Int Urogynecol J (2016) 27:1583–1589
DOI 10.1007/s00192-016-3013-9

ORIGINAL ARTICLE

Tissue reaction to urogynecologic meshes: effect of steroid soaking in two different mesh models

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Received: 23 December 2015 / Accepted: 14 March 2016 / Published online: 2 April 2016

Abstract
Introduction and Hypothesis Steroid soaking may decrease mesh-triggered inflammatory reaction in tissue. We aimed to investigate the tissue reaction to a steroid-soaked mesh material and an unsoaked mesh material in the rat model.
Methods Neutral and steroid-soaked type I macroporous polypropylene (PP) monofilament and polyvinylidene fluoride (PVF) mesh materials were implanted on the rectus abdominis muscle of 20 mature Wistar albino rats. Animals were divided into four groups: PP mesh with steroid (PP-S), PP mesh without steroid, PVF mesh with steroid (PVF-S), and PVF mesh without steroid. The rats were killed after 12 weeks, and histologic, immunohistochemical and electron microscopic examinations were performed. For immunohistochemical analysis, polyclonal rabbit anti-mouse CD3, rabbit anti-mouse CD68, rabbit anti-mouse CD15, and rabbit anti-mouse CD34 antibodies were used for the detection of lymphocytes, macrophages, polymorphonuclear leukocyte foreign body giant cells, and fibromyocyte stem cells, respectively. Samples were stained with hematoxylin and eosin for the histologic evaluation of inflammation and with Masson's trichrome stain for the evaluation of collagen deposition. Pore size and mesh ultrastructure were evaluated by electron microscopy.
Results Expression of CD3 was lower in the PVF, PVF-S and PP-S groups, and expression of CD34 was higher in the PVF-S and PP-S groups than in the PP groups ($p < 0.05$). Collagen deposition was lower in the PVF, PVF-S and PP-S groups ($p < 0.05$). Histologically, the intensity of inflammation was lower in the PVF-S and PP-S groups than in the PP mesh group ($p < 0.05$). There were no significant differences among the groups in terms of pore size and mesh ultrastructure on electron microscopic examination ($p > 0.05$).
Conclusions PVF mesh induces less inflammation than PP mesh, and in both mesh types steroid soaking further decreases inflammation without changing the pore size.

Keywords Urogynecology · Mesh · Inflammation · Tissue reaction · Polypropylene · Polyvinylidene fluoride

Introduction

Mesh implants have been widely used in urogynecology practice for the surgical treatment of urinary incontinence and pelvic organ prolapse [1]. However, in 2008 the American Food and Drug Administration (FDA) reported adverse effects related to the use of mesh in pelvic organ prolapse surgery [2]. This report drew attention to high complication rates in addition to better success rates compared with native tissue repair, and made surgeons more skeptical about the use of mesh. The FDA [3] revised the warning related to urogynecologic meshes in 2011, and most of them were withdrawn from the market [4]. Therefore, new innovations in mesh technology which cause less tissue reaction and good anatomical and functional compatibility are required to increase safety and efficacy. Today, polypropylene (PP) monofilament macropore type I

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meshes are preferred in urogynecologic surgery [5, 6]. Despite high tolerability, type I meshes also cause some degree of tissue reaction [5, 6]. On the other hand, polyvinylidene fluoride (PVF) meshes are relatively new in the market, and have comparable safety and efficacy [7].

A mesh material initiates a foreign body reaction after implantation triggered by an initial acute phase reaction [8, 9]. Migration of fibroblasts in response to chemotactic substances results in the production of glycosaminoglycans and collagen [9]. The cascade of events leads to the formation of a collagen capsule covering the mesh fibers, shielding the host from the foreign material [8]. However, the inflammatory response created by the surgical mesh in humans may be highly variable, and has been shown to be affected by many factors such as age, smoking, diabetes, and body mass index [10]. An exaggerated inflammatory process following mesh implantation may lead to increased production of reactive oxygen species by neutrophils which degrade the transplanted mesh and have been shown to cause microfractures on the mesh surface [10, 11], and finally results in changes in structural integrity and physical properties such as significant embrittlement of the mesh material that directly contributes to postoperative complications [11–13]. Therefore, advances are necessary in the area of mesh–tissue compatibility so that meshes can continue to be used with better success rates.

