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From Lab to Clinic

Assessment of Electrospun and Ultra-lightweight Polypropylene Meshes in the Sheep Model for Vaginal Surgery

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Abstract

Background: There is an urgent need to develop better materials to provide anatomical support to the pelvic floor without compromising its function.
Objective: Our aim was to assess outcomes after simulated vaginal prolapse repair in a sheep model using three different materials: (1) ultra-lightweight polypropylene (PP) non-degradable textile (Restorelle) mesh, (2) electrospun biodegradable ureidopyrimidinone-polycarbonate (UPy-PC), and (3) electrospun non-degradable polyurethane (PU) mesh in comparison with simulated native tissue repair (NTR). These implants may reduce implant-related complications and avoid vaginal function loss.
Design, setting, and participants: A controlled trial was performed involving 48 ewes that underwent NTR or mesh repair with PP, UPy-PC, or PU meshes (n = 12/group). Explants were examined 60 and 180 d (six per group) post-implantation.
Intervention: Posterior rectovaginal dissection, NTR, or mesh repair.
Outcome measurements and statistical analysis: Implant-related complications, vaginal contractility, compliance, and host response were assessed. Power calculation and analysis of variance testing were used to enable comparison between the four groups.
Results: There were no visible implant-related complications. None of the implants compromised vaginal wall contractility, and passive biomechanical properties were similar to those after NTR. Shrinkage over the surgery area was around 35% for NTR and all mesh-augmented repairs. All materials were integrated well with similar connective tissue composition, vascularization, and innervation. The inflammatory response was mild with electrospun implants, inducing both more macrophages yet with relatively more type 2 macrophages present at an early stage than the PP mesh.
Conclusions: Three very different materials were all well tolerated in the sheep vagina. Biomechanical findings were similar for all mesh-augmented repair and NTR. Constructs induced slightly different mid-term inflammatory profiles.
Patient summary: Product innovation is needed to reduce implant-related complications. We tested two novel implants, electrospun and an ultra-lightweight polypropylene textile mesh, in a physiologically relevant model for vaginal surgery. All gave encouraging outcomes.

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1. Introduction

In women, the prevalence of pelvic organ prolapse (POP) is 5–10% [1]. The overall life-time risk for POP surgery is 20% [2]. Surgical techniques seek to provide support to the pelvic organs without compromising their function. Initially, polypropylene (PP) meshes, as used in hernia repair, were used for vaginal insertion as well but were found to induce implant-related complications (IRC) of approximately 10% [3]. The severity and difficulty of treating IRC have led to several manufacturers withdrawing their meshes from the market. Current techniques in pelvic reconstruction surgery are being re-examined, and stakeholders agree that there is an urgent need to develop and critically assess materials to improve long-term cure rates without increasing the risk of complications [4,5].

The materials used most commonly consist of knitted durable PP. Over time, heavyweight materials have been replaced by more open, lighter meshes as the latter experimentally induce a milder host response, potentially reducing the risk of complications [6]. There are at least three hypotheses regarding why current implants cause adverse effects in women:

1. Physical mismatching between the mechanical properties of the material and those of the host tissue, that is, the PP implants cope badly with sustained deformation [7].
2. The response to the bulk PP material stimulates a chronic foreign body reaction which is ever ongoing.
3. Combination of the aforementioned two points—the use of the material known to provoke sustained inflammation in a specific site in the body for which it is not appropriately designed.

An alternative to knitted constructs is to use non-textile electrospun materials with an extracellular matrix-like structure [8]. Electrospun materials facilitate cell adherence, infiltration, and natural extracellular matrix production [9,10]. We spun polycarbonate (PC) modified by ureidopyrimidinone (UPy) motifs. UPy-PC is a thermoplastic elastomer with PC soft blocks and hard blocks composed of interacting and phase-separated hydrogen bonding units based on the 2-ureido-[1H]-pyrimidin-4-one (UPy) motif [11]. PC is a degradable polyester, which has been successfully used in nerve and bone regeneration guidance [12,13]. UPy-modified polymers have been designed to serve as drug delivery vehicles, for example, in a porcine myocardial infarction model [14] and in a modular approach as a bioactive elastomeric material for tissue engineering [15]. We earlier showed that reconstruction of the abdominal wall with meshes spun from supramolecular polyesters modified with UPy conserve the biomechanical properties of native tissue [16]. An alternative approach is to use non-degradable polyurethane (PU), which withstands in vitro repetitive strain better than the heavier weighted PP (Gynecare, Johnson & Johnson, weight: 96.6 g/m^2) [7]. Also, PU was well integrated in the rabbit abdominal wall inducing a predominantly macrophage type 2 (M2) response when compared with commercially available heavyweight Gynecare PP, which induces a sustained inflammation predominated by macrophages type 1 (M1) [17].

The vaginal environment differs biomechanically and generates a different inflammatory response compared with other body locations [18]. Neither the degradable UPy-PC nor the non-degradable PU electrospun implants have been tested in an animal model for vaginal surgery. Therefore, we aimed to use the sheep model to evaluate these two materials and to compare the outcomes with a simulated native tissue repair (NTR) and implantation with a novel generation lighter-weighted PP, which has better biomechanical properties and yields a more favorable inflammatory response than other PP constructs [19–21]. Neither of the materials has been tested in the sheep model for vaginal surgery before. We assessed the functional repair including tissue morphology, contractility, and passive biomechanical properties of the vagina and the host cellular response.

