Endometrial autotransplantation in rabbits:

Potential for fertility restoration in severe Asherman's syndrome

Running title: Endometrial autotransplantation in rabbits

Benjamin P Jones[1,2], Saaliha Vali[1], Srdjan Saso[1,2], Ximo Garcia-Dominguez[3], Maxine Chan,[2] Meen-Yau Thum[2,4], Sadaf Ghaem-Maghami[1,2], Baljeet Kaur[2,5], Luís García-Valero[3], Linda Petrucci[3], Joseph Yazbek[1,2], Jose S. Vicente[3], Isabel Quiroga[6], Francisco Marco-Jiménez[3], J Richard Smith[1,2]

[1] West London Gynaecological Cancer Centre, Hammersmith Hospital, Imperial College NHS Trust, London, W12 0HS London, UK.

[2] Department of Surgery & Cancer, Imperial College London, Du Cane Road, London W12 0NN, UK.

[3] Institute of Science and Animal Technology (ICTA), Universitat Politècnica de València, C/Camino de vera s/n, 46022 València, Spain.

[4] Lister Fertility Clinic, The Lister Hospital, Chelsea Bridge Road, London, SW1W 8RH

[5] Department of Histopathology, Imperial College London, Du Cane Road, London W12 0NN, UK.

[6] The Oxford Transplant Centre, The Churchill Hospital, Oxford University Hospitals NHS Trust, Old Road, Oxford, OX3 7LE

Corresponding Author:

Mr Benjamin P Jones MBChB BSc (Hons) MRCOG

Department of Surgery and Cancer, Imperial College London,

Du Cane Road, London W12 0NN, United Kingdom.

Telephone: 07740358900 E-mail: Benjamin.jones@nhs.net

Abstract

Objective: Uterine transplantation is now considered a feasible treatment for women with absolute uterine factor infertility and has been successfully performed for a woman with Asherman's syndrome (AS). The endometrium is a clinically and histologically distinct entity from the surrounding myometrium. Endometrial transplantation (ETx) may offer a less invasive option, with less immunogenic impact, to restore fertility in women with severe AS. The objective of this study was to assess the feasibility of ETx by evaluating surgical and reproductive outcomes following endometrial autotransplantation in a rabbit model.

Study design: A longitudinal study assessing surgical, biochemical, radiological, reproductive and histological outcomes following endometrial autotransplantation in ten New Zealand white rabbits.

Results: Ten procedures were performed, including 8 endometrial auto-transplants (ETx) and 2 endometrial resections (ER), to control against endometrial regeneration. Eight procedures were successful, whereas two rabbits from the ETx group died intra-operatively. Three rabbits were euthanised at 48, 72 and 96 hours post-operatively to assess gross and histological appearances. Two rabbits, one from the ETx group and one from the ER group, died four weeks and eight weeks post-operatively. Three rabbits subsequently underwent two cycles of in-vitro fertilization. The first cycle resulted in an implantation rate of 57% in the un-operated uteri. In two rabbits who underwent ETx, an implantation rate of 28.6% was seen. In the second cycle, an implantation rate of 61.9% (13 implantations) was observed in the control uteri. In the two ETx females, an implantation rate of 14.3% was seen. No pregnancies were seen in either cycle after ER. Despite successful implantations in both cycles in the ETx rabbits, no livebirths were achieved. Following death or euthanasia there was gross and microscopic evidence of viable endometrium following ETx, but not following ER.

Conclusion: This study has revealed, for the first time, the feasibility of ETx with gross and microscopic evidence of viable endometrium, and the demonstration of clinical pregnancies. Whilst further studies are essential, including the achievement of successful livebirths, ETx

may represent a potential fertility restoring opportunity for women with severe, treatment refractory cases of AS.

Key words

Asherman's syndrome, Endometrium, Gynaecology, Infertility, Pregnancy, Transplantation

Introduction

Uterine synechiae, following trauma to the endometrium, were first described in 1894 following postpartum curettage.[1] It was not until half a century later that Joseph Asherman made the association between the frequency of uterine synechiae, or intra-uterine adhesions (IUA), with preceding trauma, thus coining the term Asherman's Syndrome (AS).[2] IUA are defined as bands of fibrous tissue on opposing walls of the endometrium and/or cervix leading to partial or complete obliteration of the cavity.[3] Whilst the pathophysiology remains poorly understood, it is widely considered that trauma to the basal layer of the endometrium is responsible. This frequently arises as a consequence of endometrial curettage to manage retained products of conception following miscarriage or postpartum.[4] The risk appears to increase with repeated procedures, with a prevalence of up to 40% in women who have undergone a secondary procedure for removal of placental remnants or a repeat curettage for incomplete miscarriage.[5] Other less common precipitating factors include myomectomy, Caesarean section or endometritis.[4,6,7]

AS affects up to 1.5% of women of reproductive age,[8] and is the responsible aetiology in 5% of infertile women.[9] Some women with AS have a degree of functional endometrium, which may result in pelvic pain, retrograde menstruation, oligomenorrhea and subfertility. Others have complete absence of functional endometrium and develop amenorrhea and absolute uterine factor infertility (AUFI). Previous studies have identified infertility to be present in 43% of women with AS.[4] In those who do become pregnant, AS also impacts outcomes, with a systematic review identifying that one in five women who miscarry have IUA.[10]

The mainstay of treatment includes the restoration of uterine function using operative hysteroscopy and adhesiolysis.[11] Secondary prevention using a physical barrier such as an intra-uterine device or a catheter balloon is also frequently used.[11] Improvement in menstrual irregularity and fertility has been demonstrated in several small uncontrolled retrospective series' following hysteroscopic adhesiolysis.[12,13] However, high rates of infertility,

miscarriage, poor implantation and abnormal placentation often persist,[14] with some studies reporting that less than a quarter of women subsequently achieve livebirth after adhesiolysis.[12,15] In women with severe AS that results in AUFI, the traditional options to acquire motherhood include adoption or surrogacy. The novel use of autologous stem cell treatment has also shown promise with reports of resumption of menstruation,[16,17] successful conception with IVF, [18] and successful spontaneous pregnancies in treatment refractory cases.[19]

Recently, uterine transplantation (UTx) following concomitant hysterectomy was undertaken for a woman with AUFI secondary to AS.[20] However, the presence of a structurally supported and vascularised uterine structure raises the possibility of endometrial transplantation (ETx) as a potentially less invasive and immunogenic option. Following numerous feasibility studies in an animal setting by our team, we hypothesise that the endometrium is an anatomically distinct entity that can be resected separately from the myometrial surface. Moreover, in our clinical experience in gynaecological operating, endometrium can be repaired by suturing it back onto the myometrial surface. This is evident during myomectomy or after Modified Strassman Procedure,[21] when entering the cavity is unavoidable, with resultant good hysteroscopic appearance and clinical outcomes.