The use of systemic steroid has been shown to reduce tissue reactions in the animal models [14]. Studies have been performed to investigate the effects of soaking the mesh in antibiotic solution or coating it with collagen on the tissue reaction, but no previous study has investigated the effects of soaking the mesh in steroid solution [15–17]. We hypothesized that soaking the mesh in steroid solution may reduce the intensity of the inflammatory reaction, and we aimed to investigate the structural and immunohistochemical tissue reactions to a steroid-soaked mesh and an unsoaked mesh in the rat model.

Materials and methods

The study protocol was approved by the Institutional Review Board and Animal Use Committee, and complied with guidelines for the care and use of laboratory animals for research (Committee meeting number 2014/11, date 10 December 2014; study number PAUHDEK-2014/032).

Type I macroporous PP monofilament mesh (I-STOP®; CL Medical inc., Winchester, MA), and polyvinylidene fluoride (PVF) mesh (DynaMesh®; FEG Textiltechnik mbH, Aachen, Germany) were used in this experimental study. PP and PVF meshes were implanted in 20 mature Wistar albino rats with an average weight of 250 g. Ten rats received mesh that had been soaked in steroid solution, and the other ten rats received unsoaked mesh. The rats underwent surgery with a midline incision under sterile conditions after injection of ketamine hydrochloride (90 mg/kg, Ketalar®; Pfizer, Espoo, Finland) and xylazine (10 mg/kg, Keproxylazine 20®; Biopharm, Istanbul, Turkey), and the incisions were closed with 3.0 polyglactin sutures. In the ten rats receiving the unsoaked mesh, two 1 × 1-cm pieces of PP mesh were fixed in direct contact over the rectus abdominis muscle 1 cm apart on the right side, and two 1 × 1-cm pieces of PVF mesh were placed 1 cm apart on the left side in the same way. In the other ten rats, the same procedure was performed after soaking the mesh pieces in 40 mg methyl prednisolone dissolved in distilled water (Prednol-L®, 40-mg ampoule; Mustafa Nevzat Pharmaceuticals, İstanbul, Turkey) for 1 h. Thus the following four groups were formed: PP with steroid (PP-S), PP without steroid (PP), PVF with steroid (PVF-S), and PVF without steroid (PVF).

As mesh-related chronic inflammatory reaction settles in 4 weeks and mesh complications are usually seen in the first 2 – 3 months [8, 9, 14], we sacrified the rats after 12 weeks. Implants were removed en-bloc with the underlying muscle tissue. One specimen from each region was used to investigate the inflammatory process, and the other for electron microscopy.

Histochemical and immunohistochemical analysis

Samples for histologic examination were fixed in 10 % buffered formalin and processed accordingly for histologic assessment. Slides were stained with hematoxylin and eosin (H&E) (Fig. 1) and Masson's trichrome (Fig. 2) and examined by

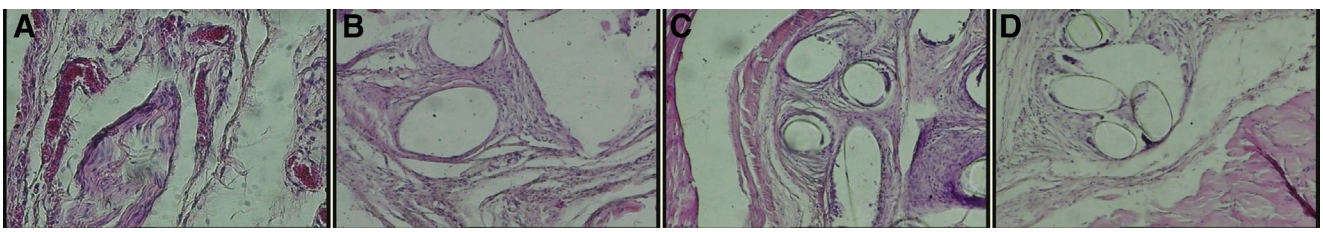

Fig. 1 Representative H&E-stained histologic cross sections (×100) of tissue from the four mesh treatment groups: **a** polypropylene mesh without steroid soaking; **b** polypropylene mesh with steroid soaking; **c** polyvinylidene fluoride mesh without steroid soaking; **d** polyvinylidene fluoride mesh with steroid soaking