2. Materials and methods

2.1. Implants

Three types of implants were used: (1) ultra-lightweight textile PP Restorelle (Coloplast, Humlebaek, Denmark; fiber diameter 80 μm; pore size 1.6–2.0 mm) [16], (2) electrospun UPy-PC, and (3) electrospun PU [17]. The electrospinning process of the single-layer UPy-PC [16] and tri-layer PU mesh, which had fibers oriented in a random-aligned-random design, are described in Supplementary material 1. The microstructure of both electrospun meshes was confirmed by electron microscopy (data not shown; Supplementary Fig. 1), with a thickness of around 300 μm, fiber diameter of 1–2 μm, and pore sizes of 10–20 μm. Vaginal implants measured 35 × 35 mm.

2.2. Animals, surgical procedure, and study design

Anesthesia and surgical procedures are detailed in Supplementary material 2. Prior to surgery, 48 multiparous Lakens sheep were randomly divided into four groups: three groups underwent mesh implantation and the fourth group underwent primary NTR by a single surgeon (LH). Based on a power calculation for the primary outcome variable (passive biomechanics; Supplementary material 3), six animals per group were required. Ewes underwent posterior vaginal wall surgery as previously described [22]. Following hydrodissection, the rectovaginal septum was dissected to create space for the implant. Meshes were fixed with interrupted non-degradable 3/0 PP (Prolene, Ethicon, Zaventem, Belgium) sutures in the corners and halfway along each side (Fig. 1A and 1B). NTR consisted of rectovaginal dissection, plication of the fascial structure over the rectum with three degradable 3/0 polyglactine 910 (Vicryl, Ethicon) sutures and the borders of the operative field were marked with non-degradable PP sutures similar to the mesh groups. The vaginal wall was closed with a running 3/0 polyglactin 910 (Vicryl) suture. A vaginal tampon was inserted for 24 h. Ewes were examined for postoperative complications and euthanized at 60 or 180 d after surgery.

2.3. Harvesting of implants

Ewes were premedicated and euthanized with intravenous pentobarbital (20 ml/50 kg Release, Ecuphar, Oostkamp, Belgium). Further details

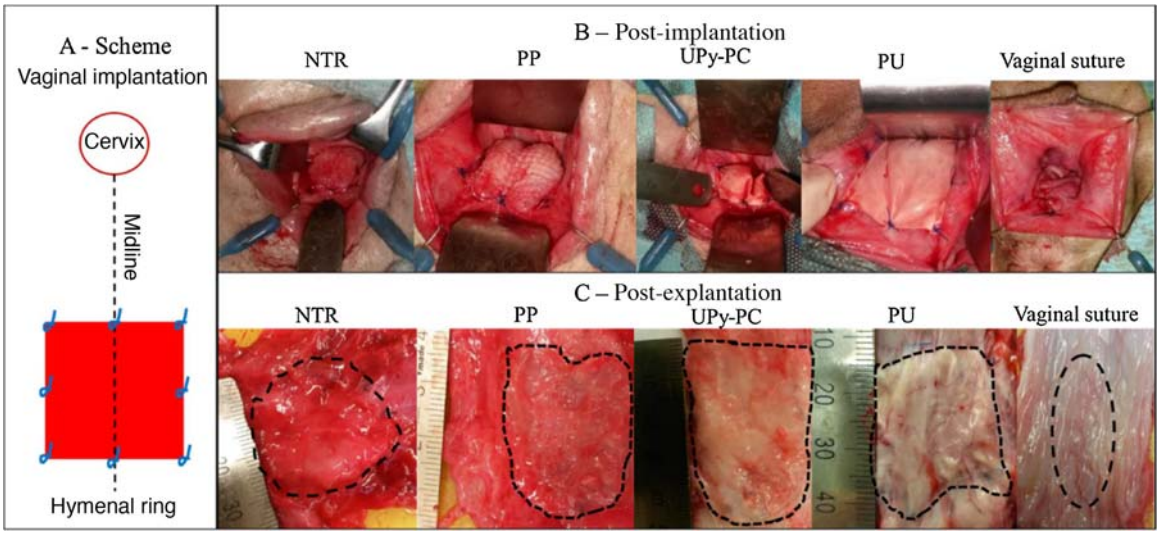

Fig. 1 – (A) Schematic drawing of posterior vaginal wall mesh implantation 3 cm from the hymenal ring, fixed with permanent polypropylene stitches. (B) The visual appearance of native tissue repair prior to plication in the first figure, implanted meshes after fixation prior to vaginal closure in the next three figures. The final figure is the vaginal wall after closure. (C) The appearance of materials on the vaginal wall post-explantation identified by the presence of non-degradable sutures. The final figure shows the healed vaginal closure.
NTR = native tissue repair; PP = polypropylene; PU = polyurethane; UPy-PC = ureidopyrimidinone polycarbonate.

are provided in Supplementary material 4. During the gross anatomical examination, we looked for IRC (defined as in humans; ie, prominence, separation, and exposure) [23]. Exposure of the PP suture is reported separately. We also looked for fluid collection, infection, and synechiae (Fig. 1C and Supplementary Fig. 3). The length and width of the implant area marked by the PP sutures were measured (Supplementary Fig. 4) to calculate the shrinkage [16]. In the NTR group, similar measurements were marked as a proxy for "shrinkage" of the dissection and suturing area. The vagina and perivaginal tissues were resected "en bloc", the explant was prepared, and cut into three pieces for active (3 × 7 mm) and passive biomechanical measurements (diameter, 30 mm) and histology (5 × 5 mm). The strip for active biomechanics was immediately tested. The sample for passive biomechanics was kept in 0.9% NaCl saline solution at room temperature until testing (<5 h after sacrifice). The histology specimen was fixed in 10% formalin solution.

