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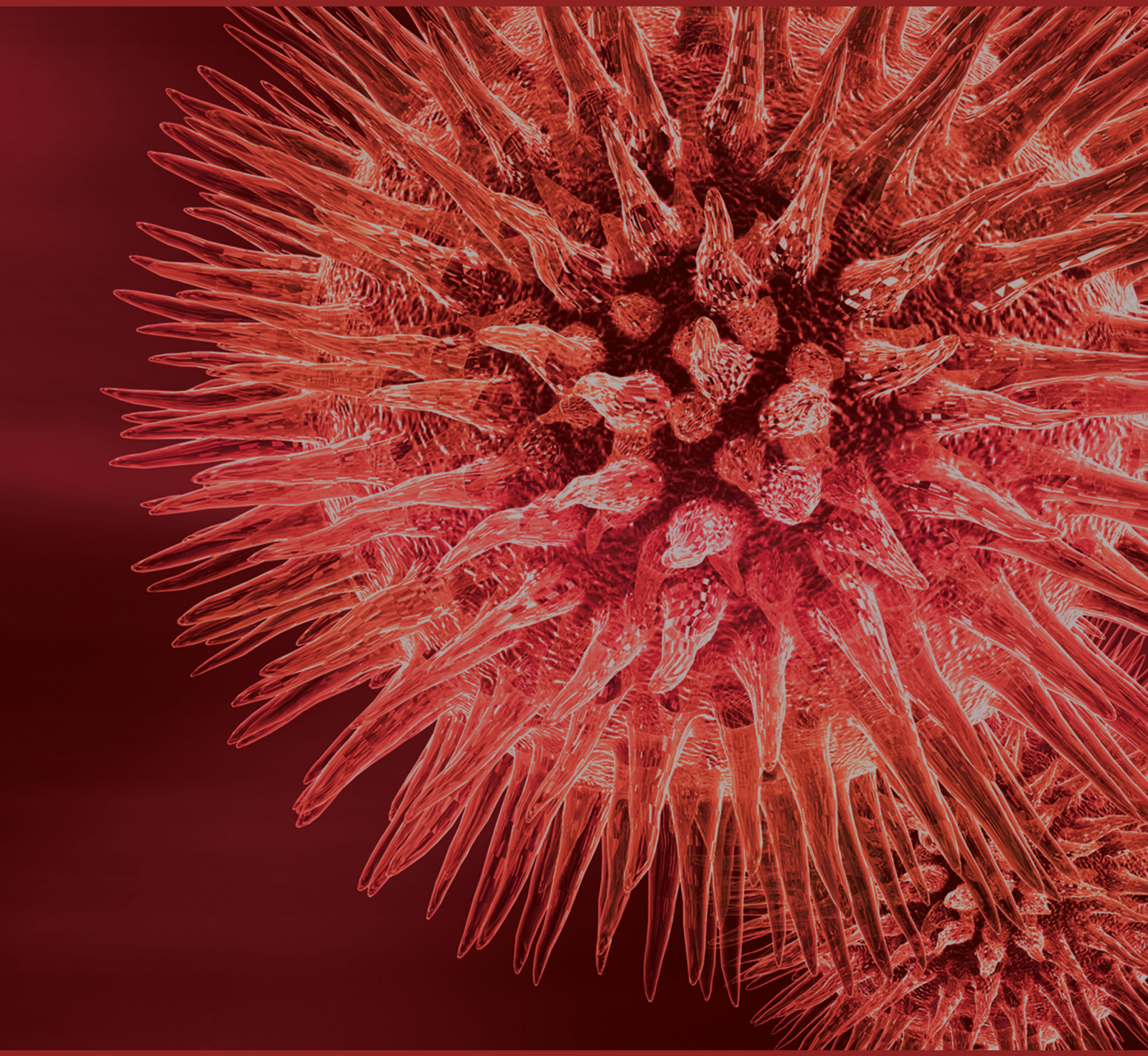
Implants in Urogynecology

Guest Editors: Thomas Otto, Bernd Klosterhalfen, Uwe Klinge, Mihaly Boros, Dirk Ysebaert, and Koudy Williams



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Editorial

Implants in Urogynecology

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Implants aim to substitute or to support in case of own tissue deficiency and therefore played an increasing role for pelvic floor reconstruction in last decades. Several scientific theories (i.e., integral theory) and promising results from tertiary centers promoted the rising application of alloplastic materials [1]. With industry being deeply engaged in this field from the very beginning a huge variety of products was launched over the years and was approved due to simple administrative procedures (US: 510K; Germany/EU: medical product law and device regulation). Aggressive marketing helped to spread these products around the world, since there are millions of female patients in our aging society suffering from incontinence and pelvic floor prolapse. In a Public Health Notification (PHN), from 2008, the Food and Drug Administration (FDA) reported more than 1000 unexpected and severe adverse events, mostly associated with transvaginal placement of surgical mesh to treat pelvic organ prolapse (POP) and stress urinary incontinence (SUI). In 2011 and 2012, second and third FDA amendments were questioning the role of mesh application for POP and SUI repair and proposing a change to Class III status that would allow the request of premarket approval and postmarket surveillance studies [2]. A minority of patients (less than 5% according to Manufacturer and User Facility Device Experience MAUDE database) suffered from the complications but due to partly severe course and rising public interest the trend for mesh application stopped. Meanwhile, manufacturers in USA are confronted with >100 000 lawsuits. The allegations of the manufacturers are still severe. The companies are accused of misleading. The plaintiffs claim that it is "the legal duty of the manufacturers to ensure the efficacy and safety of transvaginal meshes," but instead they provide patients with "false and misleading information about the efficacy and safety of products." Several mesh products were withdrawn from the market. The majority of manufacturers are expected to compromise quickly with the plaintiffs, threatened by the numerous lawsuits and the bad course of the so-called "Bellwether Trials" for the industry.