The aim of this study was to assess the feasibility of ETx by undertaking a short-term viability study on endometrial auto-transplantation in the rabbit model.

Materials and Methods

Ethics

All experimental procedures used in this study were performed in accordance with Directive 2010/63/EU EEC for animal experiments and reviewed and approved by the Ethical Committee for Experimentation with Animals of the Universitat Politècnica de València, Spain (2017/VSC/PEA/00130). XGD, FMJ and JSV each hold an authorisation certificate issued by

the Valencian governmental administration to undertake research in animal models. In addition, XGD is authorised to supervise the welfare and care of the animals intra-operatively.

Subjects

Ten female adult LP synthetic line rabbits were obtained from Universitat Politècnica de València in Spain. The LP line was founded on reproductive longevity criteria by selecting females from commercial farms, irrespective of their origin. The initial criteria included a minimum of 25 prior pregnancies with > 7.5 livebirths per partum. They were subsequently preferentially selected by litter size at weaning for the subsequent 12 generations. The rabbits were maintained on a 12:12-h light: dark cycle and at constant temperature (20 ± 1 °C) with relative humidity (40% to 60%).

Study design

Rabbits were randomly assigned to two groups: Group A - Females which underwent endometrial resection of the right uteri with subsequent re-implantation into the same uterus (n=8) and; Group B - Females which underwent endometrial resection of the right uteri, without subsequent re-implantation (n=2). In both groups, the endometrium within the left uterus remained intact as a control side. Group A was used to assess the feasibility of ETx, whilst group B was used to control for endometrial auto-regeneration.

The experiment was divided into short (from 0 to 96 hours after autologous endometrium transplantation) and long (6 months after autologous endometrium transplantation) periods. The 'short period' experiment (n=3) was developed to assess the immediate post-operative outcomes and early endometrial response by euthanising a single animal at 48, 72 and 96 hours and assessing the macroscopic and histological appearance. The 'long period' experiment (n=7) was developed to evaluate long term clinical and reproductive outcomes. It entailed long-term follow up of the remaining animals, through fertility treatment and pregnancy until death or euthanasia. The study design is summarised in **Figure 1**.

Surgical technique

A 4-5cm midline laparotomy was undertaken. Following identification and exteriorisation of the uterus (**Figure 2; A**), an avascular window was identified in the broad ligament. Single use vascular clamps (Vascu-Statt® II, Scanlan, St. Paul, MN, USA) were used to occlude the uterine arterio-venous circulation (**Figure 2; B**). A midline incision was then made along the full length of the right uterus (**Figure 2; C**). A plane was developed between the endometrium-myometrium interface using cold knife dissection. A tri-phasic technique was subsequently utilised, by initially dissecting each side laterally from the edge to the mesenteric border, before removing the endometrium in its entirety from the cervix to the Fallopian tube (**Figure 2; D**). **Figure 3** demonstrates the histological analysis of a sample of endometrium resected using this technique, which clearly identifies the entire endometrium, including the stratum basalis, is included.

Following resection (**Figure 2; E**), the endometrial pieces were stored in cold University of Wisconsin (UW) solution (**Figure 2; F**), before being re-implanted in multiple 1-2cm pieces with 5/0 polypropylene (Prolene) (**Figure 2; H+I**). The uterus was then closed with 5/0 Polypropylene (Prolene) before the vascular clips were removed (**Figure 2; J**). Abdominal closure was performed with 3/0 polydiaxone (PDS) and 3/0 polyglactin 910 (Vicryl) was used for skin closure (**Figure 2; K**). The left uterus was left untouched as a control in all cases. The two endometrial resection procedures included the same surgical technique but following resection of the endometrium, it was not re-implanted, and the uterus and abdomen were closed in the same fashion.

Haematology and Biochemistry

Peripheral blood samples were obtained prior to surgery; at 24, 48, 72 and 96 hours post-operatively (short study) and on the 7th, 14th, 21st and 28th day (long study) post-operatively. Haematological and biochemical analysis was undertaken using Full Blood Count (FBC),

including white blood cells (WBCs), lymphocytes, monocytes and granulocytes in addition to a C-Reactive Protein (CRP). Within 10 minutes of collection, samples were analysed using an automated haematology analyser (MS 4e automated cell counter, Melet Schloesing Laboratories, France), according to manufacturer instructions. CRP concentration was measured using a human immunoturbidimetric test (CRP OSR 6147 Olympus Life and Material Science Europe GmbH, Lismeehan, O'Callaghan Mills, Co. Clare, Ireland).

Ultrasound examination

Transabdominal ultrasound (4–12 MHz linear probe, MyLab 60 machine, Esaote, Spain) was used to monitor uterine dimensions (maximum diameter in midsagittal section; **Figure 4**) at 24, 48, 72 and 96 hours and on the 7th, 14st, 21st and on the 28st post-operative day. The does were awake and unsedated during the examination.

Histopathology

Rabbits were euthanised at 48 (n=1), 72 (n=1) and 96 (n=1) hours after surgery, and after death, or following euthanasia at 6 months after autologous ETx to evaluate gross and microscopic changes. Samples were fixed in Bouin's solution and embedded in paraffin wax. Sections were stained with hematoxylin and eosin (H&E) according to standard protocol.