2.4. Active biomechanical testing

Vertical organ baths were filled with 37 °C Krebs solution and bubbled with carbon dioxide and oxygen (Supplementary material 5). Specimens were measured, weighed, hung in the system (Fig. 2A), twice pretensioned to 0.5 mN and allowed to equilibrate for 60 min. Next, specimens were subjected to contractile stimulation by increasing concentrations of KCl (10, 20, 40, 50, 80, 120 mM). Contractile forces were recorded using custom-made software. Measurements were analyzed using Origin software (OriginLab Corporation; Northampton, USA). All values were normalized to sample weight, transducer calibration, and gravitation constant. Maximum contraction force at 80 mM KCl was compared.

2.5. Passive biomechanical testing

Pre-implantation "dry" materials were subjected to a uniaxial test in dry and wet conditions according to a standardized protocol [16,24]. Explant tensiometry was performed using the ball burst test (Fig. 2A) with an 11.5-mm plunger on a Zwick tensiometer (200 N cell load) and TestExpert software (Zwick GmbH & Co. KG, Ulm, Germany) as described previously [25,26]. The thickness of the explants was measured, they were clamped with the epithelium facing up, the plunger was centered over the explant, and preloaded to 0.1 N. The plunger speed was 10 mm/min. The test was aborted either when the specimen ruptured or the load force reached 200 N. Force (N)-displacement (mm) curves (Fig. 2B) were used to define the stiffness (ie, $\Delta F/\Delta x$). To avoid uncertainties due to sample clamping and reference position, the structural stiffness was measured as the tangent of the force-displacement curve at a predefined force of 30 N.

2.6. Morphological study

Hematoxylin and eosin staining and Goldner's trichrome staining were performed to quantify the foreign body giant cells (FBGCs), polymorphonuclear cells, blood vessels, and connective tissue [16,17,27]. Immunohistochemistry was performed to detect neovascularization (cluster of differentiation 34 [CD34]), neuronal network (protein gene product), myofibroblast and smooth muscle (α-smooth muscle actin [SMA]), leukocytes (CD45), and M1 (human leukocyte antigen–antigen D related) and M2 (CD163) macrophages (Supplementary material 6). Semi-quantitative readings were recorded by three researchers blinded to the treatment groups [17]. The M2/M1 ratio was calculated. The impact of implants on the thickness of the lamina muscularis was assessed by measuring its thickness on α-SMA stain.

2.7. Statistics and ethics

Statistical analysis was performed using the GraphPad Prism version 7.0 software (GraphPad Software, Inc; La Jolla, USA). Data normality was tested by the Kolmogorov-Smirnov test. Two-way analysis of variance was used for normally distributed data, and multiple comparisons were performed between individual groups using Tukey's test. The Kruskal-Wallis test followed by the Dunn's post hoc test was used for data that was not normally distributed. Data are reported as mean ± standard deviation or median and standard error of the mean as appropriate. The significance level was defined as $p < 0.05$. This experiment was approved by the Ethics Committee on Animal Experimentation of the Faculty of Medicine, KU Leuven, Belgium.