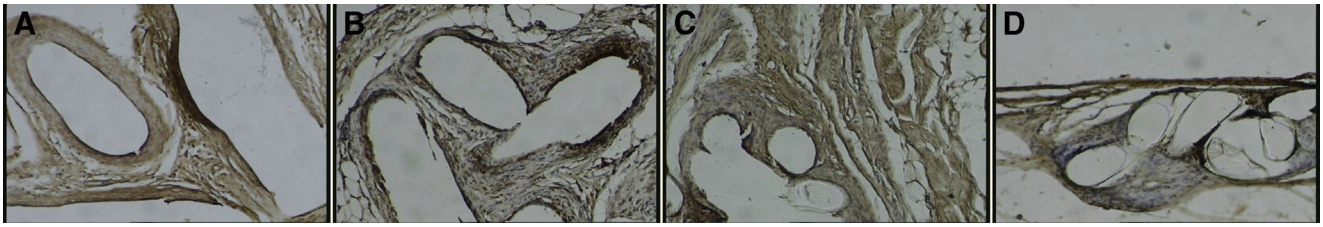

Fig. 2 Photomicrographs of Masson's trichrome-stained sections (×100) of tissue from the four mesh treatment groups: **a** polypropylene mesh without steroid; **b** polypropylene mesh with steroid; **c** polyvinylidene fluoride mesh without steroid; **d** polyvinylidene fluoride mesh with steroid

light microscopy (Olympus BX51 phase contrast microscopy 200) blindly by the examiners (G.M.A., S.T.).

Masson's trichrome staining was used to evaluate the intensity of collagen deposition (Fig. 2). Granuloma formation, necrosis, inflammation, and the presence of necrosis were evaluated on H&E-stained slides (Fig. 1). Specimens were specifically analyzed for the inflammatory reaction, fibrosis and muscle infiltration, and scored using a previously reported grading scale [14]: *1*; sparse, affecting less than 25 % of the area, *2*; mild, affecting 25–50 % of the area, *3*; moderate, affecting 50–75 % of the area, and *4*; dense or marked lesion, affecting 75 % or more of the area. Ten areas were screened under ×100 magnification and the mean was taken as the score.

The antibodies used included polyclonal rabbit anti-mouse CD3 (MyBioSource, San Diego, CA) for lymphocytes, rabbit anti-mouse CD68 polyclonal antibody (MyBioSource) for macrophages, rabbit anti-mouse CD15 antibody (Santa Cruz Biotechnology, Dallas, TX) for polymorphonuclear (PMN) leukocytes and foreign body giant cells, and rabbit anti-mouse CD34 polyclonal antibody for fibromyocytes and stem cells (Fig. 3). The morphology of the inflammatory reaction was evaluated by quantitative cell analysis. The intensity of inflammation was defined as the percentage of cells positive for each inflammatory marker in H&E-stained slides in ten fields of a 10 × 10 grid (100 0.1-mm^2 fields).

Electron microscopic analysis

The electron microscopic analyses were performed by a single observer (N.K.) using a field emission electron microscope (FESEM; Carl Zeiss, Supra 40 VP). The samples were initially fixed in glutaraldehyde solution. After washing in sodium phosphate-buffered solution, the samples were dehydrated through a series of increasing concentrations of acetone, then critical point dried, mounted on stubs and sputter-coated with gold/palladium. The pore sizes of the meshes were measured using the FESEM (Fig. 4).

Statistical analysis

The SPSS 11 package (SPSS, Chicago, IL) was used for the analysis. Parametric variables are expressed as means ± standard deviation and nonparametric variables as medians and quartiles. The four mesh treatment groups were compared in terms of the degree of inflammatory tissue response using the Kruskal-Wallis test with Scheffé correction for multiple