Embryo transfer

Four does were prepared for embryo donation with 3 µg of long acting follicle stimulating hormone agonist (Corifollitropin alfa; Elonva, Merck Sharp & Dohme S.A, Spain) as described previously.[22] Ovulation was induced with 1 µg buserelin acetate (Suprefact; Hoechst Marion Roussel, S.A., Madrid, Spain) given intramuscularly. Females were inseminated with 1ml of pooled semen 60 h after gonadotropin injection, and donor females were euthanised at 72 h post-insemination. A total of 84 morulae were recovered by perfusion of each oviduct and uterine horn with 10 mL pre-warmed Dulbecco Phosphate Buffered Saline (DPBS)

supplemented with 0.2% of Bovine Serum Albumin (BSA). Fresh embryos were transferred into oviducts laparoscopically to 3 does, in two consecutive sessions, utilising the procedure described in detail previously.[23] Ovulation was induced in recipient does (2 ETx females and 1 endometrial resection female), with an intramuscular dose of 1 mg of buserelin acetate 72 h before transfer. Reproductive outcomes were assessed using implantation rate, which was assessed laparoscopically 14 days following embryo transfer, and livebirth rate.

Statistics

Statistical analysis was performed with SPSS 21.0 software package. Descriptive statistical analysis was described as mean +/- SD. A general linear model was fitted for the analysis of FBC (WBCs, lymphocytes, monocytes and granulocytes), CRP and uterine dimensions, including the experimental group (ETx and ER) as fixed effect. Differences of $p<0.05$ were considered significant.

Results

Ten procedures were performed, including 8 endometrial auto-transplants (ETx) and 2 endometrial resections (ER). Surgical data is displayed in **Table 1**. Eight procedures were successful; two rabbits from the ETx group died intra-operatively, one due to anaesthetic related issues, and the other due to haemorrhage which contributed to difficulty in titrating anaesthetic concentrations. The average rabbit weight was 5.3 +/- 0.31kg. The mean retrieval and implantation times were 35.2 +/- 15.9 minutes and 14.8 +/- 3.6 minutes respectively. The number of pieces of endometrium retrieved per case was 10.2 (+/- 5.2), whilst the number re-implanted was 4.9 +/- 1.0. The average vascular clamp duration was 52.1 +/- 15.8 minutes. The mean overall surgery and anaesthetic times were 1h 22hm +/- 20.8m and 1h 43m +/- 25.9m respectively. Estimated blood loss was 17.0 +/- 10.6mls.

Total and differential WBC counts were elevated post-operatively, and higher WBC counts were observed at 48 hours after ETx (4.3 +/- 2.79 Vs 15.4 +/- 2.79; p=0.05), with the exception of granulocytes (p=0.143). There was no significant difference in CRP between ETx and ER animals during the first 48 hours post-operatively, but between 72-96 hours the CRP was significantly higher in the ETx group (155.3+/-15.79 Vs 95.5+/-15.79 for 72 hours; p=0.08 and 147.2+/-15.79 Vs 92.7+/-15.79 for 96 hours; p=0.046)

Ultrasonographically, comparison of uterine depth post-operatively between ETx, ER and the intact uteri is displayed in **Figure 5**. There was a significant difference in uterine depth between ETx animals and intact uterus groups until 22 days (528 hours) post-operatively (p=0.000). From 1 month (696 hours) onwards uterus depth was similar between all experimental groups (8.2+/-0.61 Vs 7.2+/-0.61 Vs 6.9+/-0.61 for ETx, ER and the intact uteri at 696 hours, respectively; p=0.195).

Two rabbits, one from the ETx group and one from the ER group, died four weeks and eight post-operatively of undetermined cause. Three rabbits subsequently underwent embryo transfer using the pooled embryos. Reproductive outcomes are shown in **Table 1**. During the first cycle, undertaken three months post-operatively, seven embryos were transferred into each uterus of the three remaining animals, two of which were following ETx and the other following ER.

All three recipient animals subsequently became pregnant (**Figure 6**). In the un-operated uteri, an implantation rate of 57% (12 implantations) was observed. In the operated uteri of the two ETx rabbits, an implantation rate of 28.5% (4 implantations) was observed. In the operated uterus of the ER female, an implantation rate of 0% was observed. In the second cycle, undertaken 4.5 months post-operatively, a further seven embryos were transferred into each uterus of the three females. As previously, all three recipient animals became pregnant (**Figure 7**). In the un-operated uteri, an implantation rate of 61.9% (13 implantations) was seen. In the two ETx females, an implantation rate of 14.3% (2 implantations) was observed. As previously,

no embryo implantation was seen after ER. Despite successful implantations in both cycles in the ETx rabbits, no livebirths were achieved.

Following euthanasia of the rabbits at 48, 72 and 96 hours, macroscopic evaluation of the endometrium identified healthy-appearing endometrium after ETx, as early as 96 hours post-operatively (**Figure 8**). Subsequent histological assessment demonstrated the fingerlike projections associated with normal endometrium (**Figure 9; A**) but with stromal haemorrhage and scanty surface erosion (**Figure 9; B**). The gross appearance of the endometrium six months following ETx (**Figure 10; B**), was similar to normal endometrium (**Figure 10; A**), and fetal tissue was evident (**Figure 10; C**). The presence of viable appearing convoluted endometrium with no surface erosions was subsequently confirmed histologically (**Figure 9; D**). The uterus of the ER rabbit euthanised six months post-operatively had a macroscopically scarred cavity with no villous endometrium (**Figure 10; D**) and with marked absence of the fingerlike projections associated with normal endometrium on histology (**Figure 9; C**).

Discussion

The data presented herein demonstrates, for the first time, gross and microscopic evidence of viable endometrium following ETx, along with the achievement of clinical pregnancies, albeit in the absence of achieving successful livebirth.

The decision to use the rabbit model was multifactorial. Not only do they have the advantage of being an intermediate size between rodents and larger animals like primates, but they have a longer life span when compared to other animals such as rodents.[24] Moreover, the immunological genes of rabbits have been demonstrated to be closer to those of humans than other small animals such as rodents.[25] Furthermore, female rabbits have a duplex uterus with two separate uterine horns and two cervices, which makes them an ideal candidate for reproductive studies. Finally, our research team have extensive experience in operating on the

rabbit pelvis, following multiple feasibility studies using the rabbit model, in addition to rabbit UTx studies undertaken in the past.[26,27]

The induction of ovulation in the does five days prior to ETx. This was previously demonstrated in one of our feasibility studies to significantly increase the uterine and endometrial size, facilitating the dissection, albeit increasing the potential for haemorrhage owing to associated increased vascularity. However, the use of the bulldog temporary vascular clips provides vessel occlusion, as has been demonstrated in other models previously,[28] which greatly reduced the potential for bleeding.