Due to reported complications and consecutive law issues especially in USA there is a high uncertainty among clinicians and patients about the application of urogynecologic implants. New regulation strategies are urgent and in debate now.

There is a lack of appropriate preclinical tests and research on the risks of surgical meshes for use in female pelvic floor. However, what do we know by now? Tension-free vaginal tape (TVT) developed as a gold standard for the treatment of female SUI with good long-term functional results of 87% after 17 yrs of follow-up [3]; similar results were found for midterm follow-up of TOT (transobturator tape). Various single incision slings for female SUI and male slings are used for over 10 years but there is still a lack of good scientific

Table 1: IDEAL stages (Dahm et al., 2014) [11].

Phase	Type of urologist involved	Purpose (study design)
Idea (1)	Very few, innovators	Proof of concept (structured case reports)
Development (2a)	Few, innovators and early adopters	Procedure development (prospective development studies)
Exploration (2b)	Many, early adopters and early majority	Refinement, community learning and consensus, and learning curve evaluation (preliminary collaborative cohort studies building toward randomized trials)
Assessment (3)	Many, early majority	Formal comparison of benefits and short-term safety (randomized controlled trials)
Long-term follow-up (4)	All eligible	Surveillance, quality assurance, and long-term safety (registry)

data. In particular, there is a lack of knowledge to identify patients at high risk for mesh related complications, in which the risk benefit ratio is not balanced. Indication for pelvic floor devices should be focused on patients with low risk for mesh complications and high risk for failure of mesh-free procedures.

Artificial urinary sphincter is a gold standard therapy for severe male SUI but complete numbers of explanations (about 30%) and other complications are still missing. The current Cochrane Review included 19 randomised trials of anterior vaginal wall prolapse and found no significant differences for subjective postoperative outcome and quality of life, de novo dyspareunia, SUI, and reoperations with or without mesh-assisted reconstruction. Better anatomical results but more reoperations due to mesh erosions (10%) were found in the mesh-group [4]. The erosions are associated with other complications, as infections, bleedings, or chronic pain due to nerve lesions. The most severe complications include organ perforations, massive bleeding, and sepsis. Long-time complications are scarring and shortening of the vagina and recurrent POP and/or SUI.

What is the future for the use of alloplastic material for pelvic floor reconstruction?

Surgeons should perform surgery for SUI or POP only if they are adequately trained in this subspecialist area and are aware of all potential therapeutic options and complications. The surgeon experienced in the technique has less complications than less experienced surgeons [5].

The proper education of the patient is an obligation prior to operation. The pros and cons should be outlined for each patient prior to final selection of a surgical technique. Patients should be evaluated for risk factors and in case of recurrence the reasons for unsuccessful initial treatment and the feasibility of repeated surgical treatment should be evaluated [6]. The indications for meshes should be restricted to high-grade or recurrent prolapse, additional risk factors (obesity, lung emphysema, prolapse of multiple compartments, enterocele, and cystocele with lateral fascia defect). Postoperative control of results is important. A PF- (pelvic floor-) sonography is a very useful tool to control the mesh position. In case of complications or recurrence strategies mesh removal can be evolved based on PF-sonography [7]. Specialised centers should be consulted in case of complications; mesh removal is often a surgical challenge and can be associated with severe injuries and complications.

Material features like biocompatibility are crucial factors for foreign body reaction and ingrowth of the material. New studies for materials showed less complications if a type 1 mesh was used (monofilament, macroporous, and light-weighted) [8]. Further basic research studies on material features are important [9].

Finally, a structured development process and long-term registers for the implants are needed in order to provide better patient counselling and to promote technological improvements of alloplastic materials.

The current scientific framework, based largely on uncontrolled case series, does not serve patients well and has no future. In an era of comparative effectiveness, much stronger evidence and possibly cost-utility studies will be needed to evaluate treatment benefits and harms of the surgical therapies with the application of alloplastic materials.

In 2009, the Lancet dedicated a series to the topic of "Surgical Innovation and Evaluation" and its current status. A 5-stage description of the surgical development process was proposed, the so-called IDEAL model (innovation, development, exploration, assessment, and long-term study), which allows assigning every surgical innovation to its particular corresponding step of development (Table 1) [10, 11].

After the specification of the recommendations concerning IDEAL to the field of urology, several scientific groups utilized the IDEAL model of surgical innovation in the development of a novel surgical technique in order to show how surgical research may be concluded when strictly driven following standardized recommendations [11, 12].

A last stage of IDEAL requires long-term safety studies and registers. Up to date only a small number of implanted materials are evaluated in clinical trials. To provide the quality assurance of the medical products it is urgent to create national and international registers.

Such registers are already established by surgeons for inguinal and abdominal hernia repair (i.e., EuraHs) [13]. This knowledge could be implemented for the purpose of urogynecology by establishing a specialised implant register. The register would open the possibility to gain high quality results on indications, complications, and individual decisions concerning surgical methods and choice of material.

Central registers are therefore the future instrument to provide the surgeon in a cost-effective and timely manner with the information for a responsible and individualized preoperative selection of the product.

The surgical procedures and the implementation of new techniques should be evaluated in consideration of human rights network and bioethical aspects. The Hippocratic oath "first do not harm" is a challenge in urogynecology and should lead every therapeutic decision.

We hope that the readers of this journal will find in this special issue not only accurate data and updated reviews on the recent development and indications for mesh application for POP and SUI but also the answer to such important questions as immunological and inflammatory reactions on the implantation of alloplastic materials and their impact on the biocompatibility in the host, latest imaging and other technologies for clinical evaluation and advances in biocompatibility of implants, next generation implants, strategies for clinical evaluation, and long-term surveillance of alloplastic materials (IDEAL).

