Feasibility of the New Zealand white rabbit as an animal model for the study of biological grafts in the pelvic floor dysfunctions

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Conflict of Interest: The authors declare that they have no conflict of interest

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Abstract
Objective: to investigate the feasibility of the New Zealand White (NZW) rabbit to study human acellular dermal matrix (hADM) biomaterials in pelvic reconstructive surgery.

Study design: 20 white female NZW rabbits were randomized into 2 groups, the experimental group (hADM graft) and the control group (Polypropylene graft; PP). In each animal, grafts were surgically implanted subcutaneously in the abdominal wall and in the vaginal submucosa layer for 180 days. The graft segments were then removed and the surgical and clinical results were analysed.

Results: The main surgical challenges were: a) to obtain the adequate vaginal exposure and the maintenance of the integrity of the vaginal mucosa layer; b) to keep aseptic conditions; c) to locate and dissect the breast vein during abdominal surgery; and, d) to withdraw blood samples from the ear artery.

The most abnormal findings during the explant surgery were found in the PP group (33% of vaginal mesh extrusion) in comparison with the hADM group (0% of vaginal graft extrusion), p=0.015. Interestingly, macroscopic observation indicated that the integration of the vaginal grafts was more common in the hADM group (40%) than in the PP group, in which the vaginal mesh was identified in 100% of the animals (p=0.014).

Conclusions: The NZW rabbit is an excellent model to assess materials to be used as grafts for pelvic reconstructive surgery and vaginal surgery. Animals are easily managed during the procedures, including the surgical intervention and vaginal mucosa handling.

Introduction:
Pelvic floor dysfunctions are a common condition that affect a third of the adult female population. In both urinary incontinence (UI) and pelvic organ prolapse (POP), surgical treatment has shown the best results. In both pathologies, surgical repair may involve the use of non-absorbable, synthetic prostheses.

The use of a synthetic mesh, usually polypropylene (PP), has been associated with severe complications such as erosion, retraction, and pain. One in every thirty women that undergoes UI surgery with PP mesh needs repeated surgery within the following ten years due to mesh-related complications [1]. As for POP reconstructive surgery, mesh-related complications are difficult to manage and the reported risk of reintervention reaches 3-10%, although its incidence in real world use is probably higher [2].

In July 2018, the use of mesh implants to treat stress urinary incontinence was suspended by the National Health Service (NHS) of the United Kingdom. And in April 2019 the United States (US) Food and Drug Administration (FDA) banned mesh implants placed vaginally to treat pelvic organ prolapse. With growing concern for safety, there is a worldwide agreement on the need of research and
innovation to find alternative materials to use in pelvic reconstructive surgery. This need of new materials with an effective and safe mesh design has approached the development of acellular matrices (AM). AM are a new generation of biocompatible materials processed to obtain decellularized scaffold of fibres whose architecture and extracellular matrix remain intact.

In recent years, many different types of biological meshes have been marketed and their efficacy evaluated [3,4]. Specifically, human dermal matrices (hADM), available in the US for more than 15 years, have been used in more than 2 million implant procedures and information is available on its clinical safety and efficacy in different clinical applications [5,6]. Reconstructive surgeries such as chronic wounds closure, immediate breast reconstruction, abdominal wall and hernia repair, and tendon reinforcement are likely to use dermal matrices [5,7,8]. However, the gynaecological application of dermal matrices has been poorly evaluated. Therefore, it is necessary to carry out studies to assess hADM in the repair of pelvic floor dysfunctions.

Unlike synthetic meshes that simply act to reinforce damaged tissue, hADM aim to act as natural scaffolds with full integration in the soft tissues that surrounds them and even induce tissue regeneration. This tentative function is compatible with the hypothesis of hADM sustaining biocompatibility with the recipient tissue, and able to abrogate the complications associated with synthetic meshes that induce local inflammation.

Our group aimed to investigate the properties of hADM placed surgically in a vaginal location and to evaluate whether the rabbit is a good model for the study of biomaterials for pelvic reconstructive surgery.

Material and methods
1. Experimental Design and subjects of study:
Due to the lack of research of hADM in gynecology, one of the challenges was to choose the most appropriate animal model. The NZW rabbit model was chosen due to the characteristics of this species, which fulfil the needs for the evaluation of the hADM, as the size of its vagina is suitable for the intended vaginal surgery. Moreover, this model also allows the selection of multiparous individuals, to facilitate vaginal surgery. Their accommodation is simple: they are docile in behaviour, can be handled by a single researcher and do not require a large infrastructure. Due to all these reasons, the NZW rabbit was chosen as a model in this experimental study. Smaller animals (i.e. rat) would not have allowed vaginal surgery and larger animals (i.e. ewes or sows) would have been more difficult and expensive to barn and were, therefore, discarded for the purposes of this study.