The main limitation of this study was the failure to achieve a livebirth following ETx, and the inferior reproductive outcomes when compared to the contralateral 'control' uteri. Despite evidence of viability on gross and microscopic appearance, it is likely defective tissue vascularisation may have been a contributing factor, leading to problems with implantation of the embryo and pregnancy loss. Restricted endovascular invasion during placentation can also lead to several antenatal complications including intra-uterine growth restriction, preterm birth and intra-uterine death, as demonstrated following pregnancies achieved in women after endometrial ablation.[29] For ETx to become a feasible treatment for women with AS, future studies will need to consider ways to potential re-vascularisation between the endometrio-myometrial interface, in order to optimise the chances of a livebirth. A further limitation includes the small sample size, although following the proof of concept demonstrated herein, this paves the way for further studies to expand upon.

When compared to UTx, ETx involves the transplant of less tissue, which may result in less immunogenic burden. However, the use of immunosuppression will remain essential to prevent rejection. Whereby cervical biopsies have been shown to be a consistent and achievable method of detecting rejection in the graft in UTx,[30-32] ETx would instead demand hysteroscopy and endometrial biopsy, which increases the opportunity for bacteria to be introduced inside the

cavity. Whilst endometrial biopsies have been shown in the baboon model to be less consistent in the detection of rejection of the uterus than cervical biopies,[30] it would be the only way to prove the diagnosis of rejection after ETx histologically. Moreover, the use of hysteroscopic guided endometrial biopsies have successfully been used in cases of UTx performed in India,[20,33] although detailed immunological outcomes and correlation between endometrial and cervical biopsies are awaited.

Conclusion

This study demonstrates gross and microscopic evidence of viable endometrium following ETx, along with the achievement of clinical pregnancies. Given the inadequate clinical and reproductive outcomes following conservative management of AS and the challenges that novel bioengineering strategies present, this may present a novel avenue for women with AUFI secondary to AS to acquire motherhood. Despite the promising results demonstrated herein, it is essential further studies are undertaken, in particular to assess and optimise pregnancy development after ETx. Moreover, further data is needed to assess the impact of cold and warm ischaemia times, as well as the allotransplant studies, before this is considered in human models.

Author's roles

BPJ conceived the study design, undertook the series of operations and wrote the manuscript. SV did a literature review and contributed to writing the article. SS helped conceive the article and reviewed the final draft. MYT helped conceive the original concept and revised the final draft. SS, SGM, IQ and JY reviewed and contributed expertise to the manuscript. LP performed the ultrasound assessments during the study and revised the final manuscript. XGD, JSV, LGV and FMJ prepared the rabbits, managed them intra-operatively and post-operatively and performed the embryo transfers. In addition, FMJ helped conceive the original concept, coordinated the study design, helped write the manuscript and revised the final draft. JRS

conceived the original concept, coordinated the study design, undertook the operations and helped revise the final draft. JRS is the guarantor for this paper and accepts full responsibility for the work and/or the conduct of the study.

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Disclosure of interests

None

Details of Ethics Approval

This study was undertaken at the Institute of Science and Animal Technology (ICTA), at the Polytechnic University of Valencia in Spain. All animals were handled in accordance with the principles of animal care published by Spanish Royal Decree 53/2013 (BOE 2013). The experiments were approved by the Committee of Ethics and Animal Welfare Committee of the Polytechnic University of Valencia (2017/VSC/PEA/00130)

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Figure and table legends

Figure 2 – Endometrial transplantation surgical technique

Figure 3 – Histological analysis of endometrial samples excised using surgical technique (LE; Luminar epithelium, SF; Stratum functionalis, SB; Stratum basalis, SM; Submucosa)

Figure 4 – A) Demonstration of post-operative ultrasound technique and B) Measurement of maximal mid-sagittal uterine depth

Figure 5 – Comparison of maximum uterine depth between un-operated control uteri, endometrial transplantation and endometrial resection groups throughout study. *denotes significant differences between experimental groups.

Figure 6 – Laparoscopic identification of implantation during first IVF cycle, with evidence of pregnancies in both ETx uteri (A&B), no evidence of pregnancy in the ER uteri (C), and confirmation of pregnancies in the control uteri (D-F)

Figure 7 – Laparoscopic identification of implantation during second IVF cycle, with evidence of pregnancies in one ETx uteri (A), no evidence of pregnancy in the other ETx or the ER uteri (B-C), and confirmation of pregnancies in the control uteri (D-F)

Figure 8 – Comparison of the macroscopic appearance of the uterine cavity between A) 48 hours post endometrial transplantation and B) 96 hours post endometrial transplantation

Figure 9 - Comparison of the uterine histology between A) an un-operated control uterus, B) 96 hours post-operatively, C) 6 months after endometrial resection and D) 6 months post-operatively after IVF

Figure 10 – Comparison of the macroscopic appearance of the uterine cavity between A) an un-operated control uterus, B) 6 months post-operatively after IVF, C) 6 months post-operatively after IVF with presence of fetal tissue and D) 6 months after endometrial resection