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Review Article

Biomaterials for Pelvic Floor Reconstructive Surgery: How Can We Do Better?

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Stress urinary incontinence (SUI) and pelvic organ prolapse (POP) are major health issues that detrimentally impact the quality of life of millions of women worldwide. Surgical repair is an effective and durable treatment for both conditions. Over the past two decades there has been a trend to enforce or reinforce repairs with synthetic and biological materials. The determinants of surgical outcome are many, encompassing the physical and mechanical properties of the material used, and individual immune responses, as well surgical and constitutional factors. Of the current biomaterials in use none represents an ideal. Biomaterials that induce limited inflammatory response followed by constructive remodelling appear to have more long term success than biomaterials that induce chronic inflammation, fibrosis and encapsulation. In this review we draw upon published animal and human studies to characterize the changes biomaterials undergo after implantation and the typical host responses, placing these in the context of clinical outcomes.

1. Introduction

Stress urinary incontinence (SUI) and pelvic organ prolapse (POP) are important health problems that cause a sizable personal, societal, and economic burden [1]. SUI is defined as the "involuntary leakage of urine on exertion, sneezing or coughing" [2, 3]. POP is the "the descent of one or more of the anterior vaginal wall, posterior vaginal wall, the uterus (cervix), or the apex of the vagina (vaginal vault or cuff scar after hysterectomy)" [4]. SUI and POP are thought to share a common pathogenesis, weakening of the muscular and connective tissues of the pelvic floor. Multiple etiological factors have been implicated including ageing, obesity, pregnancy, and childbirth, as well as genetic factors and menopause [1, 5–7].

Following failure of conservative management including physiotherapy, corrective surgery is considered to be the most effective and durable treatment for both SUI and POP. Most of the older surgical techniques relied upon suturing the local tissues to the back of the pubic bone (colposuspension) or using an autologous fascial sling. More recently there has been a growing trend to reinforce repairs using both synthetic and biological materials. This practice has been adapted from hernia surgery where there is established evidence that repairs reinforced with synthetic mesh provide superior outcomes.

Synthetic meshes were popularized in pelvic floor surgery for SUI following the work of Ulmsten and Petros [8]. The mid-urethral tape (MUT) involved a minimally invasive approach to implant a thin synthetic mesh underneath the mid-urethral point. Early reports of cure rates in the range of 80–90% further propelled the uptake of this technology. Following the early success of MUT and a randomized control trial against colposuspension, synthetic mesh for SUI was soon introduced [9]. This was not based on long term supportive data but rather a grandfather clause which permitted introduction of a new material based on its similarity to an index product, which was used for hernia repair, namely,

polypropylene mesh. A long term follow-up, the Ward and Hilton [9] study, demonstrated a 4% exposure of mesh rate. Subsequently mesh was introduced for the treatment of pelvic organ prolapse (POP) and this has resulted in a significant problem with mesh exposure which has led to enormous medico-legal problems, particularly in the United States of America.

The following decade has seen a rapid rise in reports of mesh for POP related complications, but it is clearly important to differentiate mesh exposure (erosion) used for SUI from that used for POP. Thus reports of debilitating complications of vaginal mesh implantation have emerged including vaginal wall erosion (0–25.6%), chronic pain (0–5.5%), and sexual problems (1.9–17%) [10]. Although it can be debated whether these rates are high, the complications are often difficult to treat, requiring further hospital visits, further tests, and further reconstructive surgery. The situation has not escaped the attention of medical regulatory bodies such as the FDA who have issued statements warning patients and surgeons of the potential dangers of mesh use for POP [11, 12]. More recently there has been a wave of class action litigation law suits raised against device manufacturers by patients who have suffered mesh complications, such that several major manufacturers have withdrawn products from the market.

Biological grafts are alternatives to synthetic mesh. The most commonly used material, autologous fascia, has been used for over 100 years in the treatment of SUI with good efficacy. The main drawback however is the need to harvest the graft from a donor site (fascia lata from the thigh or rectus fascia from the abdominal wall) and potential morbidity (e.g., wound infection, scar, nerve injury, and hernia) [13]. There is a limitation on how much graft can be harvested which precludes its use in POP which is associated with relatively large fascial defects. This can be avoided by using grafts derived from cadavers or alternatively animal derived collagen matrices (e.g., porcine dermis, porcine small intestine, and bovine dermis). However, these materials require extensive processing decellularization, sterilization, and cross-linking processes to resist degradation [14]. While this renders materials nonimmunogenic, it can impact their biomechanical properties [15]. There is also the risk of viral or prion transmission [13]. Clinical studies are limited; however clinical experience is that all of the materials appear to be associated with graft failure in the medium term due to the body's response to the material, leading its encapsulation and subsequent degradation with limited remodeling.

It is likely that biomaterials are subject to multifactorial problems because of (1) their physical properties (e.g., porosity and degradability), (2) their mechanical properties (e.g., stiffness and strength), or (3) the nature of the patient's immune response to the implanted biomaterials. In addition, surgical and patient specific factors (e.g., individual anatomy and comorbidities) are likely to play a role, though these are not modifiable by material design.

To provide a simple context for this review we depict the current hypotheses of how failures of implant might occur through several routes in cartoon form in Figure 1 where the implanted material is shown conceptually as a hammock attached to two trees (the supporting structures of the pelvic floor).

In the case of successful implantation, it is currently thought that the material induces an acute inflammatory response, which leads to constructive remodeling and material integration (Figure 1(d)).