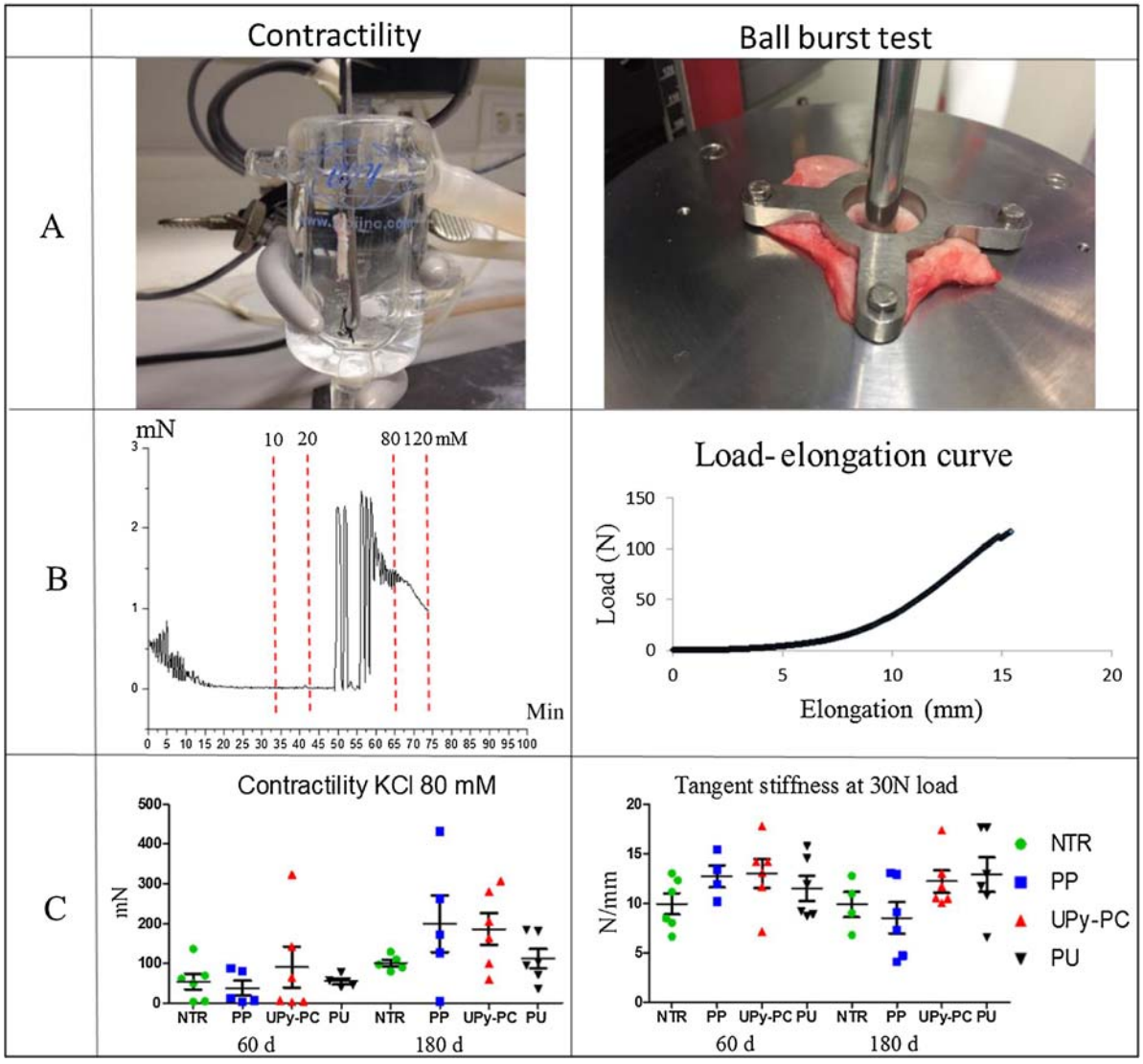

Fig. 2 – Examination of mechanical properties and propensity of tissue to contract. (A) The appearance of apparatus used to examine tissue contractility and to assess mechanical strength and stiffness of tissue using a ball burst apparatus. (B) Representative contractility (force-time) and ball burst (load-elongation) curves. (C) Results of vaginal contractility and stiffness with comparable results for all groups at both time points. NTR = native tissue repair; PP = polypropylene; PU = polyurethane; UPy-PC = ureidopyrimidinone polycarbonate.

3. Results

3.1. Biomechanical characteristics of meshes prior to implantation

The stiffness of all materials was significantly reduced in wet conditions compared with dry conditions (Supplementary Fig. 2). The UPy-PC electrospun meshes had the lowest stiffness in these conditions. PP implants lost 25–30% of their stiffness within 10 cycles of loading, whereas the two electrospun materials showed relatively little change in response to cyclic deformation.

3.2. Gross anatomy

We did not observe any IRC. All implants looked well incorporated into the deeper vaginal tissues. There were two exposed PP sutures ($n = 1$ NTR, $n = 1$ UPy-PC), and seven ewes developed limited vaginal synechiae along the mid-vaginal suture line that were not dividable by blunt dissection (-$n = 2$ NTR, $n = 3$ PP, $n = 2$ UPy-PC; Supplementary Fig. 3). Macroscopically, UPy-PC implants appeared partially degraded in half of the ewes at 60 d and in 90% of the ewes by 180 d. PU and PP implants appeared to be still intact. Shrinkage of vaginal implants was comparable between mesh groups and to that of the NTR at both time points (overall average, 35.6 ± 9.3%; data in Supplementary Table 2).

3.3. Mechanical properties

The highest contraction force was seen at 80 mM KCl (Fig. 2B); therefore, this concentration was used for comparative purposes. All the vaginal tissues contracted to a similar extent, and this was not significantly different to