Table 1: Surgical data and post-operative data including reproductive outcomes

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	Rabbit 1	Rabbit 2	Rabbit 3	Rabbit 4	Rabbit 5	Rabbit 6	Rabbit 7	Rabbit 8	Rabbit 9	Rabbit 10	Mean (+/-SD)
Weight (g)	5200	5000	5300	5500	5000	5600	5700	5100	5800	5000	5320 +/- 308.4
Resection time (min)	61	30	19	51	43	47	43	15	24	19	35.2 +/- 15.9
Number of pieces retrieved	<5 mm – 6 5–10 mm – 4 >10 - 5	40 mm – 2 20 mm – 2 <20 - 4	10–20 mm – 55 –10 mm - 11	50-60-mm - 1 30-40 - 1 10–20 mm – 25 –10 mm - 3	20-30 mm - 1 10–20 mm - 05 –10 mm – 2 <5-mm - 16	10–20 mm - 35 –10 mm – 4 <5-mm – 0	10–20 mm - 15 –10 mm – 10 <5-mm – 0	10–20 mm - 15 –10 mm – 10 <5-mm – 0	70-80 mm - 1 30-40 mm – 1	10–20 mm - 6	10.2 +/- 5.2
Time of clamps (min)	65	68	30	78	52	55	51	28	51	43	52.1 +/- 15.8
Implantation time (min)	n/a	18	20	17	n/a	16	9	12	13	13	14.8 +/- 3.6
Number of pieces re-implanted	n/a	40 mm X1 20 mm X 2	5 × 10 mm	1 × 5-6cm 2 × 2 cm 1 X 1 cm	n/a	3 × 10–20 mm 2 × 5–10 mm	1 × 10–20 mm4 × 5–10 mm	1 × 10–20 mm5 × 5–10 mm	5 × 10–20 mm1 × 5–10 mm	10–20 mm - 5	4.9 +/- 1.0