The aim of this review is to characterize these changes and responses, from the available human and animal studies, and relate them to clinical outcomes, thereby guiding the design of novel materials for this challenging clinical application.

2. Methods

The MEDLINE database was searched for articles describing studies investigating the *in vivo* response to biomaterials used routinely in pelvic floor surgery or that have been studied in the context of clinical trials. The search was limited to the years 1990 to 2013. The following search terms were used: "pelvis," "pelvic floor," "vagina," "*in vivo*," "*in vitro*," "biocompatibility," "prolapse," "incontinence," "biomaterial," "sling," "mesh," "polypropylene," "autografts," "allografts," and "xenografts." Abstracts were screened for relevance by 2 reviewers before full articles were retrieved. Articles were included if they described the changes in physical or biomechanical properties of materials after implantation in animals or humans or the histological features of the host response to the implanted material. Implantation sites were restricted to subcutaneous, intravaginal, or abdominal muscles.

3. Results

In total 10 studies assessing autologous materials, 11 assessing allograft materials, 24 assessing xenografts, and 24 assessing polypropylene meshes compared with other synthetic meshes were included. These studies are summarized in Tables 2, 3, 4, and 5.

3.1. Biological Materials

3.1.1. Autologous Materials. Autologous grafts harvested from the rectus fascia and fascia lata have long been used in SUI surgery. A major advantage of autografts over synthetic materials is that erosion is almost unheard of [16]. A possible disadvantage to using autografts is that the connective tissues of patients with SUI may be inherently weak predisposing to failure. Nevertheless the overall long term outcomes with autografts are largely excellent with reported rates of cure generally over 90% [17, 18].

Biomechanical Properties of Autologous Materials. Four studies describing changes in mechanical properties of autologous materials over a 12–16-week period were found. Uniaxial stress strain testing of autologous rectus fascia before and after implantation in rabbit vagina and anterior abdominal wall showed no significant decrease of ultimate tensile strength (UTS) (the maximum stress a material can take before failing) and Young's modulus (YM) (material stiffness), at twelve weeks after implantation [19, 20]. However, there was a reduction in surface area of the grafts by 50%

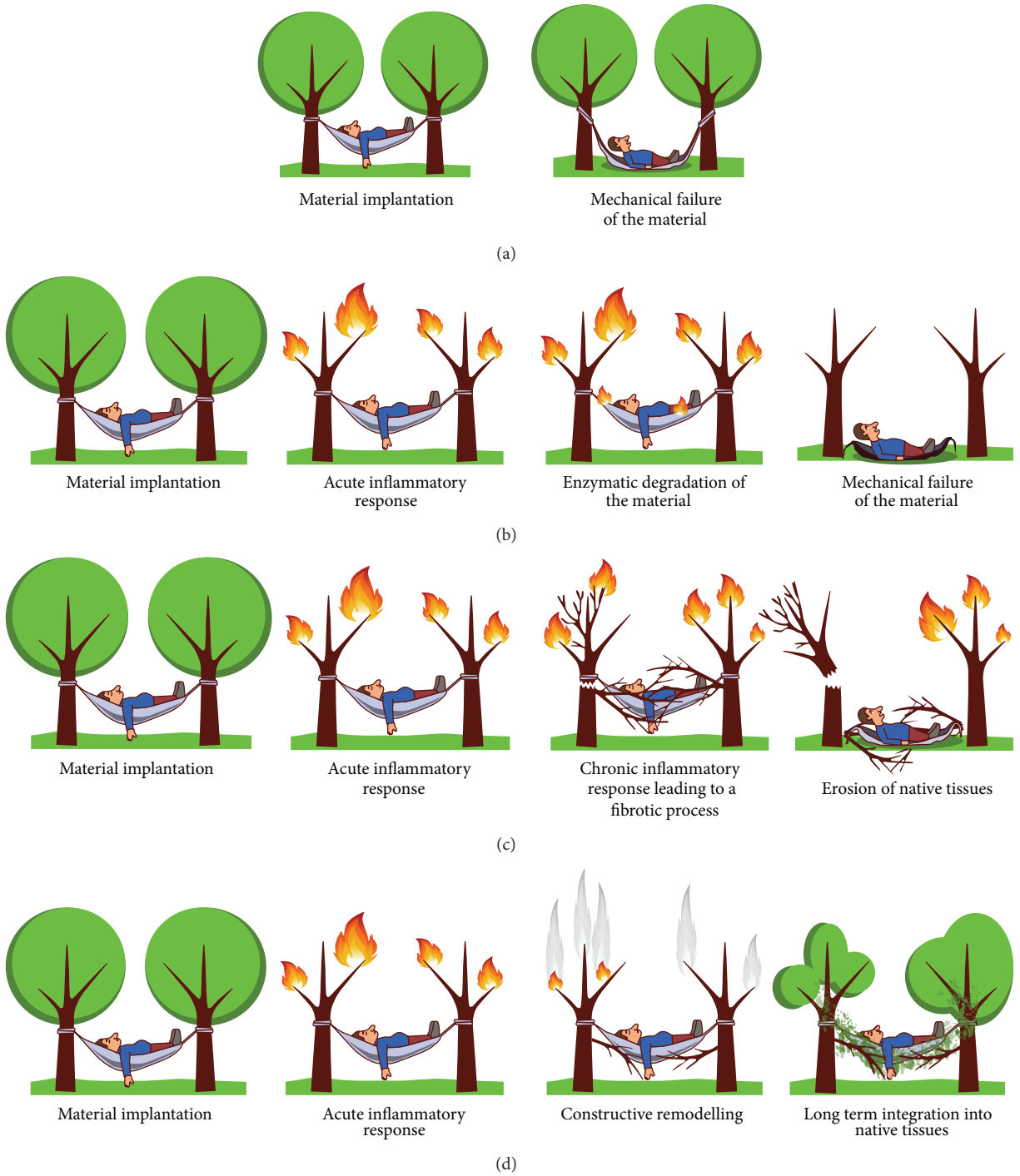

Figure 1: Cartoon of how patients can respond to materials implanted in the pelvic floor: (a) mechanical failure, (b) material recognized as non-self and isolated from body tissues with encapsulation, (c) exposure (erosion), and (d) optimal result for implanted material.