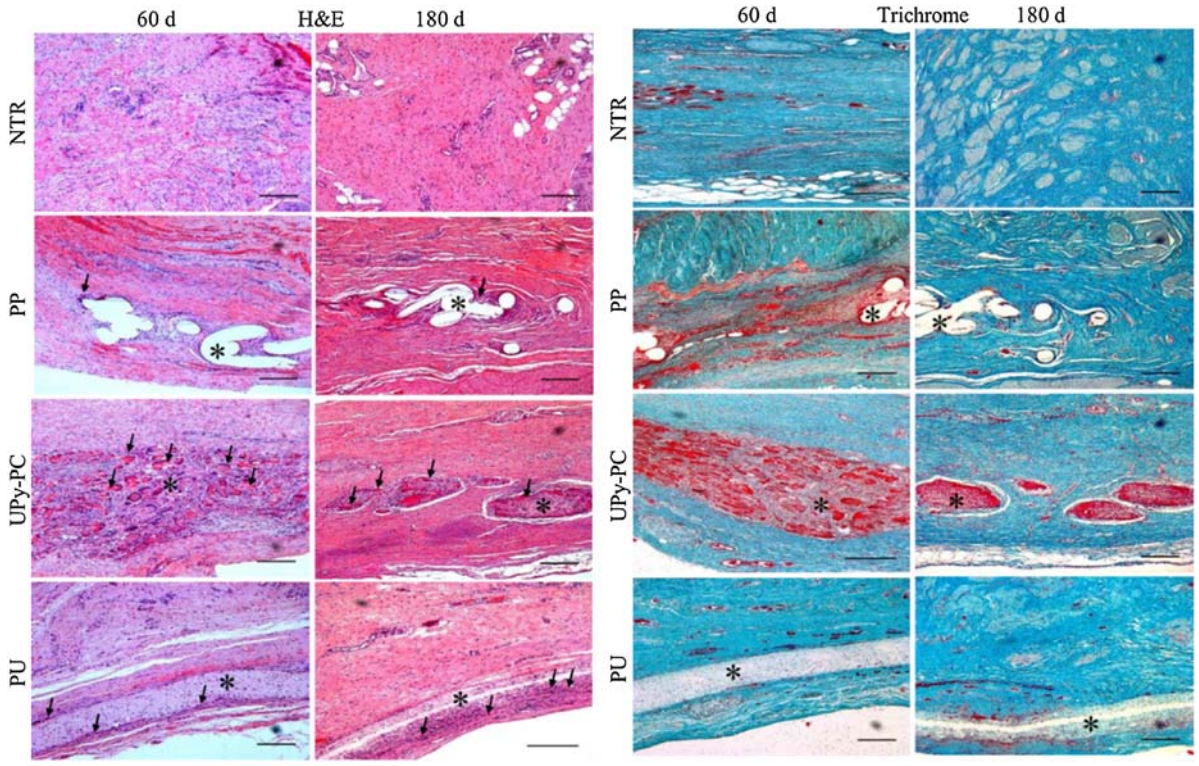

Fig. 3 – Representative figures of H&E and Goldner's trichrome staining of NTR, PP, UPy-PC, and PU explants at the location of mesh (100 × magnification) with vaginal epithelium facing up. Mesh structures are represented by asterisks and foreign body giant cells by black arrows. With the Goldner's trichrome staining, the connective tissue is stained blue and cells are stained red.
H&E = hematoxylin and eosin; NTR = native tissue repair; PP = polypropylene; PU = polyurethane; UPy-PC = ureidopyrimidinone polycarbonate.

that of the vaginal tissue from the NTRs (Fig. 2C). The ball burst test also showed comparable mechanical properties which did not differ significantly from that in NTRs (Fig. 2C).

3.4. *Cellular responses to implants*

The infiltrate in the NTR explants showed very few inflammatory cells and virtually no FBGCs (Fig. 3). In the other specimens, the implants could be recognized as being under the lamina propria and muscularis. There were no differences in the cellular infiltrate around the materials at 60 and 180 d, apart from the fact that in the UPy-PC group, the material was progressively resorbed. At 60 d, the UPy-PC mesh material was clearly recognizable over the entire length of the specimen. By 180 d, there was no recognizable material for two explants; in two, it was visible in some areas; and in another two, it was present over the entire explant.

There was an abundance of inflammatory cells around the surface of all meshes (Fig. 4). In PP implants, inflammatory cells were around the filaments, with looser connective tissue and vessels in between. In electrospun implants, the inflammatory infiltrate was denser filling the gaps between the more densely packed fibers. At 60 d, there were significantly more FBGCs in UPy-PC implants than in PU implants (Fig. 5A), yet not at later time point.

The macrophage infiltrates (both M1 and M2) were most vigorous for the two electrospun meshes (UPy-PC and PU) as seen both at 60 and 180 d (Fig. 6G). However, the extent of macrophage infiltration ratio of M2:M1 was very close to 1 for all groups by 180 d without any significant differences between them. The amount of connective tissue, thickness of the lamina muscularis, and neovascularization were similar for all groups. Immunoreactivity for α-SMA tended to be lower in NTR samples, the difference being significant only when compared with UPy-PC at 60 d and to PU at 180 d. The neuronal stain showed small nerves close to the implants or dissection area (NTR); however, the density of nerves was comparable for all groups.

4. Discussion

This is the first study in which three candidate vaginal mesh materials are compared for their effect on the vagina using a large animal model relevant to human vaginal prolapse surgery. In earlier sheep experiments, we demonstrated that vaginally inserted heavyweight (58 g/m^2) PP implants can induce IRC [25–27]. In contrast, the current experiments confirm that an 18-g/m^2 PP implant produced less contraction and no erosion and was comparable with the two electrospun materials studied.