The study is carried out by Barcelona Tissue Bank (BTB), the Hospital de la Santa Creu i Sant Pau, and at the Research Institute of the Hospital de Sant Pau-IIB Sant Pau.

The study protocol was approved by the Internal Animal Care and Use Committee (CEEA-IRHSCSP) and the competent government authority
(Generalitat de Catalunya, Animal Experimentation Commission, project number 9669). All animal procedures were carried out in strict accordance with the guidelines from Directive 2010/63/EU of the European Parliament on the protection of animals used for scientific purposes. In addition, we followed the ARRIVE guidelines and committed to the 3Rs of laboratory animal research. The animal experimental project was performed in the Animal Experimental Service of the IRHSCSP, ISO 9001:2015 accredited.

This study followed the ethical precepts of the Declaration of Helsinki and was approved by local ethics committee. Human tissue was processed according to guidance for clinical use (EEC regulations 2004/23/CE and 2006/17/CE) and to the legal requirements for the use of biological samples for research in Spain (Law 14/2007 and RD 1716/2011). Ethics institutional review board (IRB) approval was obtained (CEIm Hospital Valle Hebrón, Barcelona; PR (BST)314/2019).

A total of 20 female multiparous NZW rabbits were randomly allocated to receive control (PP mesh) or experimental (hADM) grafts.

Each rabbit received 4 grafts: 2 grafts in the vaginal submucosa layer and two in the subcutaneous tissue of the abdominal wall, over the muscular fascia.

Regarding the vaginal grafts, one (5x5 mm) was placed in the anterior vaginal wall and used for histological and immunohistochemical studies. The second (10x5 mm) was placed in the submucosa of the posterior vaginal wall and was used to perform the biomechanical study.

The size of the abdominal grafts was the same than vaginal grafts, but both were stitched together in the right caudal quarter of the abdominal wall.

The implants were removed 180 days later, at which time the animals were also euthanized.

Our research group proposes the use of a hADM recently developed at the BTB for pelvic reconstructive surgery, as a safer alternative to current synthetic meshes.

2. Graft preparation
2.1. Preparation of hADM samples.

hADM was obtained from skin tissue procured from the back and lower limbs of a human donor by manual dermatome. The tissue was processed in clean rooms in accordance with Good Manufacturing Practices (GMP) regulations in the BTB. The processing consisted on selection of homogeneous fragments in thickness, decontamination in antibiotic solution for 16-24 h and decellularization by chemical and mechanical treatment. Ten sequential washes were carried out in 0.9% NaCl to remove any left-over reagent. The 10x5 mm samples were prepared and stored in glycerol solution in a double bag at room temperature until use. Microbiological controls were performed throughout the graft processing.
2.2. PP graft preparation

The material (Gyneband®) was delivered in a sterile container, ready for medical use in humans. Under conditions of surgical asepsis, it was removed from the container and cut into 10x5 mm and 5x5 mm pieces immediately before proceeding with the implant surgery.

3. Surgical procedure

Animals were anesthetized with ketamine (15 mg / kg subcutaneous; sc) and medetomidine (0.5 mg / kg sc). Each rabbit received a prophylactic antibiotic dose (Ceftiofur 50mg / kg sc) and nonsteroidal anti-inflammatory (meloxicam 1mg / kg intramuscular -im-).

Before surgery, blood samples (6cc) were obtained from the ear artery to study inflammatory markers. Areas of surgical incision were previously shaved and disinfected. Serial extractions were performed in days: 0 (day of implantation surgery), 7, 30 and 180 (day of euthanasia).

**Abdominal implants:** A transverse incision was made in the abdominal midline, at the level of the intermammillary line of the last two nipples on the right side of the rabbit, to expose the anterior abdominal fascia. Both fragments of the graft (hADM or PP) were positioned and fixed with prolene (Ethicon) 5/0 discontinuous suture (Picture 1C). The abdominal wall was closed with 4/0 vicryl rapide (Ethicon) thread in two layers: continuous suture for subcutaneous tissue, and continuous intradermal suture for skin tissue.