suggesting that significant degradation had occurred [19, 20]. A comparison of mechanical strength of autologous materials used for sling was carried out by Choe et al. [21]. They harvested dermis, rectus fascia, and vaginal mucosa from 20 women undergoing vagina prolapse surgery and they tested displacement and maximum load with the Instron tensiometer. This study showed that fascia lata had the highest mean maximum load to failure (217 N), followed by human dermis (122 N), rectus fascia, and vaginal mucosa (both 42 N) in women undergoing surgeries for various reasons [21]. Autologous rectus fascia showed no significant decrease in tear resistance using the trouser tear test after 4 months of subcutaneous implantation in rodents [22]. In summary in all four studies there was agreement that the mechanical properties did not change significantly over a 12- to 16-week duration [19–22].

Host Response to Implanted Autologous Materials. Eight studies analysed the host response to autologous materials over a time period up to 90 days [19, 20, 23–29]. In the majority of studies, unless stated otherwise, biomaterials were assessed after implantation by conventional blindly scored histology (staining of fixed samples by haematoxylin and eosin (H&E)), trichromes, and/or the presence of proangiogenic cells.

Hilger and colleagues assessed human cadaveric skin and autologous fascia after implantation in the abdominal and vaginal walls of New Zealand white rabbits. Materials were harvested at 6 and 12 weeks. Histological analysis demonstrated that autologous fascia promoted a relatively minimal inflammatory response and neovascularization but moderate collagen infiltration when compared to fenestrated porcine dermis and porcine collagen-coated polypropylene mesh [20]. Jeong and coworkers described similar results noting minimal inflammatory response and neovascularization in rabbits when autologous fascia was implanted under the eye lid for up to 8 weeks [24].

Two studies assessed histological changes in paravaginal tissue after the implantation of autologous fascial slings for SUI in women. In the study by FitzGerald et al. biopsies of the sling were taken from 5 patients requiring revision surgery due to persistent incontinence. The time since the initial surgery ranged from 3 weeks to 4 years. The grafts explanted after up to 8 weeks showed moderate uniform fibroblast infiltration and neovascularization. Collagen remodelling was evident in parts of the graft biopsied at 4 years, with no evidence of chronic inflammation [23]. Woodruff and colleagues performed a similar study in 24 patients undergoing sling revision for poor efficacy (2 patients), urinary retention (9), and sling obstruction (13), 2–34 months after implantation [27]. All grafts showed moderate uniform fibroblast infiltration and moderate collagen fibers. All grafts showed moderate degradation. There was no evidence of encapsulation.

In summary these eight studies suggest that when autologous fascia is implanted there is a minimal to moderate inflammatory response, a moderate degree of collagen production, and a suggestion that grafts undergo a degree of remodelling over the long term.

3.1.2. Allografts. Allografts used in pelvic floor reconstruction usually consist of fascia. The donors are screened for infectious diseases before the grafts undergo cleaning, freeze drying, and gamma irradiation to eradicate any infective or immunogenic material. A concern with these grafts is that they are often donated by the elderly who have an age related weakening in connective tissues [30]; additionally processing techniques such as freeze drying and solvent dehydration may reduce the tensile strength [31]. Cadaveric grafts are advantageous in that they avoid donor site complications. In terms of efficacy, results are mixed. Some have shown cadaveric fascia to demonstrate similar subjective cure rates to autologous fascia at around 90% at 2 years [32]. However others have shown that on urodynamic testing 42% of cadaveric graft patients had SUI whereas no patients with autologous grafts had SUI [33].

Biomechanical Properties of Allografts. Five studies investigated the change in mechanical properties after implantation of allografts in animals. All these studies utilized uniaxial stress strain testing. The time after which samples were explanted ranged from 60 days to 12 weeks [20, 22, 34–36].

After implanting human cadaveric dermis in rabbit vagina, Hilger et al. reported a decrease in ultimate strength of 86.6% at 12 weeks; in comparison autologous fascia lost only 28.6% [20]. Conversely, Rice and colleagues found an increase in tensile strength of cadaveric dermis (AlloDerm) from 0.142 to 0.226 MPa, increasing by about 80% of its initial strength, 60 days following subcutaneous implantation [36]. Walter et al. reported that, after 12 weeks, following implantation of cadaveric fascia lata in rabbit vagina, the tensile strength decreased by approximately 90% [34]. Spiess et al. implanted human cadaveric fascia lata subcutaneously on the abdominal wall of 20 rats randomized into 2 survival groups at 6 and 12 weeks. They found no significant decrease in tensile strength from 0.167 kg at week 6 and 0.185 kg at week 12 [35]. Kim et al., similarly, implanted human cadaveric fascia in 20 rats, randomized into 2 survival groups of 2 and 4 months. They found no significant difference in fracture toughness before implantation and after implantation in human cadaveric fascia (from 2120 to 1145 J/m^2, $P = 0.09$) [22].

In summary, the available studies show disparate results with respect to the changes in mechanical properties of allografts following implantation. This may be attributable to the heterogeneity in the type of allografts used, the animals studied, the sites of implantation, and the assessment at different time points.

Host Response to Implanted Allografts. In total eight studies assessed the host response to allografts in both animals and humans. The time since implantation ranged from 2 days up to 65 weeks [20, 26, 27, 36–40].

