carried out between February and March, 2018, at the Experimental surgery Laboratory of Universidad del Valle Health Faculty, in Cali, Colombia, with the participation of the surgical staff of Centro Médico Imbanaco in Cali. The sheep were intervened by a lead surgeon specialized in liver transplantation from São Paulo University Medical School in Brazil, who is currently enrolled in the uterine transplant doctoral program of that university. The lead surgeon participated in the pre- and postoperative work towards the development of human uterine transplantation carried out by the professional team of Hospital Das Clínicas of the São Paulo University Ribeirão Preto Medical School in Brazil. The surgical team also included two liver transplant surgeons with formal certification and training in France and the United States who perform high-complexity hepatic, biliary and pancreatic procedures, as well as two university professors specialized in obstetrics and gynecology. Additional team members included two veterinarians; one animal scientist specialized in minor species, professor of the National Apprenticeship Service (SENA) in Tuluá; and one professor of pharmacology and regenerative medicine and one bacteriologist who are part of the professional staff of the Health Faculty at Universidad del Valle. Sample size: 8 sheep.

*Procedure.* The sheep were assessed by the veterinarian and the animal science specialist to screen for the selection criteria. The surgical intervention consisted of uterine explantation and orthotopic transplantation, including ovaries and tubes through laparotomy. Preoperative and intraoperative management of the donor and recipient, and postoperative follow-up of the recipient sheep, are described below.

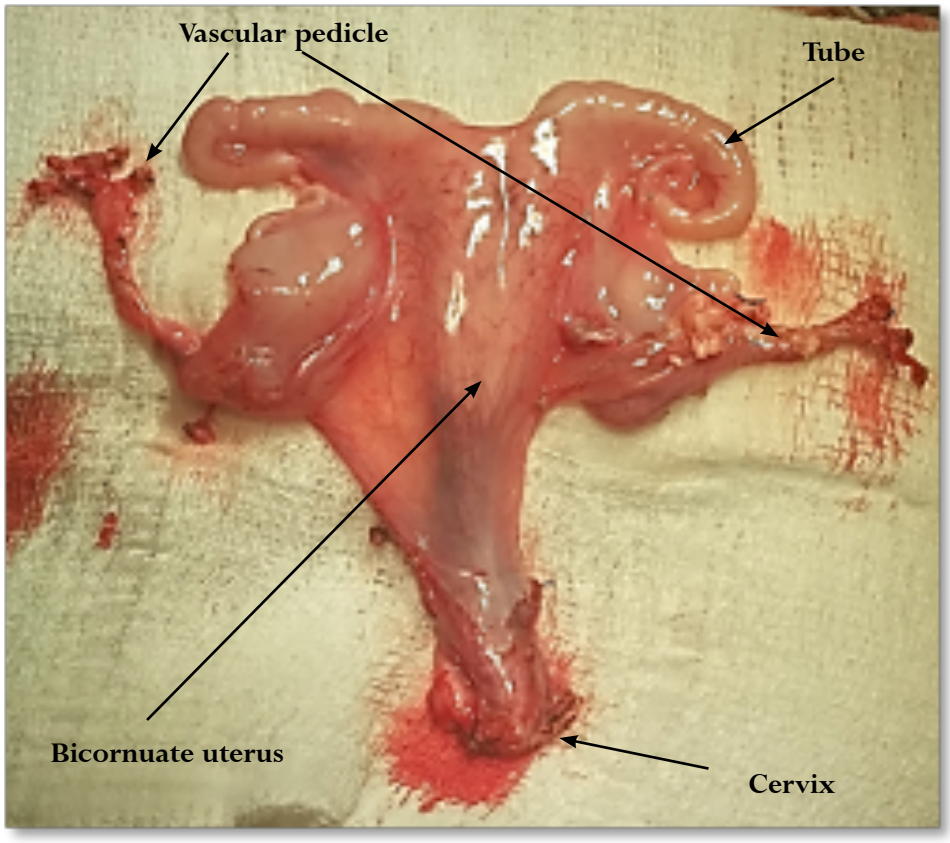
All the sheep were tested in advance for blood group compatibility using cross-matching, in order to rule out direct familiarity. Preoperative preparation of each animal included at least 18 hours of fasting for solid foods and a minimum of 6 hours for fluids (water). During the pre-anesthetic period, all the sheep received an intramuscular dose of midazolam 0.5 mg/kg for sedation and anxiolysis. Antibiotic prophylaxis consisting of a single dose of procaine G penicillin (4,500,000 IU), penicillin G sodium (1,500,000 IU), streptomycin sulphate (7.5 g), triamcinolone acetonide (15 mg included in a commercial form of 6,000,000 IU) was administered before the intervention.