**Vaginal implants:** A transverse incision was made in the anterior vaginal wall, approximately 1 cm from the vaginal entrance. The vaginal mucosa layer was dissected and the 5x5 mm graft was implanted and fixed with the same procedure as in the abdominal implant (Picture 1B). The same procedure was repeated on the posterior vaginal wall, using the 10x5 mm graft (Picture 1A). The vaginal mucosa was closed with a 4/0 vicryl thread using an interrupted suture.

Once the implants had been placed, a preventive dose of buprenorphine (0.01mg/kg, sc) was administered. To avoid licking and infection of the wound, rabbits wore a protective collar for 7 days after surgery. Animals could move freely in their pens and were under a strict veterinary control. During the entire period of study animals were daily supervised and weekly weighted and complications related to the implant were closely monitored.

After 180 days, rabbits were anesthetized as described before and the grafts were explanted, removing the prosthesis together with surrounding tissue. Animals were euthanized under deep anaesthesia according to the protocol by administration of 150 mg / kg intravenous pentobarbital.
4. Variables and parameters investigated at surgery and at follow-up

**Surgical variables:** surgical time duration, complications and difficulties were annotated by the investigator during the implant surgery.

**Clinical complications during animal follow-up:** Signs of pain/stress in the animals were evaluated by the Grimace Scale. This scale allows an objective evaluation of pain and distress of animals through the facial expression, specially noticing orbital closure, flattening of the cheeks, angulation of the nostrils, stiffness of the whiskers and subsequent rectification of the ears. Each item was scored from 0 to 3, being: 0 = not present, 1 = moderately present and 2 = obviously present.

Pain / discomfort (any value > 1) were treated with an additional painkiller dose (buprenorphine, 0.01mg/kg, sc).

Signs of loss of well-being: anxiety, depression, inactivity, restlessness, shrieks, or groans, grinding of teeth, tonic immobility, rejection of water and / or food,
weight loss were also surveyed. Clinical signs of surgical site complication were equally inspected and annotated.

Macroscopic observation of explants: During explant surgery, the macroscopic aspect of the explants was evaluated. Attention was focused on presence of:

a) evidence of seroma (accumulation of serous fluid around the graft); b) signs of local infection (erythema or purulent suppuration); and, c) evidence of extrusion of the graft (cutaneous necrosis or dehiscence of the surgical wound with exposure of the graft).

5. Statistical analysis.
As descriptive data analysis we used the median, and also the mean with standard deviation. The relationship between categorical variables was analyzed using the corresponding contingency tables, calculating the percentage in each group and application of chi-square test with the approximation of the probability ratio. In the ordinal variables, the comparison between two groups was made with non-parametric Mann-Whitney test. In all cases, the usual level of significance was 5% (alpha = 0.05). All analysis was performed with the statistical IBM-SPSS package (V25).

Results
A total of 20 animals were included, 10 in the experimental (hADM) group and 10 in the control (PP) group. 1 rabbit in the control group died due to causes non-related to grafts.

1. Surgical challenges during surgical graft implantation:

Exposure of the vaginal surgical field:
Due to the small size of the surgical field, a recurring difficulty was the vaginal exposure. This challenge was solved by placing an eyelid retractor in the vaginal introitus. The rest of the instruments were regular microsurgical devices.

Integrity of the vaginal mucosa layer
Grafts were implanted at the level of the vaginal submucosa layer, so a meticulous vaginal dissection was needed. Because it is an extremely thin layer, another difficulty in most of the experiments was to maintain the integrity of the vaginal mucosa layer during the graft implantation. The maintenance of this layer is crucial to minimize the risk of future implant extrusions. Despite these difficulties, it was possible to preserve the mucosa in 100% of cases.

Aseptic conditions
It was difficult to keep aseptic conditions due to the large amount of hair in this animal model. The methods used to achieve adequate asepsis in the surgical field were an extensive shaving of the NZW’s abdomen and external genitalia, and a careful and precise handling of the animals during surgeries.

Location and dissection of the breast vein during abdominal surgery.
During abdominal surgery, the last two nipples on the right side of the animal were used as anatomical reference measure to locate the explant position during its surgical removal.
The breast vein is located at the intermammillary line. This makes necessary its careful dissection to avoid accidentally damage it during implantation surgery. In one case, the vein was damaged and we had extensive bleeding that resolved with a haemostatic suture; however, the animal presented postoperatively an abdominal wall hematoma that resolved spontaneously.

**Blood extraction from the ear artery.**

Blood withdrawal from the ear artery may be a difficult procedure. Blood was obtained in 79 occasions. In 6 cases (4.74%) we experienced difficulties that led to the collection of insufficient blood volume to complete the studies. These difficulties occurred in both groups.