Human cadaveric dermis and cadaveric fascia have been found to be well integrated onto the abdominal wall [37, 40, 41] and rectus muscle [36, 38] in different animals, including rats, rabbits, and pigs, as noted by moderate fibroblast infiltration, new collagen production, and neovascularization where materials were implanted from 2 days up to 62 weeks. Human cadaveric dermis, after 12 weeks of implantation, was similarly well integrated into vaginal tissues of rabbits. However, it appeared highly fragmented suggesting significant degradation [20]. Krambeck et al. also describe a faster degradation of cadaveric fascia implanted subcutaneously on the abdominal wall of rabbits with a fascial defect for 6 and 12 weeks compared to polypropylene or autologous fascia [26]. VandeVord and colleagues also found moderate cell infiltration and angiogenesis at 12 weeks following the insertion of human cadaveric dermis and cadaveric fascia slings under the bladder neck of rats; however there was a moderate encapsulation after implantation [39]. Finally, in the study by Woodruff et al. in 5 women who received human cadaveric dermis grafts, biopsies 2–65 months after implantation showed significant graft degradation with residual areas of graft appearing acellular and encapsulated [27].

In summary, some studies suggest that allografts demonstrate infiltration by host cells, new collagen production, and

neovascularization whilst other studies suggest that a variable degree of graft degradation occurs along with encapsulation in the long term. There is a degree of agreement that allograft induces an acute inflammatory response as inflammatory infiltrates have been found populating the grafts.

3.1.3. Xenografts. A number of grafts from animals, mainly porcine and bovine, have been used in pelvic floor surgery. These materials undergo extensive processing after harvesting to decellularize them and render them non-immunogenic. Additionally there are FDA regulations on animal source and vaccination status which must comply with [42]. Porcine dermis may be artificially cross-linked using hexamethylene diisocyanate to make it more resistant to enzymatic digestion [43]. Clinical studies showed lower continence rates for porcine dermis (approx. 80%) and increased reoperation than that for synthetic tape or autologous fascia [44]. Porcine small intestine submucosa (SIS) has shown cure rates from 79 to 93% at 2- and 4-year follow-up, respectively [45, 46]. However one study has raised concerns that SIS may not be strictly acellular and may contain porcine DNA [47].

Biomechanical Properties of Xenografts. Nine studies investigated the mechanical properties of xenografts before and after implantation. All these studies assessed either porcine dermal collagen matrix, both cross-linked and non-cross-linked, or porcine small intestine submucosa.

Hilger et al. assessed non-cross-linked porcine dermis xenografts implanted on the abdominal wall and vaginal wall of rabbits. After 12 weeks, half of the grafts implanted in the vaginal wall were absent. The other half as well as grafts implanted into the abdominal wall showed an average reduction of 84.1% in ultimate strength [20]. Another study assessed the long term mechanical integrity of cross-linked porcine dermis. After 9 months following implantation in the abdominal and vagina walls, grafts had degraded by 36% and 46%, respectively. When subjected to mechanical testing non-degraded graft fragments showed similar strength compared to baseline values whilst degraded fragments decreased by more than 50% [48].

Liu and colleagues implanted SIS and porcine dermal collagen matrix in rats with surgically created abdominal wall defects. The maximum load (at failure) at baseline for SIS and dermal collagen matrix was 22.81 N and 43.16 N, respectively. Following 12 weeks of implantation, there was no significant change in the maximum load of cross-linked porcine dermal collagen matrix and SIS [49]. Similarly other workers observed an increase in the ultimate tensile strength of SIS after 90 days of implantation from a baseline value of 7.5 and 9.8 N/cm^2 at baseline, respectively, to 19.56 and 13.3 N/cm. These results were averages of 48 implants in rats [50]. Rice et al. also found an increase in tensile strength of SIS after 60 days of implantation in a rat abdominal wall defect from 0.142 MPa at day 0 up to 0.226 MPa after 60 days of implantation [36]. Similarly, Zhang et al. implanted SIS in abdominal wall of rats and they found increased strength for SIS from 0.35 MPa to 0.41 after 4 weeks [51]. Badylak et al. repaired surgically created abdominal wall defects in dogs with SIS (8 × 12 cm); they performed serial ball burst strength tests after 1, 4, 7, and 10 days and then at 1, 3, 6, and 24 months) [52]. There was an initial decrease in ball burst strength from 73.37 pounds to 39.97 pounds by day 10. After day 10, the strength began to increase and after 2 years there was an increase to 157.20 pounds in burst strength. Jenkins et al. showed an increase in strength in cross-linked porcine matrices after 6 months of implantation in the preperitoneal area from 0.07 ± 0.01 N up to 22.36 ± 3.3 N [53]. In contrast, Ko and colleagues found no significant difference in ultimate tensile strength of SIS after 4 months of implantation in a porcine wall defect, with values ranging from 41.3 to 74.8 N/cm^2 [54].

In summary it appears that non-cross-linked porcine dermal collagen matrices are degraded rapidly (within 3 months) and lose most of their mechanical integrity within this period. By contrast cross-linked porcine dermal collagen matrix is more resistant to degradation and maintains its mechanical properties for at least 3 months, whereas SIS appears to increase in strength after as long as 2 years after implantation.