Operation time (min)	106	107	68	117	72	72	n/a	65	72	66	82.8 +/- 20.8
Anaesthesia time (min)	130	139	94	142	93	93	n/a	80	88	75	103.8 +/- 25.9
EBL (mls)	10	20	10	30	10	10	40	10	20	10	17 +/- 10.6
IVF attempted	No	2 cycles	No	No	2 cycles	No	No	No	2 cycles	No	
Pregnancies in operated horn	No	Cycle 1–2 Cycle 2 - 1	n/a	n/a	No	n/a	n/a	n/a	Cycle 1–2 Cycle 2 - 0	n/a	
Pregnancies in control horn	n/a	Cycle 1–3 Cycle 2 - 3	n/a	n/a	Cycle 1–5 Cycle 2 - 5	n/a	n/a	n/a	Cycle 1–4 Cycle 2 - 5	n/a	
Deceased	Died 1-month post op	Euthanised after 2 cycles IVF	Euthanised 96 hours post op	Euthanised 72 hours post op	Yes - sacrificed after 2 cycles IVF	Died intra-operatively due to anaesthesia	Died intra-operatively due to blood loss / anaesthesia	Euthanised 48 hours post-op	Euthanised after 2 cycles IVF	Died 2 months post-op	

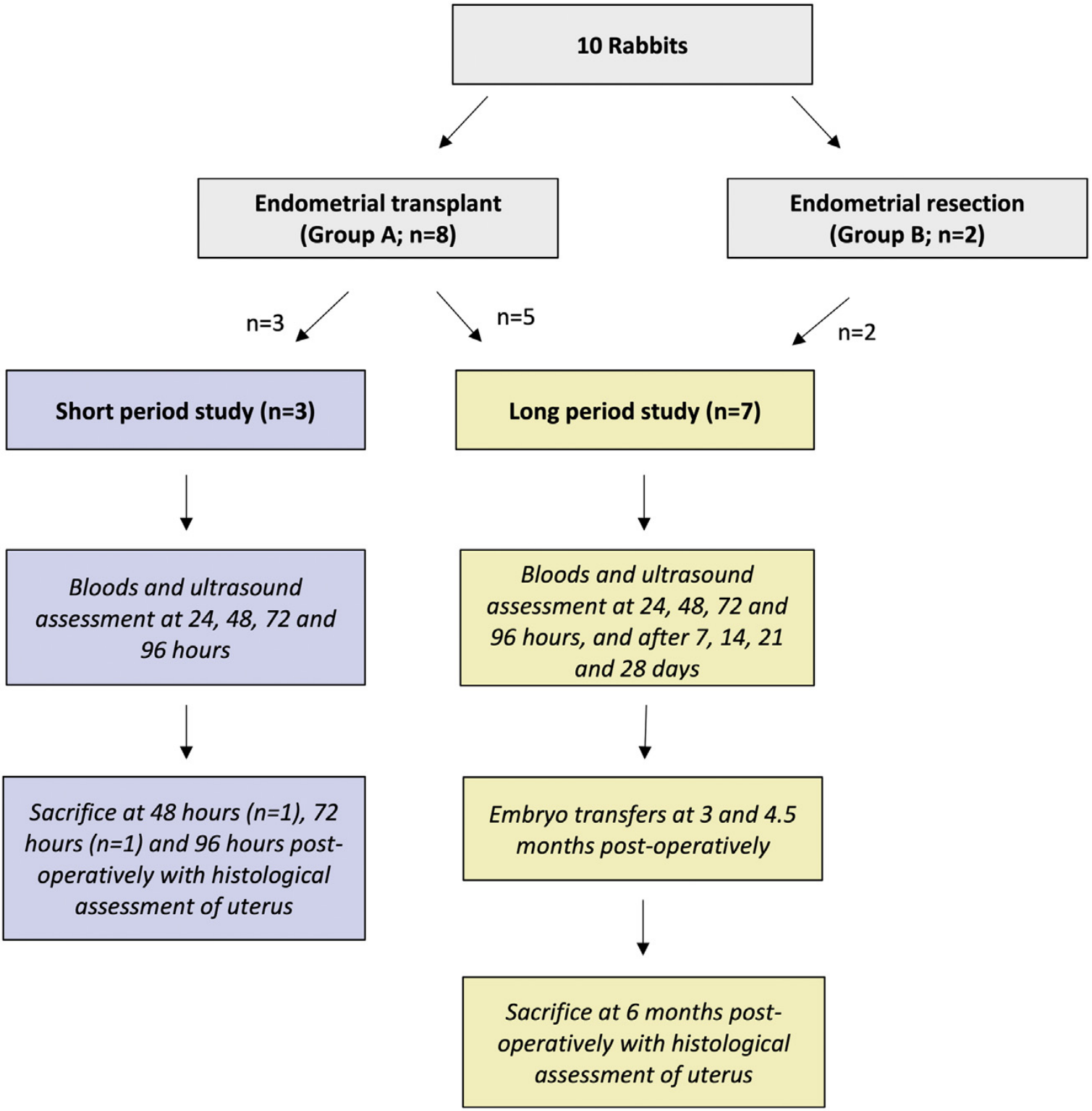
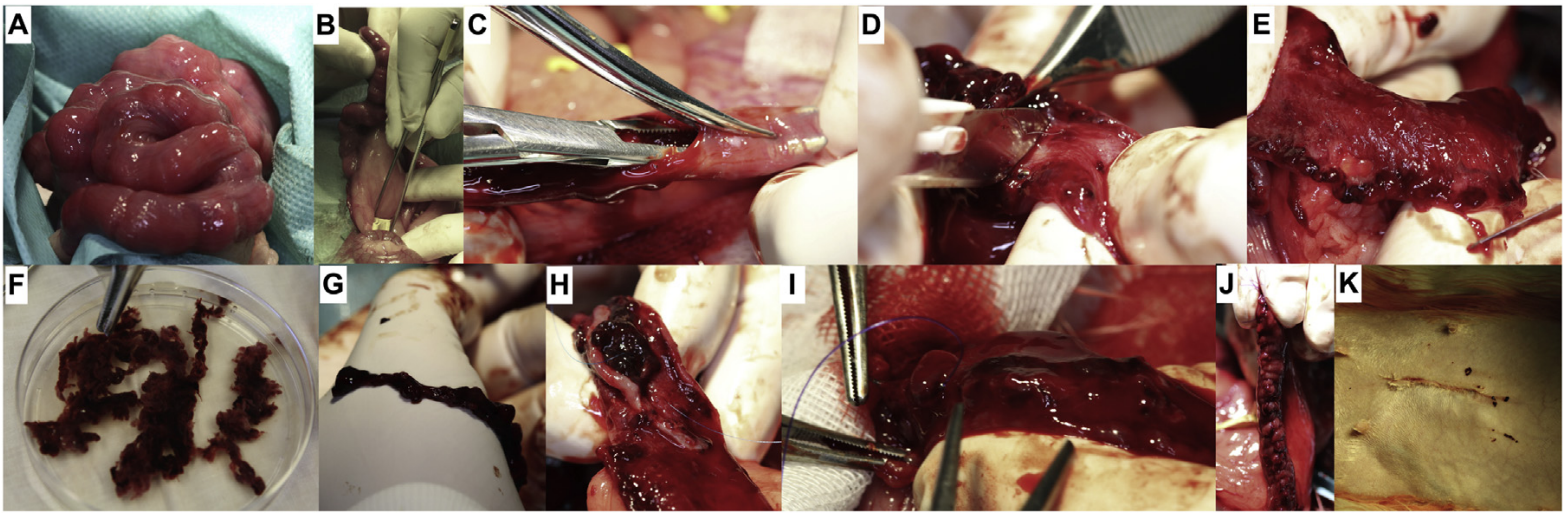