Surgical variables, clinical findings during the animal follow-up and macroscopic study of explants are described in Table 1.

<table>
<thead>
<tr>
<th>Surgical time of implant surgery</th>
<th>Control (PP) group (N=10)</th>
<th>Experimental (hADM) group (N=10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75' (Sd*=37)</td>
<td>80' (Sd*=35)</td>
<td>0.760</td>
</tr>
<tr>
<td>Surgical complications of implant surgery</td>
<td>1 (10%)</td>
<td>0</td>
<td>0.305</td>
</tr>
<tr>
<td>Abdominal wound infection</td>
<td>3 (30%)</td>
<td>1 (10%)</td>
<td>0.582</td>
</tr>
<tr>
<td>Dirty genitalia</td>
<td>1 (10%)</td>
<td>3 (30%)</td>
<td>0.582</td>
</tr>
<tr>
<td>Stereotypes harm lesions</td>
<td>2 (20%)</td>
<td>2 (20%)</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal mesh extrusion</td>
<td>2 (20%)</td>
<td>0</td>
<td>0.474</td>
</tr>
<tr>
<td>Accidental facial injury</td>
<td>1 (10%)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Death (normal autopsy)</td>
<td>1 (10%)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal wound hematoma</td>
<td>1 (10%)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Average vaginal pH</td>
<td>8.47</td>
<td>8.38</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>Average weight gain</td>
<td>884g</td>
<td>714.5g</td>
<td>P&lt;0.641</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical findings during the animal monitoring</th>
<th>Control (PP) group (N=10)</th>
<th>Experimental (hADM) group (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal mesh extrusion</td>
<td>3 (33%)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal mesh extrusion</td>
<td>1 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>Chronic infection signs in abdomen location</td>
<td>3 (33%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Chronic infection signs in vaginal location</td>
<td>1 (11%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Vaginal graft not visible</td>
<td>0</td>
<td>4 (40%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Macropscopic study of explants:</th>
<th>Control (PP) group (N=10)</th>
<th>Experimental (hADM) group (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal mesh extrusion</td>
<td>3 (33%)</td>
<td>0</td>
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</tbody>
</table>

**Table 1:** Surgical variables, clinical findings during the animal follow-up and macroscopic study of explants.

*Sd = Standard deviation

2. **Surgical complications of implant surgery:**
Only one animal suffered mild haemorrhage in the subcutaneous tissue during abdominal surgery, which was resolved with an haemostatic suture.

3. Clinical complications during follow-up

Clinical complications and actions taken during follow-up and are described in Table 2. The Grimace scale was 0 in all animals and in all evaluations during follow-up.

**Table 2. Incidences at follow-up**

<table>
<thead>
<tr>
<th>Control group:</th>
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<tbody>
<tr>
<td>A. Three cases (30%) of abdominal surgical wound infection. Resolved with antibiotic treatment.</td>
</tr>
<tr>
<td>B. One case (10%) of filthiness in the genital area. No intervention needed.</td>
</tr>
<tr>
<td>C. Two cases (20%) of minor self-inflicted damage. Resolved with antiseptic and environmental enrichment measures.</td>
</tr>
<tr>
<td>D. Two cases (20%) of extrusion of the abdominal mesh. In one there was spontaneous resolution (correct subcutaneous location of the mesh at the time of euthanasia). In the second case the extrusion persisted.</td>
</tr>
<tr>
<td>E. One case (10%) of minor facial injuries due to an accidental incorrect position of the protective collar on the first postoperative day. Resolved favourably with antiseptic measures.</td>
</tr>
<tr>
<td>F. One case (10%) of death in the control group, 58 days after surgery. Necropsy showed no complications at the mesh level or other pathological findings of interest.</td>
</tr>
<tr>
<td>G. One case (10%) of abdominal wound hematoma which was spontaneously resolved.</td>
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</table>

<table>
<thead>
<tr>
<th>Experimental group:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. One case (10%) of abdominal wound infection. Resolved spontaneously.</td>
</tr>
<tr>
<td>B. Three cases (30%) of filthiness in the genital area. Resolved in one case by shaving and extensive washing under sedation.</td>
</tr>
<tr>
<td>C. Two cases (20%) of minor self-inflicted damage. Resolved with antiseptic and environmental enrichment measures.</td>
</tr>
</tbody>
</table>

Discussion

This study shows that NZW rabbit is a good model to study the behaviour of biomaterials placed in the abdominal and vaginal areas.