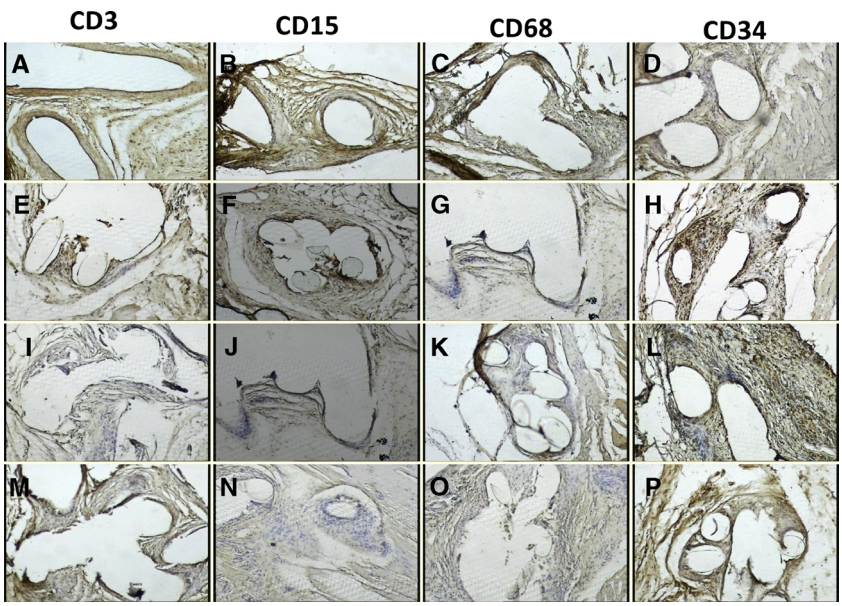

Fig. 3 Immunostained sections (immunoperoxidase-hematoxylin, ×100) focused on the area adjacent to mesh fibers and the area between mesh fibers: **a**, **e**, **i**, **m** lymphocyte marker CD3; **b**, **f**, **j**, **n** polymorphonuclear cell marker CD15; **c**, **g**, **k**, **o** macrophage marker CD68; **d**, **h**, **l**, **p** fibromyocyte and stem cell marker CD34

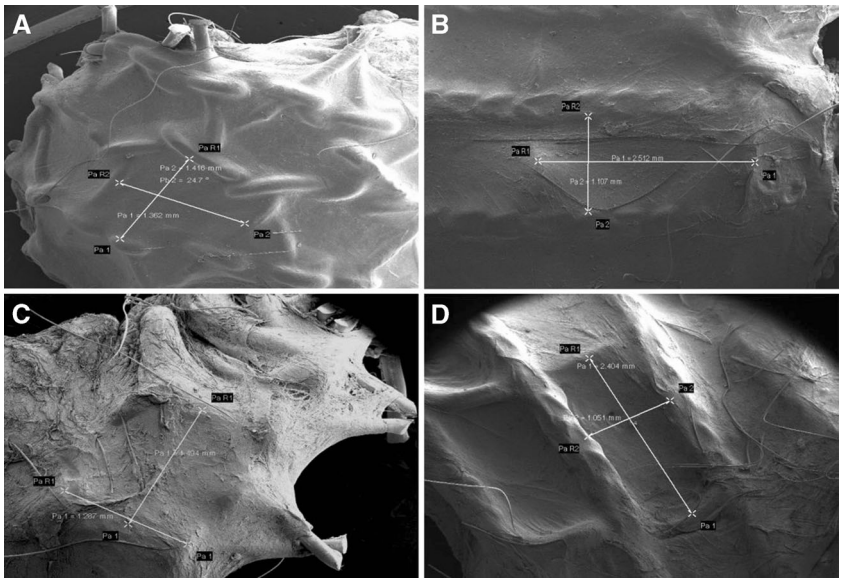

Fig. 4 Scanning electron micrographs showing the appearance of the pores and their measurement in specimens from the four mesh treatment groups: **a** polypropylene mesh without steroid (×51); **b** polyvinylidene fluoride mesh without steroid (×54); **c** polypropylene mesh with steroid (×58); **d** polyvinylidene fluoride mesh with steroid (×49)

comparisons. An independent sample *t* test was used for comparison of pore sizes between steroid-soaked and unsoaked meshes for each type of mesh. Statistical significance was assumed at p values <0.05.

Results

All 20 study animals survived for the whole 12-week post-implantation study period without any complications. No differences were seen macroscopically between steroid-soaked and unsoaked meshes. Microscopically measured markers of the inflammatory process in the different groups are summarized in Table 1. An extensive inflammatory reaction, collagen deposition, necrosis, and positivity for CD3, CD15 and CD68 were considered as indicators of reduced biocompatibility. Statistically significant differences were found for CD3, CD34, CD15 and CD68 biomarkers between groups ($p < 0.05$; Table 1). Lower levels of CD3 were seen in the PVF, PVF-S and PP-S groups, and higher levels of CD34 were seen in the PVF-S and PP-S groups compared with the PP group ($p < 0.05$; Table 1). Levels of CD15 which was used for the detection of PMN leukocytes and foreign body giant cells were significantly lower in the PVF-S group than in the PP group ($p < 0.05$). Levels of CD68 were significantly lower in the