Fig. 1. Study design.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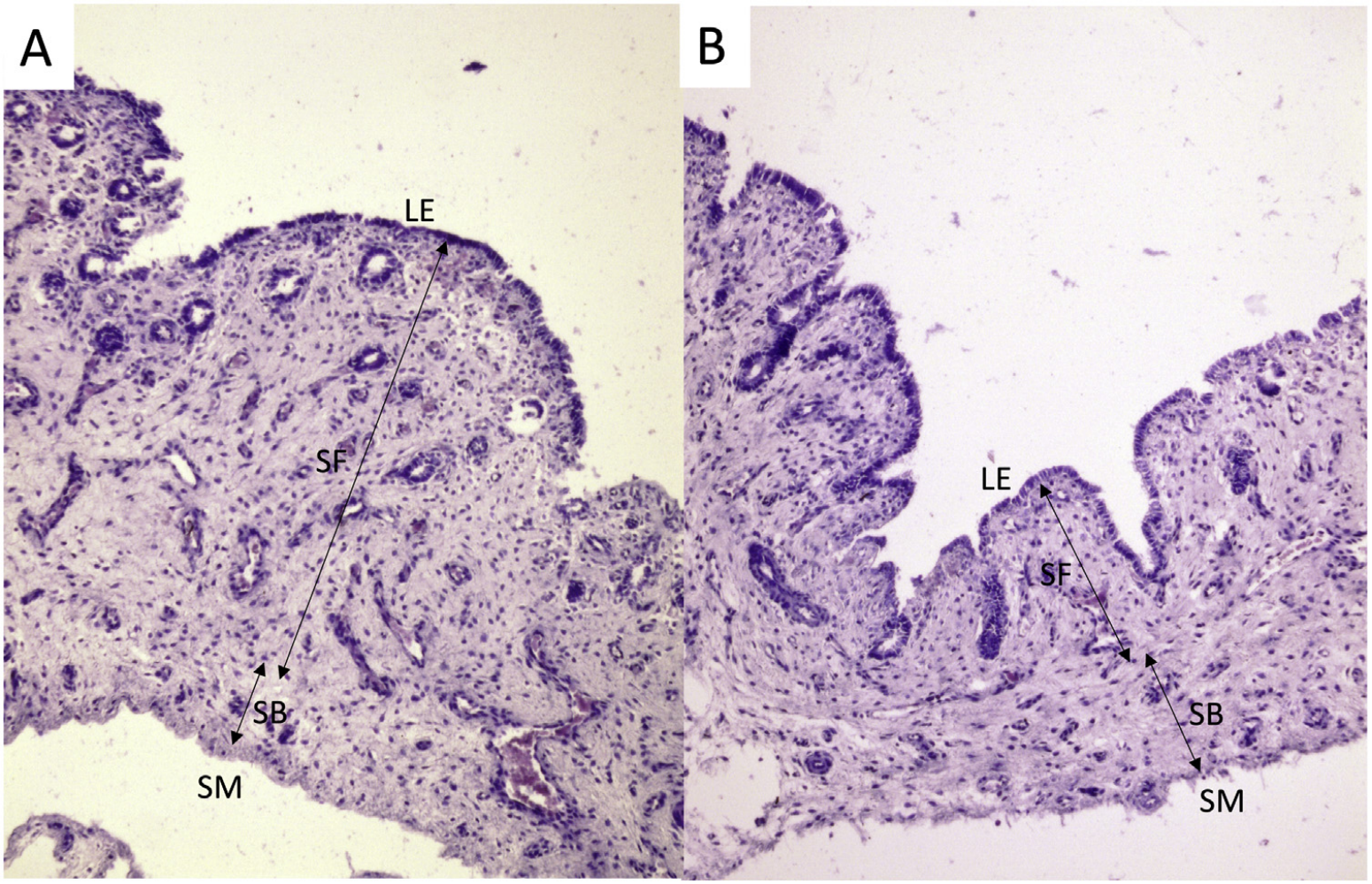
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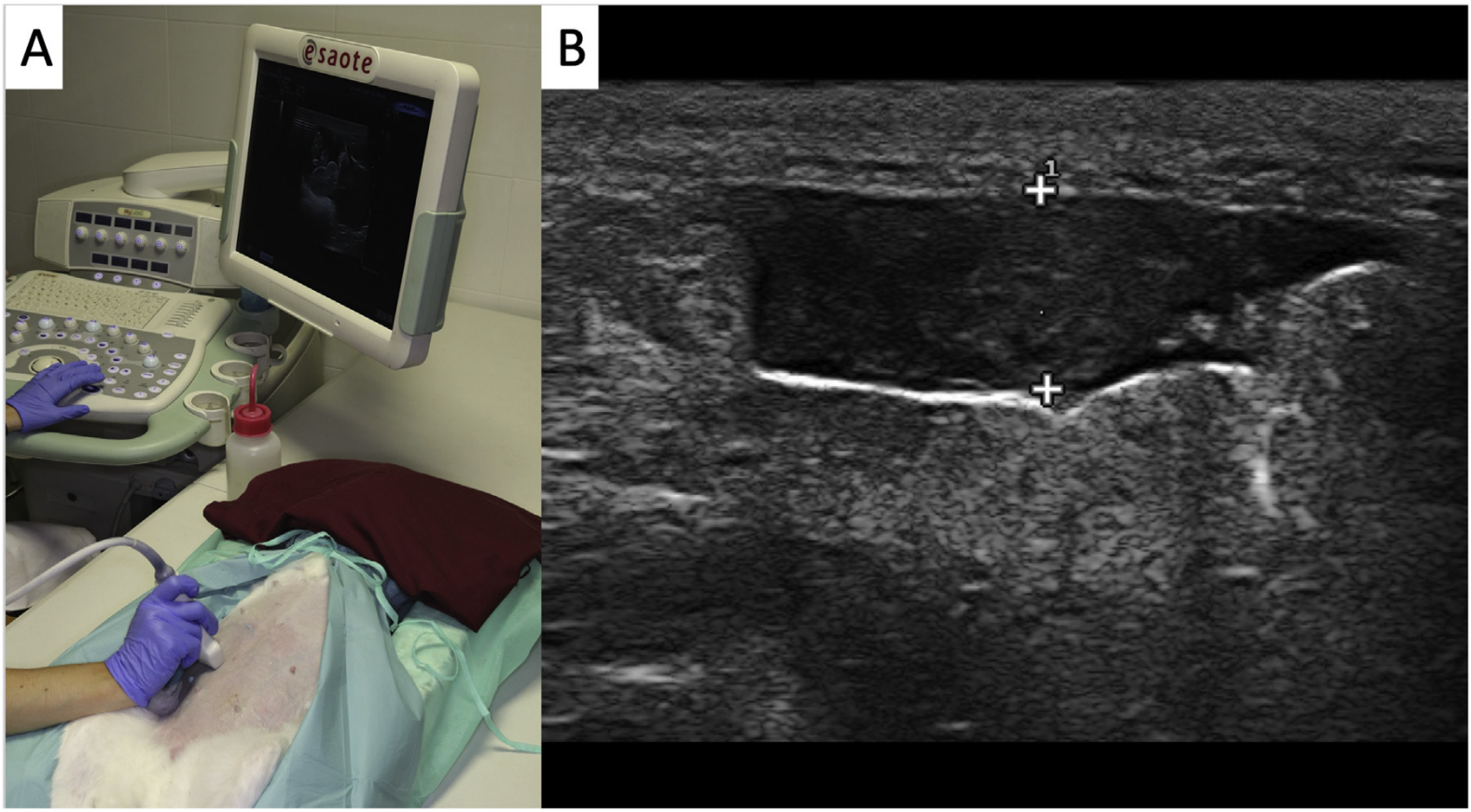
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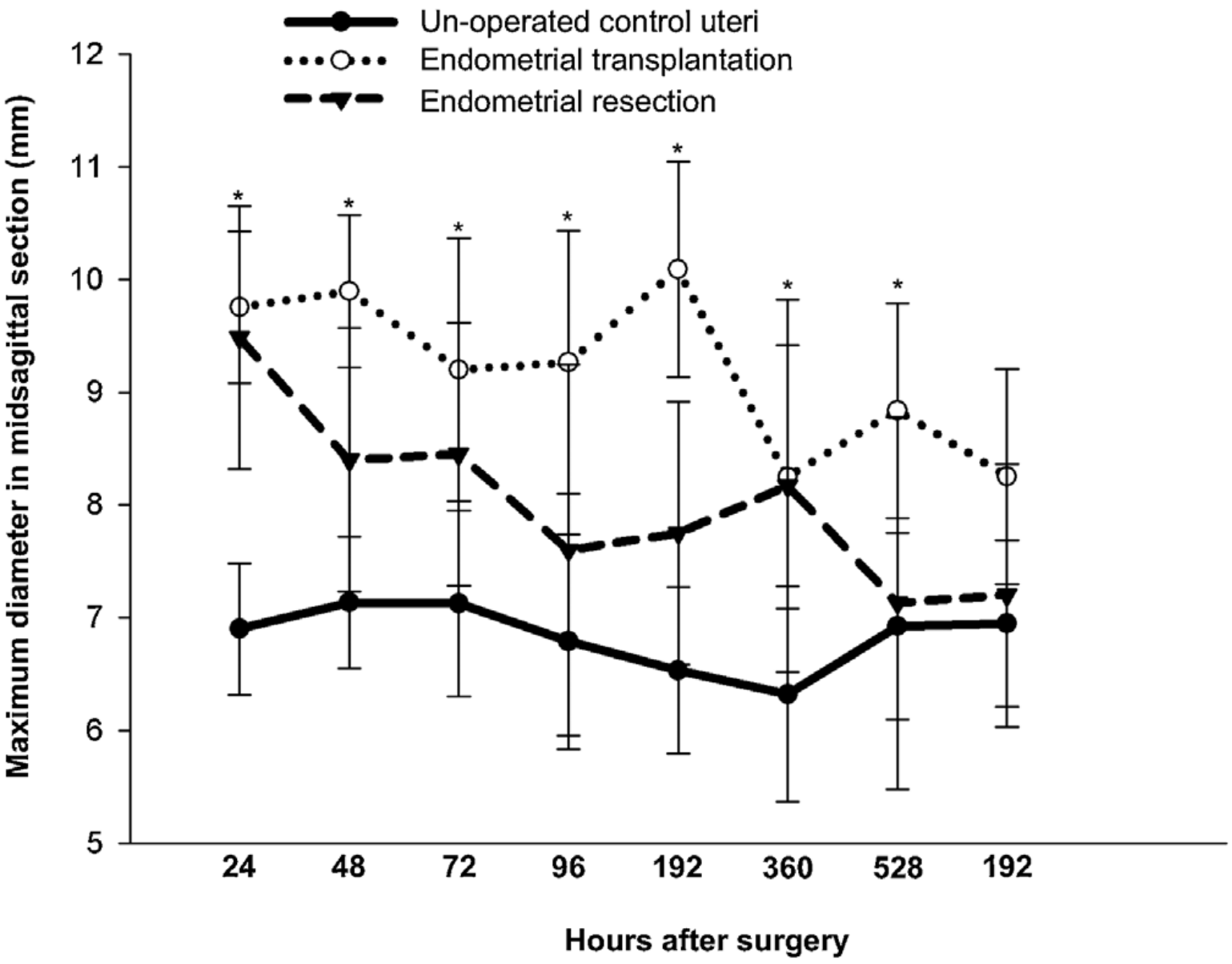