*Description of the technique and procedure in the donor sheep:* The anesthetic procedure was performed and supervised by a veterinarian with expertise in veterinary anesthesiology. Anesthesia induction was achieved using intravenous propofol at a dose of 5 mg/kg, followed by orotracheal intubation with appropriately sized tube (7.5 or 8 mm). Anesthesia maintenance was achieved with 1.5% isoflurane in 100% oxygen plus a continuous intravenous infusion of fentanyl at a rate of 10 ug/kg/min; neuromuscular blockade with 0.05 mg/kg intravenous pancuronium was used before orotracheal intubation; capnography was maintained between 35 and 45 mmHg.

Before making the incision, the abdominal wall was scrubbed thoroughly with soap and chlorhexidine solution. A surgical abdominal access was secured immediately through a median infraumbilical approach. Given the limitation for urethral canalization, cystostomy was used for bladder catheterization by means of a 10-12 F Foley catheter which was left in place with continuous closed drainage. Pelvic vascular and visceral structures were identified. Ligation, repair and sectioning of the round ligament in its pelvic attachment were then performed in order to preserve as much length as possible to provide fixation for the transplanted organ; gonadal vessels were dissected to the point where they arise from the iliac vessels and repaired; ureter repair was also performed. Then, dissection and repair of the uterine vein and artery to the point where they arise from the internal iliac artery were performed, including separation from the ureter. The same steps were repeated in the contralateral side. Intra-abdominal dissection was performed after identifying the uterine cervix, releasing the upper two-thirds of the vagina; gonadal and uterine vessels were clamped and sectioned, followed by sectioning and closure of the vagina using a running suture. Fascial closure was accomplished with 1-0 polypropylene suture, and the skin was closed with absorbable monofilament material. At the end of the procedure, 0.02 mg/kg of intravenous flumazenil was used for anesthesia reversal.

After removal of the uterus, tubes and ovaries, the explanted uterus was flushed under stringent antisepsis conditions on a sterile tray, using 1 liter of Ringer's lactate with the addition of 5000 units of heparin, catheterizing a vessel and verifying the permeability of each of the uterine arteries for intravascular irrigation; the explanted organ was placed in 0.9% normal saline solution at a temperature of 4°C to create a condition of hypothermia. This was followed by the procedure known as "bench surgery" in which the vascular pedicles were prepared (2 arteries and 2 veins) by means of careful dissection. Organ perfusion was achieved with 1 liter of Ringer's lactate, verifying fluid outflow through the gonadal veins. The sectioned vessels of the lower vascular plexus were occluded and outflow was again verified. All the organs were connected to continuous perfusion for irrigation through the gonadal arteries after performing bench surgery (Figure 1), maintaining hypothermic conditions between 4 and 6°C with the use of isotonic solution during a period of 20 to 24 hours. The continuous perfusion machine was designed by basic science professors of the Health Faculty at Universidad del Valle. 69

**Figure 1.**
Appearance of the ovine uterus for transplantation after bench surgery, in uterine transplantation in a sheep, Cali, Colombia, 2018




*Surgery in the recipient sheep:* Before implantation, the uteri were kept submerged and perfused in a normothermic solution at a constant temperature of 37°C. At the end of the procedure for removal of the uterus, vagina, tubes and ovaries, uterine transplantation was performed in four sheep in which the residual portion of the vagina was repaired with 1-0 polyglactin 910 suture, splitting the angles. This was followed by proximal dissection of the external iliac artery and vein on both sides and placement of the graft (uterus) in the pelvic cavity. Then, 20 mL of heparinized serum (prepared with 100 mL of saline solution and 5000 units of heparin) were injected through each uterine artery; end-to-side anastomosis of the gonadal artery of the graft to the external iliac artery of the recipient was performed using 8-0 polypropylene suture. After the arterial anastomosis, the ipsilateral venous anastomosis to the external iliac vein was performed using 5-0 polypropylene suture. After completion of the two vascular anastomoses, blood flow was allowed in order to obtain rapid perfusion of the transplanted organ. The same steps were then repeated in the contralateral side. The anastomoses of the gonadal vessels were checked minutely to determine the presence of leaks. Vessels which could not be re-canalized were selectively ligated. In all cases, more than one artery and vein anastomosis was achieved

on both sides. The next step was the end-to-end vaginal anastomosis using a 1-0 polyglactin 910 running suture, followed by uterine fixation with the remnants of the round ligaments to the pelvic wall on both sides, using 1-0 polyglactin suture material. Before completing the procedure, hemostasis was again verified in the abdominopelvic cavity, the Foley catheter was removed and the bladder was repaired. The final step was fascia closure with 1-0 polypropylene suture and skin closure with 3-0 polyglecaprone 25 suture.