As heavier PP implants have been shown to adversely affect connective tissue deposition and smooth muscle conservation in both primates and sheep [26,28], we expected an inflammatory response dominated by M1 macrophages, as previously observed for heavyweight PP

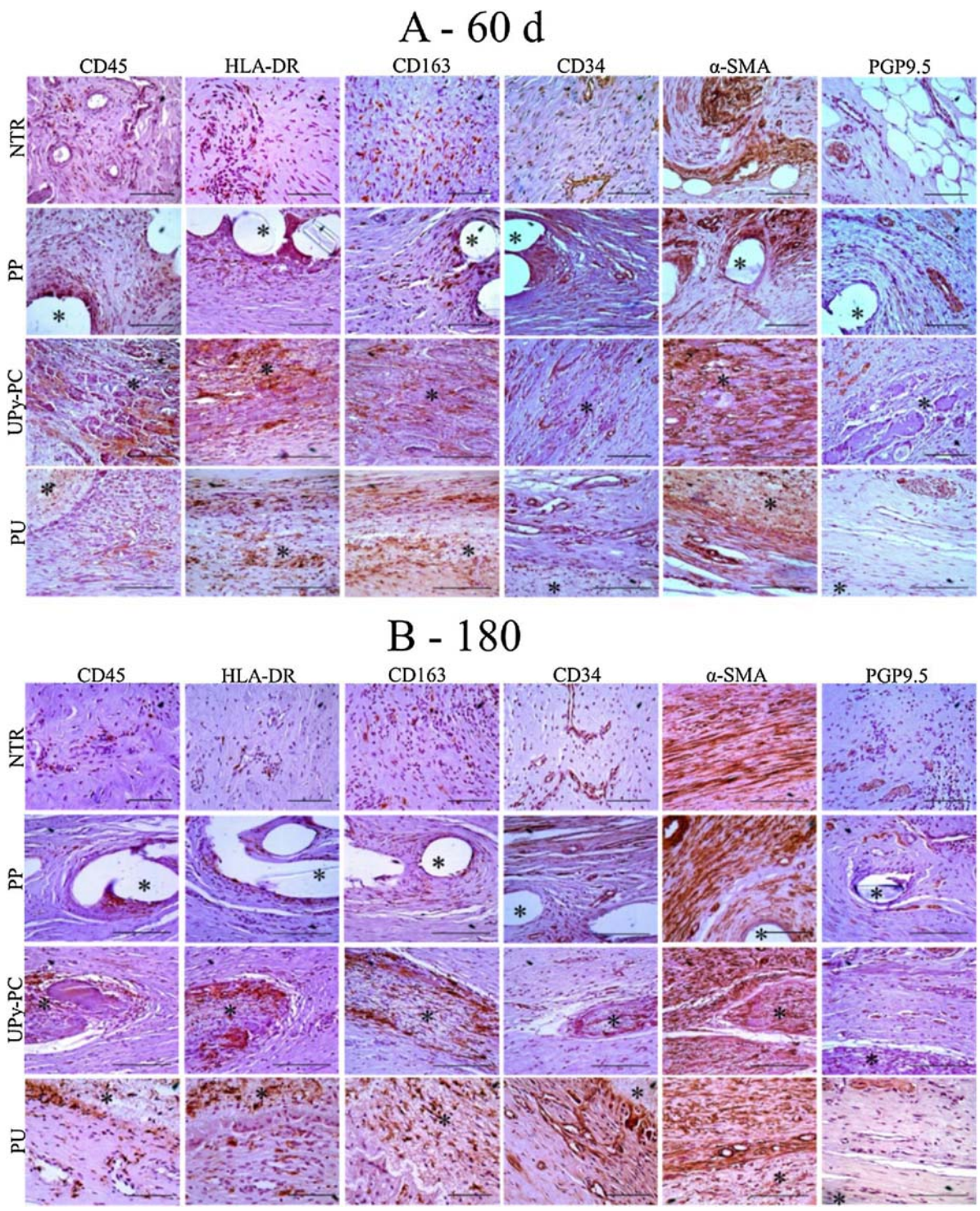

Fig. 4 – Identification of cellular infiltrate into the explanted vagina (for NTR) and materials implanted into the vagina of sheep at (A) 60 d and (B) 180 d. Mesh structures are represented by asterisks. Results shown are immunostaining for leukocytes (CD 45), macrophage type 1 (HLA-DR), macrophage type 2 (CD163), endothelial cells of the blood vessels (CD 34), myofibroblast and smooth muscle cells (α-SMA), and neurons (PGP 9.5). CD = cluster of differentiation; HLA-DR = human leukocyte antigen–antigen D related; NTR = native tissue repair; PGP = protein gene product; PP = polypropylene; PU = polyurethane; UPy-PC = ureidopyrimidinone polycarbonate; α-SMA = α-smooth muscle actin.

[17], for the PP material we used in the study. However, the type of immune response was very similar for all three materials with an M2:M1 ratio close to 1 for all at 180 d. Similarly, the appearance of the new tissue formed was similar in terms of vascularization, myofibroblasts, and neuronal network for all three. The only slight difference seen was in the extent of the inflammatory response seen to the electrospun materials compared with that to the textile material, which could be explained by the higher surface area of the electrospun materials.