Host Response to Implanted Xenografts. Twenty-four studies assessing the host response to allografts were found. Non-cross-linked porcine dermal collagen was assessed in fourteen studies [20, 26, 27, 36, 39, 50–52, 54–61]. These studies were performed on rats [36, 50, 51, 55, 58, 59], dogs [52, 55], pigs [54, 57], and rabbits [26] in addition to few clinical studies [20, 27, 39, 56]. Cross-linked porcine matrices were assessed in seven studies [40, 49, 53, 62–66]. Animal models mainly used were abdominal defects of rats [49, 62, 66], rabbits [65], minipigs [53], pigs [40, 63], and primates [64]. Some of these studies looked at the acute response [39, 49, 53, 55, 59, 66]; some other studies looked at a more intermediate response (1–3 months) [20, 26, 36, 39, 40, 49–51, 54, 55, 57, 58, 60, 62–64, 66]; another looked at longer term response (more than 3-months) [27, 40, 53, 62, 64, 65].

Hilger et al. and Pierce et al. found minimal neovascularization and collagen ingrowth in porcine dermal xenografts [20, 65]. Both studies agreed that the degradation of porcine dermis is higher when the inflammatory response is high, and it may accelerate this degradation process. They also reported fragments encapsulated, which has been also found in many studies with different species including rats [39, 62], rabbits [65], pigs [40], primates [64], and humans [27].

In contrast, non-cross-linked SIS leads to high collagen ingrowth with a moderate degree of remodeling and orientation and high neovascularization [29, 36, 39, 49–51, 54, 55, 57, 63]. On the other hand, many studies agree with a very rapid degradation of the SIS which is replaced by the host tissue [49, 51, 52, 55, 58, 66, 67]. Only two studies reported an absence of host fibroblast infiltration and fibrotic tissue penetration without neovascularization for SIS implanted in rats [62] and rabbits [26]. In humans, Cole et al. performed revision surgery on a patient who had developed a bladder outlet obstruction after SIS implantation and found that the implant had been encapsulated [60]. Nevertheless, other investigators, at 12 and 48 months, respectively, found that the SIS was replaced by native tissue in humans [56, 61].

In summary, the available studies agree that the degree of cross-linkage affects the rate of degradation and the degree of the inflammatory response of the host. Studies on cross-linked xenografts agree that cross-linked collagenous matrices induce little cell infiltration; hence there is limited collagen remodeling and graft degradation. In non-cross-linked xenografts, cell infiltration was greater with faster degradation rate and collagen production.

3.2. Polypropylene Mesh. There is a range of synthetic polypropylene meshes that have been used. These are summarized in Table 1 where they are classified as type 1, 2, 3, or 4 according to their mesh size, where 1 is macroporous (>75 μm), 2 is less than 10 μm, 3 is microporous with microporous compartments, and 4 is nanoporous (<1 μm). Thus a wide range of synthetic materials have been investigated for use in the treatment of SUI. These materials offer several advantages including lack of transmission of infectious diseases and ease of availability, as well as the sustainable tensile strength due to their nondegradable nature [68]. Mesh materials have been classified in to 4 groups based on the basis of porosity (microporous or macroporous) and filamentous structure (monofilament of multifilament) [69]. The initial clinical experience with mid-type II (microporous/multifilament fibers, e.g., expanded PTFE) and III (macroporous and microporous/multifilament fibers, e.g., Mersilene) meshes was largely negative with excision rates of up to 30% for expanded PTFE [70] and erosion rates of 17% for Mersilene (polyester) [71].

A greater pore size is thought to be advantageous as it allows the admittance of immune cells and greater collagen ingrowth into the construct [13]. This is thought to reduce the risk of mesh infection and accelerate and enhance host tissue integration. Monofilament meshes are thought to reduce the risk of infection in comparison to multifilament meshes. The theoretical concern with the latter is that bacteria may colonize the 10 μm subspaces between fibers which are inaccessible for the larger host immune cells (9–20 μm) [72]. Today a mid-type I polypropylene mesh that is macroporous and monofilament is most commonly used [73] with cure rates for SUI of >90% at 5 years.

Biomechanical Properties of Polypropylene. Seven studies investigated the mechanical properties of polypropylene meshes with implantation times ranging from two weeks in animal models up to two years. Animal models used were rats abdominal wall [35, 74], pig preperitoneal implantation [75], rats rectus fascia [76], minipigs hernia repair [77], and ewes abdominal and vaginal walls [78].

Melman et al. tested Bard Mesh, a knitted monofilament mesh made of high molecular weight polypropylene (HMWPP) and Ultrapro, a knitted macroporous composite mesh made of low molecular weight polypropylene (LMWPP) and poliglecaprone (Table 1). They have been implanted in minipigs hernia repair model for up to 5 months. HMWPP mesh decreased from maximal load at failure 59.3 N at 1 month to 36.0 N at 5 months, while LWPP mesh decreased from 61.5 to 37.8 N at 5 months [77]. Long term studies were carried out by Zorn et al. where TVT and SPARC were compared to SIS in a rat abdominal wall defect for up to 12 months. Both TVT and SPARC are macroporous meshes made of polypropylene monofilaments. SPARC did not change its mechanical properties after 12 months of implantation (maximum load at baseline 0.453 kg and at 12 months 0.497 kg). By contrast the maximum load for TVT decreased from 0.779 kg to 0.523 kg for TVT and for SIS decreased from 0.402 kg to 0.174 kg [74]. Also Bazi et al. showed how similar are the mechanical properties of Gynecare TVT and Advantage, both macroporous polypropylene monofilament meshes, compared with other meshes such as IVS Tunneller, multifilament polypropylene mesh, and SPARC. The lowest, at 25.2 N, was TVT and the highest, 34.9 N, was Advantage, with no significance between them after 24 weeks of implantation in rats rectus fascia [76]. Also other studies agree on these parameters where TVT was found to be able to comply with the highest break load (0.740 kg), compared to 0.39 kg for fascia lata after implantation in rats abdominal wall for up to 12 weeks [35], and was said to be less stiff than other synthetic materials used for meshes (0.23 N/mm compared to nylon, 6.83 N/mm) [79].