Post-operative follow-up was under the care of the veterinarian and the animal science specialist in a sheep breeding farm. All the transplanted sheep received 40 daily units of subcutaneous enoxaparin during the first postoperative week.

*Follow-up:* Direct uterine cervix assessment was performed in all the transplanted animals on days 7, 15, 30 and 180 after the surgery. Moreover, transabdominal and endorectal ultrasound scans were performed every three months by the veterinarians.

*Measured variables:* Variables included age and weight; surgical time, cold and warm ischemia times; blood loss and intraoperative complications; effectiveness as determined by achievement of functional vascular anastomoses and short-term preservation of vitality in the transplanted animals; safety as determined by the absence of postoperative infection; postoperative bleeding, graft rejection and procedure-related mortality. Ultrasound assessment of uterine and ovarian morphology was performed at 15, 30 and 180 days.

*Statistical analysis.* A descriptive analysis is presented. Continuous variables are expressed as means and inter-quartile (IQR) ranges, and categorial variables are expressed as proportions.

*Ethical considerations.* This study was approved by the Institutional Review Committee on Ethics pertaining to animal experimentation of the Universidad del Valle Health Faculty on September 26, 2017, with internal code 011-017. Surgical time was taken into consideration as the technical progress parameter, and postoperative care of the animals and veterinary assessment were also taken into consideration.

## RESULTS

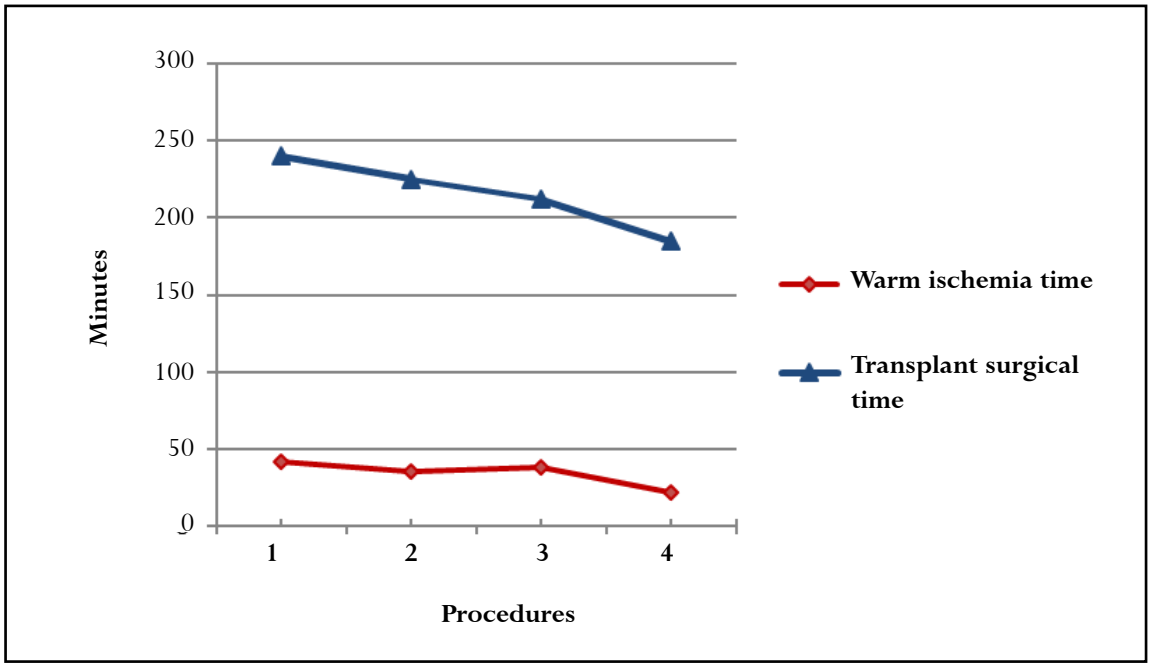
During the time described, 8 sheep were intervened. Four sheep were explanted and used as donors. The remaining 4 sheep selected as recipients underwent hysterectomy and then received the uterus, tubes and ovaries of the other sheep.