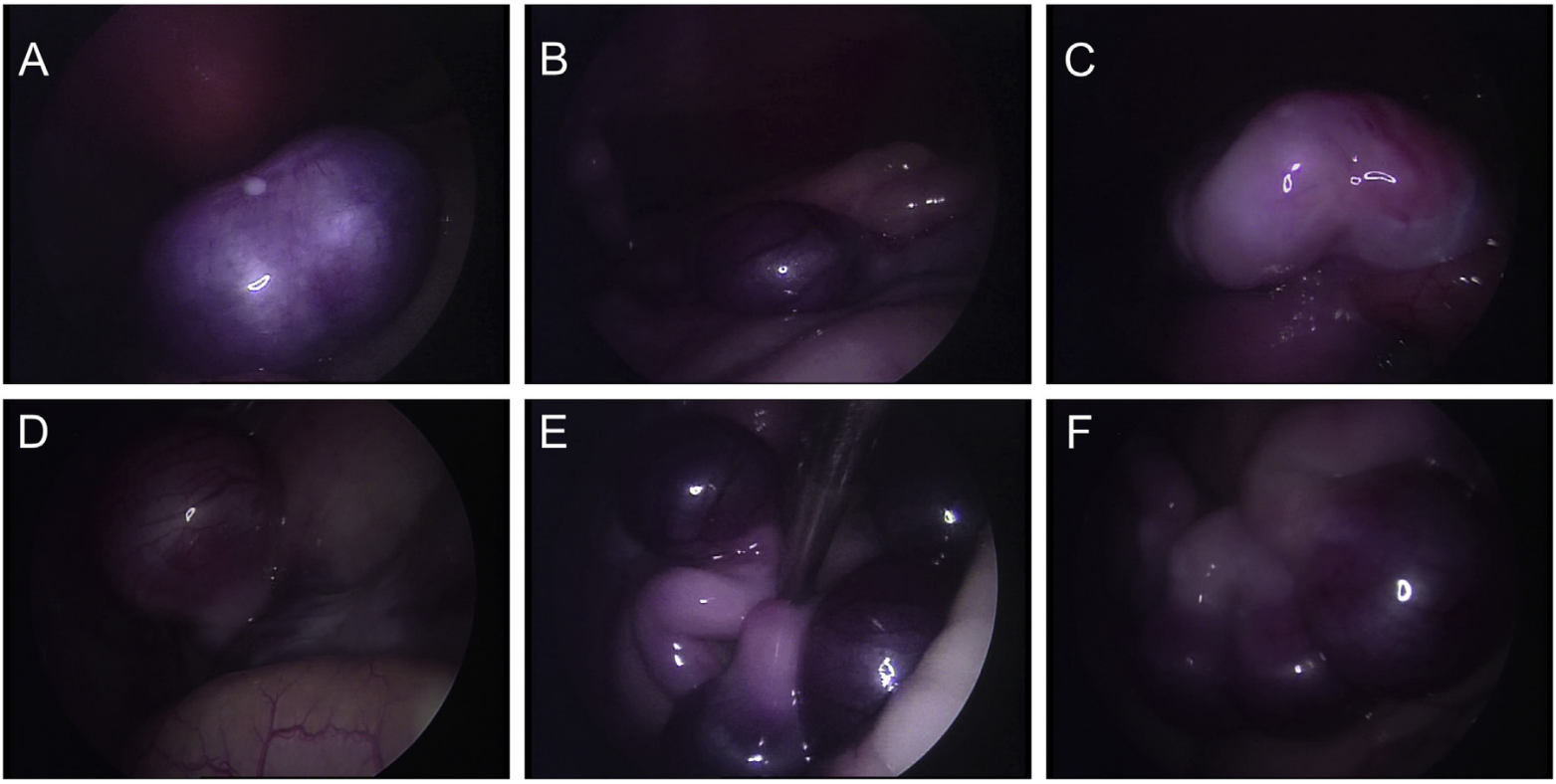

Un-operated control uteri
Endometrial transplantation
Endometrial resection
Maximum diameter in midsagittal section (mm)
12
11
10
9
8
7
6
5
24
48
72
96
192
360
528
192
Hours after surgery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