In the present study, we have evaluated the feasibility of the rabbit as an animal model for the study of biological grafts placed in the pelvic floor to resolve dysfunctions. The hADM is an acellular biological matrix, obtained from human dermis, produced to improve the biocompatibility of grafts over that of current synthetic alternatives. hADM matrices are free of allergens, DNA and other pathogens. In this study, hADMs were implanted in the rabbit's abdominal fascia and in the vaginal submucosa layer, with the aim of testing the behaviour of the matrix in different in vivo settings. We use the rabbit as a model based on previous publications, as well as on the characteristics of the animal: adequate life expectancy for the duration of the study, perineal musculature associated
with the urogenital tract\cite{9,10} and enough vaginal ability to perform a graft placement, easy animal accommodation, and availability of trained investigators in handling animal species.

Graft implantation at the level of the abdominal subcutaneous tissue and in the anterior and posterior vaginal submucosa layer of rabbits was technically simple, and it was associated with very minor surgical complications. However, adequate exposure of the vaginal field is difficult due to its small size. Hence, appropriated training of an assistant and the specific surgical material (suitable for microsurgery) are needed.

Ear blood extraction was also challenging, especially after successive extractions in the same animal because of the narrowing of the vascular lumen secondary to consecutive punctures. Therefore, it is advisable to have the help of trained personnel to perform this technique. Another cause of difficulty in blood withdrawal is the arterial vasoconstriction associated with the decrease in the body temperature of the animals, as well as pain at the puncture site if adequate anaesthesia is not achieved.

Complications at the follow-up were minor facial injuries due to an accidental incorrect position of the protective collar. To avoid other similar types of injury, protective collars were removed after observing there were no self-inflicted injuries in the surgical wound area. Animals did not show signs of pain during follow-up, so we concluded that a quick, low-invasive, and uncomplicated surgical manipulation is probably associated with low postoperative pain allowing the avoidance of protective collar placement.

The clinical complications associated with the synthetic mesh (wound infection and mesh extrusion) are more common in the control group, especially in the vaginal location where mesh extrusion happens in 33% of cases (p=0.024). However, in the experimental group the macroscopic hADM degradation at the vaginal level occurs in 40% of cases as compared with 0% in the PP group (P=0.014). Whereas in the abdominal location the macroscopic characteristics of hADM graft are kept intact in all cases.

In both groups, stereotypical self-injuries appear, so it is very important to add environmental enrichment measures in these animals. It is also very important to maintain strict hygiene measures to avoid complications derived from dirtiness.

Other animal models besides the rabbit have been used to study biomaterials in urogynaecology. Rats \cite{11-19} were used; however, due to its small body size studies at vaginal level are impossible. The same is true in mice. Authors such as Endo M, et al\cite{20}. or Tayrac R, et al\cite{21}. or Feola A, et al\cite{22}. studied biological prostheses at vaginal level in sheep. However, this model requires major surgery that induces major stress in experimental animals. Regarding the pig model\cite{23}, the drawbacks are similar to sheep; although it has enough size to perform vaginal surgery, and the anatomy is appropriated, the time required to perform the explants (180 days) makes the sows to grow up over 150 kg, therefore the handling of these animals and the costs of the study, even using
minipigs, preclude their use in some groups. In the case of the dog[24] and the primate there are additional ethical and legal conflicts concerns.

There are several authors that have used the rabbit model to study different biomaterials in gynecology[25-34]; therefore, we strongly believe that the rabbit is a good model for the study of biomaterials for abdominal and vaginal application.

The main limitation of the project is the translation of the results of the animal model to the human situation. In this specific case hADM is an heterologous matrix to the rabbit, since is prepared from human material; therefore studies are needed to verify cross-species effects.

None withstanding the first experimental model approximation, subsequent clinical studies with hADM will be necessary to verify the results obtained in a human model.

This study aims to describe the surgical complexity of the NZW rabbit model, the clinical follow-up, as well as the standardization of the model. It involves the description of the surgical difficulties of implanting prostheses at the vaginal and abdominal level in rabbits, their clinical follow-up, as well as the difficulties in barning them. This information can direct future works designed to test devices for vaginal application and will help other groups that focus their research in the urogynaecology area.

Conclusions
NZW rabbits are an excellent model to assess materials to be used as grafts for pelvic reconstructive surgery as vaginal surgery. Animals are easily managed during housing and during surgical management, including the interventions at the level of vaginal mucosa.

BIBLIOGRAPHY