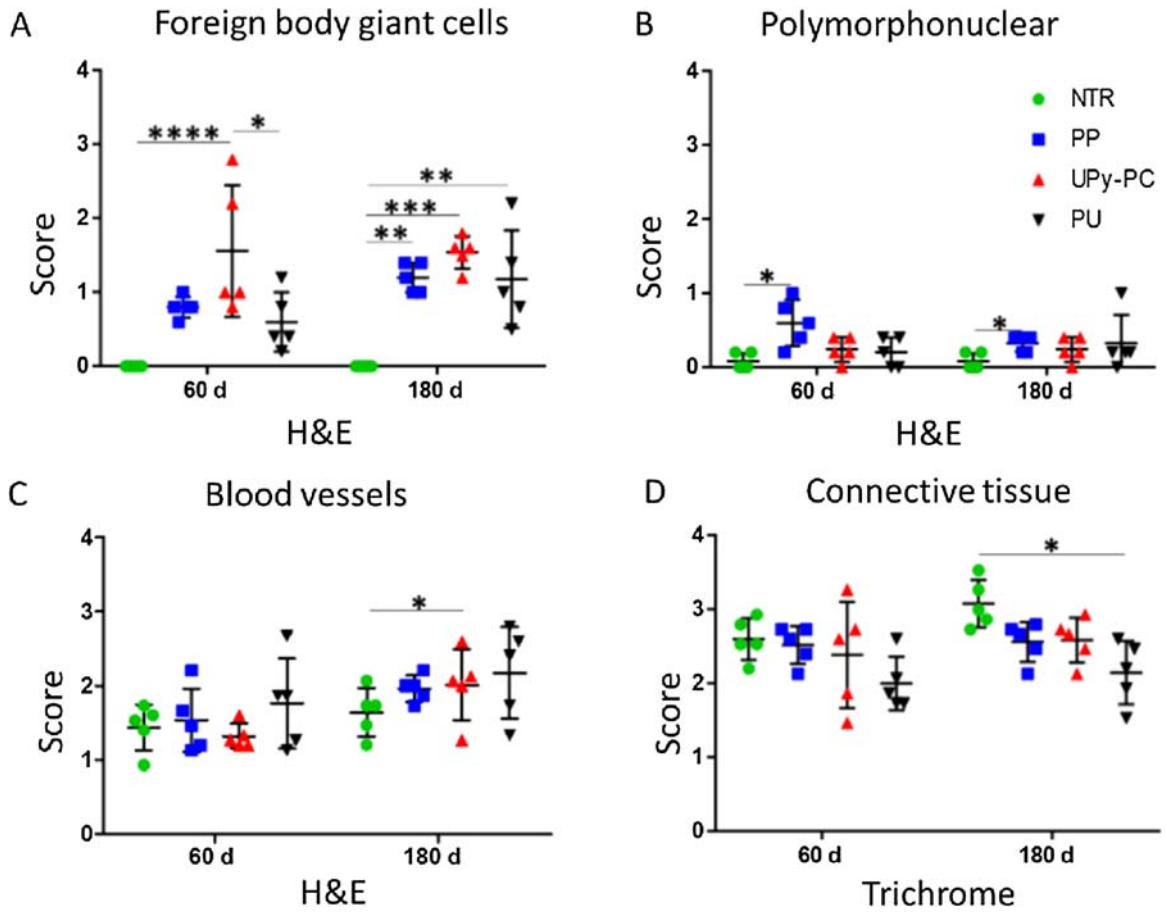

Fig. 5 – Response of the host tissue to implanted materials based on H&E and Goldner's trichrome staining. The figure shows individual observations in sheep at 60 and 180 d. (A) Foreign body giant cells, (B) polymorphonuclear cells, (C) blood vessel counts, and (D) connective tissue. Values differing significantly from the control are indicated with asterisks. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.
H&E = hematoxylin and eosin; NTR = native tissue repair; PP = polypropylene; PU = polyurethane; UPy-PC = ureidopyrimidinone polycarbonate.

The biomaterial design and concept for these three meshes follows three very different strategies to provide support to the pelvic floor. The Restorelle PP is a textile implant; although very light in weight, it still has a higher initial stiffness and undergoes more deformation when tested under cyclic loading prior to implantation compared with the two electrospun materials, which present more viscoelastic properties. We found Restorelle explants having biomechanical properties comparable with NTR and the two electrospun material explants. In addition, smooth muscle cells play a key role in vaginal contractility, and their function was also unaffected by the implants.

The degradable electrospun material was designed to replace failing tissue temporarily but induce a constructive remodeling process while being replaced by new native tissue. The UPy-PC mesh showed a rapid degradation compared with previous absorbable materials, which failed when used to treat POP [29]. Additionally, UPy motifs on it are designed to permit the future addition of bioactive properties to this polymer, which remains to be investigated. At the time of writing, this approach is not yet that developed that it can be taken to the clinic.

In contrast, non-degradable electrospun PU is designed to act as a permanent implant, which mimics the elastic properties of native fascia for a better compliance. The biomechanical and morphological properties of the explant are designed to be close to that of native tissue.

We acknowledge the limitations in this study. This animal model does not allow an in-depth study of the immune response as our sheep are not inbred animals, and more detailed molecular tools are currently lacking. The study duration was 6 mo, and exposure may theoretically surface later [3]. The simulated NTR does not truly mimic the operation in women as the ewes did not have a site-specific defect as women with rectocele would have; however, it is as close as we can get today to the human condition of POP. Furthermore, in this study, we did not include a heavyweight PP mesh as we did in an earlier study where it caused erosion in 3/10 sheep [26].