Table 1 Distribution of histopathologic findings and immunohistochemical markers between groups

	Mesh group				*p* value
	PVF		PP		
	Unsoaked	Steroid-soaked	Unsoaked	Steroid-soaked	
CD3	20.10 ± 9.36 (7 – 35)	14.40 ± 6.42 (8 – 25)	35.50 ± 7.72 (25 – 53)	19.60 ± 9.31 (8 – 35)	<0.0001
CD34	27.50 ± 19.58 (5 – 61)	52.10 ± 23.50 (5 – 77)	6.80 ± 2.74 (4 – 12)	40.30 ± 26.53 (6 – 74)	0.001
CD15	15.30 ± 7.83 (5 – 31)	12.10 ± 7.40 (3 – 25)	23.50 ± 6.19 (14 – 31)	15.10 ± 7.69 (6 – 27)	0.013
CD68	34.70 ± 10.96 (22 – 57)	22.20 ± 10.27 (13 – 45)	35.70 ± 11.63 (17 – 54)	25.70 ± 10.91 (10 – 40)	0.028
Inflammation	2.5 (1.75 – 4)	1.5 (1 – 2)	3 (2.75 – 4)	2 (1 – 2.25)	0.007
Foreign body reaction	0 (0 – 1)	0 (0 – 0)	0 (0 – 0.25)	0 (0 – 0)	0.038
Collagen	3 (2 – 3.25)	1 (1 – 1.25)	3 (2.3.25)	2 (1 – 2)	<0.0001
Muscle invasion	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0.392
Necrosis	0 (0 – 1.25)	0 (0 – 0)	1 (1 – 1)	0 (0 – 0)	0.062

The expression levels of the inflammatory markers CD3, CD34, CD15 and CD68 (measured in terms of the percentage of positive cells, as described in the text) are presented as means ± SD (range), The scores for the other parameters (scored using a grading scale according to the area affected, as described in the text) are expressed as medians (25th and 75th weighted percentiles)

PVF Polyvinylidene fluoride, *PP* Polypropylene

PVF-S and PP-S groups at first, but the differences were not significant after Scheffé correction ($p > 0.05$; Table 2).

Collagen deposition was significantly lower in the PVF-S group than in the PVF and PP groups, and lower in the PP-S group than in the PP group ($p < 0.05$). The histologic analysis showed less inflammation in the PVF-S and PP-S groups than in the PP group ($p < 0.05$; Table 2). There were no significant differences in muscle invasion and necrosis, pore size and mesh ultrastructure among the groups ($p > 0.05$).

Discussion

PVF meshes were found to induce less tissue reaction than PP meshes, and steroid soaking of the meshes decreased the inflammatory reaction. These observations are important because the main concern in the use of mesh is to minimize the inflammatory reaction while achieving high success rates. To the best of our knowledge, of studies investigating mesh biocompatibility this was one of the long-term studies with regard to postimplantation period related to mesh biocompatibility. After implantation of the mesh material, the foreign body reaction starts in 7 days and lasts for 21 days, and this is defined as the acute phase [18]. During this period, macrophages and PMN leukocytes migrate first into the environment, followed by lymphocyte infiltration [19, 20]. With time, the acute inflammatory process is replaced by the chronic reaction which promotes healing, and leads to the formation of low-intensity granulomatous inflammation [14].

The lymphocyte and macrophage markers CD3 and CD68, respectively, showed low levels of positivity. Together with PMN leukocytes, these two cell types are predominant in the acute phase of inflammation, and decline thereafter. Despite the significant differences initially detected in CD68 levels, the differences were no longer significant after Scheffé correction. This can be explained by the negligible effect of steroid on macrophages. However, as the rats were killed at the end of postimplantation week 12, the inflammation phase had progressed from acute to chronic so that the numbers of macrophages had decreased and the markers of chronic inflammation had increased. This may explain the lack of significance. Since we did not have a treatment group to investigate the inflammatory events during the first week after mesh implantation, we cannot draw a conclusion about the involvement of macrophages in the acute inflammatory response, despite promising indications. In accordance with our hypothesis, Zheng et al. found that the acute reaction reached a peak at 7–14 days and was negligible by 90 days [21]. Therefore, the reason for the lack of statistical significance may be explained by the natural flow of the inflammatory process [21]. On the other hand, increased numbers of foreign body giant cells formed by coalition of macrophages, which play a role in cleaning up cellular debris and foreign bodies, is a sign of an increased inflammatory reaction [22]. Low levels of CD15, which stains PMN leukocytes and foreign body giant cells, were detected in steroid-soaked meshes, and this can be interpreted as reduced tissue reaction to the mesh in this group.