The median weight of the donor and recipient sheep was 42 kg (range: 41 - 47) and 41.5 kg (rango: 40 - 44), respectively. The animals were of different breeds, not compatible according to cross-matching of blood groups, in order to eliminate crossing between animals of the same family group. Median warm ischemia time was 35.5 minutes (inter-quartile range [IQR]: 28.5-40); median surgical time for transplantation surgeries was 218.5 minutes (IQR: 198.5-232.5). Total uterine transplant surgery time diminished progressively from 240 minutes for the first procedure, down to 185 minutes for the last intervention, while warm ischemia time for each uterus to be transplanted dropped from 42 to 22 minutes (Figure 2).

No failed surgeries resulted from the explantation or implantation procedures. The first transplanted sheep died on postoperative day 7. Necropsy performed by the veterinarian revealed bowel obstruction and thrombosis secondary to the presence of a foreign body in the abdomen (sponge), and death was attributed to the thrombotic phenomenon.Uterus and ovaries were found to be of homogenous appearance, with no evidence of edema or areas of necrosis; anastomoses, as well as the arterial and venous vascular pedicles were patent on both sides, with no gross signs of ischemia. In the second transplanted sheep, there were

**Figure 2.**

Warm ischemia time and length of uterine transplant procedures in sheep, Cali, Colombia, 2018




A drop is observed in both surgical as well as warm ischemia times. Greater skill was acquired as the procedures advanced.

no intraoperative or early complications; infection was identified in the vaginal cavity on speculoscopy performed on the seventh postoperative day (pale uterine cervix and presence of foul-smelling green discharge). Treatment with intravaginal metronidazole was given during 7 continuous days, leading to a favorable course with resolution of the infection and macroscopic improvement of cervical appearance.

The third and fourth transplanted sheep had a favorable course. The three animals that survived the transplant procedure were found to be doing well on postoperative days 15, 30 and 180. No spontaneous pregnancy had been achieved up until that time in the follow-up period.

## DISCUSSION

We present the results of experimental surgery in sheep, consisting of the explantation and implantation of the uterus, tubes and ovaries. There were no failed procedures associated with uterine explantation or transplantation. Postoperative complications were seen in 2 sheep: one death and one non-severe vaginal infection. In terms of survival after transplant surgery, 3 sheep were in good condition after 6 months. This work provided the opportunity to train a team of Colombian surgeons in the surgical technique for uterine transplantation. In our study we implemented the surgical technique used in bench surgery to prepare the vascular pedicles of the

graft before transplantation, as has been described by other authors (19-21).

Surgical time was reduced from 4 to 3 hours, both for graft removal as well as placement; likewise, intervention time during the warm ischemia phase also became notably and progressively shorter as the last procedures were performed. In terms of surgical time, Brännström et al. describe a time range between 3 and 4 hours (22).

A limitation of this study is the inability to obtain follow-up hormonal blood levels in the sheep, given that processing in Colombia is challenging because of the issue of technical endorsement for veterinary laboratories in the region. However, the sheep model lends itself to this kind of work because of easy availability and care throughout the entire uterine transplantation process. Some authors describe the non-human primate as a more adequate model because of the similarity with the human menstrual cycle (23) and because uterine perfusion is provided mainly through the uterine, ovarian and vaginal arteries, while venous return occurs mainly through the ovarian veins (9). On the other hand, no pharmacological hormonal stimulation or assisted reproduction treatment plan were implemented with the aim of achieving pregnancies, considering that they were not part of the study objectives.

## CONCLUSION

The sheep model provides a training opportunity for medical-surgical teams wishing to perform experimental uterine transplant surgery in animals. For the authors, this experience was a transcendental leap that will enable researchers from Universidad del Valle and Centro Médico Imbanaco to make progress towards the performance of this type of transplantation in women with uterine factor infertility.

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## AUTHORS' CONTRIBUTIONS

Felipe Castro-Villegas: Study conception and design, participation as surgeon in the surgical interventions in the sheep, responsible for the analysis and final review of the manuscript.

Gustavo Canaval-Erazo: Study conception and design, participation as surgeon in the surgical interventions in the sheep, responsible for the analysis and final review of the manuscript.

Juan Manuel Rico-Juri: Participation as surgeon in the surgical interventions in the sheep.

José Óscar Gutiérrez-Montes: Participation in preparation and adjustments to continuous flow maintenance in explanted organs, and in the analysis of matching tests.

Anabel Vanin-Aguas: Participation as surgeon in the surgical interventions in the sheep.

Hoover Canaval-Erazo: Study conception and design, participation as surgeon in the surgical interventions in the sheep, responsible for the analysis and final review of the manuscript.