However, the field of developing materials for use in the pelvic floor thoroughly warrants the inclusion of animal studies in which materials can be demonstrated to fail. This was lacking during the period in which PP meshes were developed to be used in the pelvic floor surgery and in clinical medicine without any relevant animal testing. This is the first study performed using a sheep model for these materials, and more analyses are needed to determine their long-term performance. The reasons why current materials

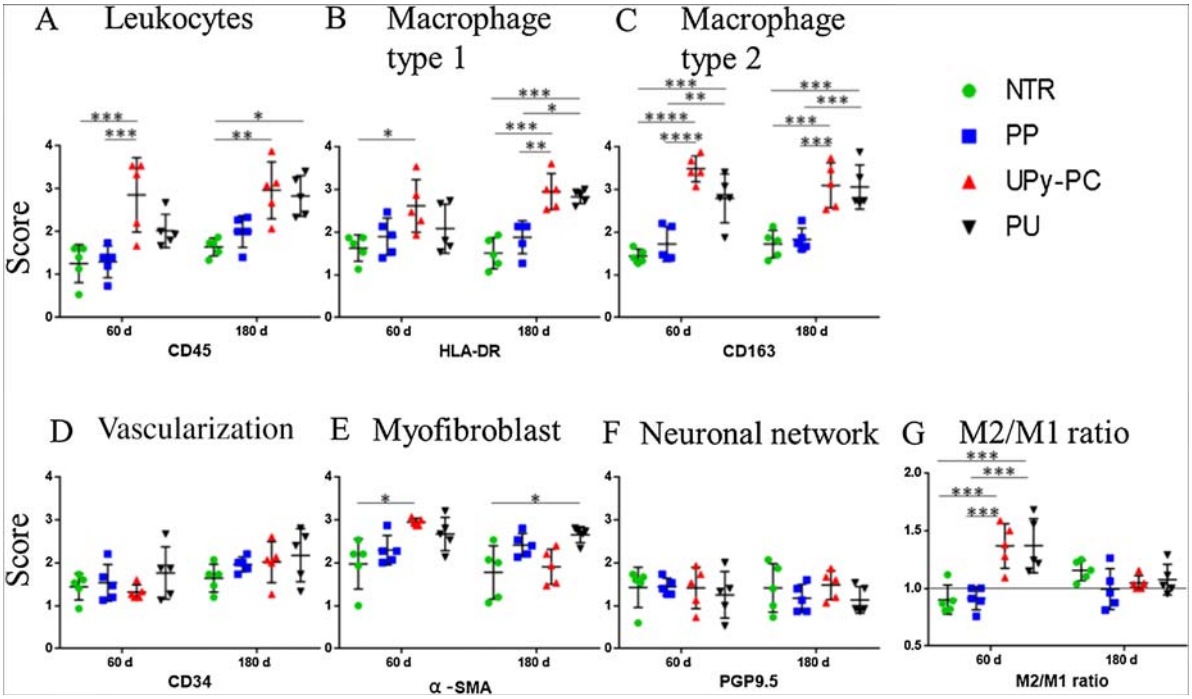

Fig. 6 – Analysis of extent of cellular infiltration into vaginal explants. Results show analyses of individual sheep at 60 and 180 d. Graphs summarizing score results from immunohistochemistry. (A) Leukocytes, (B) macrophage type 1, (C) macrophage type 2, (D) vascularization, (E) myofibroblasts, (F) neuronal network, and (G) the ratio of M2 to M1 macrophages. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.
CD = cluster of differentiation; HLA-DR = human leukocyte antigen–antigen D related; M1 = macrophage type 1; M2 = macrophage type 2; NTR = native tissue repair; PGP = protein gene product; PP = polypropylene; PU = polyurethane; UPy-PC = ureidopyrimidinone polycarbonate; α-SMA = α-smooth muscle actin.

are failing and inducing clinical complications are not fully understood. The most obvious hypothesis is that there is a mismatch between the rigid and non-elastic mechanical properties of the heavyweight PP mesh and the pelvic floor native tissues, which leads to fibrosis and contraction.

Additionally, the chemical characterization of the materials post implantation needs to be better understood. Some think that PP show micro-cracking at the surface of the filaments and that substances released could stimulate a bad inflammatory response [30].

In view of this, we suggest that future testing needs to consider both accelerated ageing tests and accelerated fatigue tests to reproduce the hydrolytic and oxidative environment of the pelvic floor as well as more extensive animal testing prior to introducing new materials clinically.

5. Conclusions

We draw two conclusions from this study: (1) mechanical properties of explants comparable with those of NTR can be achieved with very different implant materials (both a degradable and non-degradable electrospun implant as well as with a textile lightweight PP like Restorelle), and (2) the vagina tolerates all three materials without any evidence of adverse effects on vaginal mechanical properties, and equally, the host inflammatory and other cellular responses to these materials were all acceptable. While there are concerns with the degradation ratio of the UPy-PC material, we suggest that both PU and Restorelle are potential candidates to consider for further investigation.

Author contributions: Jan A. Deprest had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Hympanova, Deprest.
Acquisition of data: Hympanova, Rynkevic, da Cunha, Urbankova, Callewaert.
Analysis and interpretation of data: Hympanova, Rynkevic, Román, MacNeil, Zündel.
Drafting of the manuscript: Hympanova, Román, MacNeil, Chapple.
Critical revision of the manuscript for important intellectual content: Hympanova, Mazza, MacNeil, Chapple.
Statistical analysis: Hympanova, Román.
Obtaining funding: Gallego, Chapple, Deprest.
Administrative, technical, or material support: Gallego, Vange.
Supervision: Deprest.
Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.euf.2018.07.024.

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