Myofibroblasts, which are considered to play a pivotal role in tissue repair and remodeling, were first observed in experimental wound healing by electron microscopy. They are located in granulation tissue and exhibit bundles of microfilaments [23–25]. After any event causing tissue damage, fibroblasts in the connective tissue are converted to myofibroblasts which are responsible for remodeling and mesh integration [22]. Myofibroblasts and stem cells trigger angiogenesis and provide neovascularization [25, 26]. They help tissue integration by increasing the infiltration of multipotential cells and the integration of cells with the skeleton formed by the mesh structure [27, 28]. In accordance with this theory, we found

Table 2 Post hoc analysis of p values

	Group comparisons					
	PVF – PVF-S	PVF – PP	PVF – PP-S	PVF-S – PP	PVF-S – PP-S	PP – PP-S
CD3	0.509	0.003*	0.999	<0.001*	0.585	0.002*
CD34	0.079	0.177	0.580	<0.001*	0.643	0.008*
CD15	0.811	0.118	1	0.014*	0.839	0.105
CD68	0.108	0.998	0.352	0.072	0.916	0.262
Inflammation	0.158	0.830	0.235	0.023*	0.997	0.039*
Foreign body reaction	0.084	0.619	0.084	0.619	1	0.619
Collagen	0.003*	0.952	0.052	0.001*	0.717	0.014*

PVF Polyvinylidene fluoride unsoaked, *PVF-S* Polyvinylidene fluoride steroid-soaked, *PP* Polypropylene unsoaked, *PP-S* Polypropylene steroid-soaked

*$p < 0.05$, with Scheffé correction

increased levels of CD34, which stains myofibroblasts and stem cells, in steroid-soaked meshes, and this may be interpreted as better tissue compatibility in this group.

Fibroblasts also play an important role in the inflammatory reaction by secreting collagen in response to macrophage stimulation. This collagen accumulates in the extracellular matrix and pore spaces, and covers the mesh fibers [28, 29]. Despite differences in inflammatory response between steroid-soaked and unsoaked meshes, we did not detect any significant ultrastructural changes between the mesh groups by electron microscopy. Thus, we suggest that steroid-soaked mesh is also well-preserved and covered by a collagen layer in the same manner and unsoaked mesh without any change in pore size.

It has been shown that systemic steroid therapy reduces collagen deposition and the inflammatory reaction [14]. Similarly, in this study, we found decreased collagen deposition in steroid-soaked mesh. However, since we did not include a systemic steroid group, we could not compare steroid-soaked mesh with systemic steroid treatment. Indeed, it is not possible to use systemic steroids for long periods due to side effects.

In this study, we used a rat model to show tissue–mesh integration since it has been shown to be a suitable model for this application [14, 16]. Furthermore, the use of this model allowed two different mesh types to be compared in the same animal. We implanted PVF and PP meshes into same rat allowing objective comparisons. The PVF mesh was associated with a less-intense inflammatory reaction than the PP mesh, although the difference was not statistically significant for all parameters, and soaking in steroid solution before implantation further decreased the inflammatory reaction.

Our study had some limitations. First, we could not be sure about the amount of steroid attached to the mesh surface, but to optimize the process we soaked the meshes in solutions with the same steroid concentration for the same time. Second, the two types of mesh used may have different affinities for steroid. We therefore compared pore sizes only between steroid-soaked and unsoaked mesh of the same mesh type. Despite these limitations, our study is very valuable since it provides information from a direct comparison of two popular mesh types performed under standardized conditions.

In conclusion, PVF mesh is associated with a lower degree of inflammatory reaction in tissue, and in both PVF and PP meshes steroid-soaking further reduces the intensity of the inflammatory reaction without changing the pore size, leading to better tissue integration. Despite being an experimental animal study, our findings are strong enough to suggest a practical method to mitigate mesh-induced tissue reaction. Our preliminary observations may also have implications for mesh manufacturers who could consider investigating the feasibility of producing steroid-soaked meshes.

Compliance with ethical standards

Conflicts of interest None.

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