A recent study compared two sizes of meshes implanted in two different places in a sheep model. Gynemesh was cut in two sizes (50 × 50 mm and 35 × 35 mm) and it was implanted in 20 adult ewes, on the abdominal and vaginal walls for a period of 60 and 90 days. Results showed that grafts of both dimensions, implanted on the vaginal wall, were stiffer than the ones implanted on the abdominal wall, after a period of 90 days [78].

However, they all agree that physical characteristics of the mesh, such as monofilament or multifilament, porosity, and polymer molecular weight, hugely affect the mechanical performance of the implants *in vivo*.

Host Response to the Implanted Polypropylene. Twenty-one papers have looked at the host response to the polypropylene meshes. They have been assessed in various animal models: rats abdominal wall [50, 58, 74, 80–82], rats rectus fascia [38, 76, 83], rabbits bladder neck [84], rabbits abdominal wall [85], rabbits rectus fascia [26], rabbits vaginas [65, 86], minipigs hernia [77], pigs peritoneum [75, 87], ewes vagina [78, 88], and ewes abdominal wall [78] in addition to few clinical studies [27, 89–91]. The studies have looked at acute inflammatory responses to the most commonly used, nondegradable meshes, described in Table 1. Few studies looked at the acute inflammatory response that occurs from the day of implantation up to 30 days [50, 58, 80–82, 85, 88]. Other studies looked at the immediate responses (1–3 months) [26, 75, 78, 83, 84, 86, 87] and longer term responses (>3 months) where fibrosis and chronic inflammation can be seen [27, 65, 74, 76, 77, 89–91].

A very recent study of Manodoro et al. showed how 30% of Gynemesh grafts (50 × 50 mm), implanted in ewes after 90 days, caused vaginal erosion and exposure. The study also showed that 60% of the smaller Gynemesh meshes (35 × 35 mm) had a reduced surface (i.e., contracting) after 90 days of implantation [78].

Falconer et al. reported a study on Prolene and Mersilene meshes. The biopsies were stained with Masson's trichrome.

Table 1: Classification of synthetic materials used in pelvic floor reconstruction.

Type	Mesh pore size	Structure	Polymer	Trade name	Company
I	Macroporous >75 μm	Monofilament	Polypropylene	Uretex	C. R. Bard
				Gynecare TVT	Ethicon, Johnson & Johnson
				Bard Mesh	Bard/Davol
				SPARC	American Medical Systems
				In-Fast	American Medical Systems
				Monarc	American Medical Systems
				Lynx	Boston Scientific
				Advantage	Boston Scientific
				Obtryx	Boston Scientific
				Optilene	B. Braun
				Aris	Mentor Corp
				Perigee	American Medical Systems
				Parietene	Covidien
				Intepro	American Medical Systems
				Gynecare Prolift	Ethicon, Johnson & Johnson
				Surgipro	Covidien
				Prolene	Ethicon, Johnson & Johnson
				Prolene Soft	Ethicon, Johnson & Johnson
				Gynemesh PS	Ethicon, Johnson & Johnson
				Atrium	Atrium Medical
				Marlex	C. R. Bard
		Multifilament	Copolymer of glycolide (90%) and lactide (10%)	Vicryl	Ethicon, Johnson &Johnson
			Polypropylene and polyglecaprone	Vypro	Ethicon, Johnson & Johnson
				UltraPro	Ethicon, Johnson & Johnson
			Polyglycolic acid	Dexon	Davis and Geck
II	Macroporous <10 μm	Multifilament	Expanded PTFF	GORE-TEX	W. L. Gore
			Polyethylene terephthalate	Mersuture	Ethicon, Johnson & Johnson
III	Macroporous with microporous components <10 μm	Multifilament	PTFE	Teflon	C. R. Bard
			Polyethylene terephthalate	Mersilene	Ethicon, Johnson & Johnson
			Polypropylene	IVS Tunneller	Tyco Healthcare
			Woven polyester	Protegen	Boston Scientific
IV	Nanoporous <1 μm	Multifilament	Silicon-coated polyester	Intermesh	American Medical Systems
			Dura mater substitute	PRECLUDE MVP Dura substitute	W. L. Gore
			Expanded PTFE, pericardial membrane substitute	PRECLUDE Pericardial Membrane	W. L. Gore

Table 2: Autologous fascia.

Author	Sample	Biomechanical properties	Host response
FitzGerald et al., 2000 [23]	Autologous rectus fascia implanted in 5 patients suffering from SUI. Samples obtained, respectively, from transvaginal revision after 3, 5, 8, and 17 weeks and from replacement after 4 years.		(i) Moderate and uniform infiltration of host fibroblasts and neovascularization after 5 and 8 weeks of implantation. (ii) After 4 years of implantation, no evidence of inflammatory cell infiltrate or foreign body reaction and collagen remodeling by connective tissue organized longitudinally.
Jeong et al., 2000 [24]	Autologous lata fascia implanted in 16 rabbits randomized into 4 survival groups and examined after 1, 2, 4, and 8 weeks. Implantation into upper eyelids.		(i) Low inflammatory cell infiltration. (ii) Fibroblast infiltration and collagen remodeling.
Choe et al., 2001 [21]	Dermis, rectus fascia, and vaginal mucosa harvested from 20 women undergoing vagina prolapse surgery.	Tensiometric analysis of full strips versus patch suture slings. Displacement and maximum load calculated.	
Kim et al., 2001 [22]	Autologous rectus fascia implanted in 20 rats randomized into 2 survival groups (2 and 4 months).	No significant decrease of the fracture toughness calculated by the trouser tear test over 4 months.	
Dora et al., 2004 [19]	Autologous rectus fascia implanted in 15 rabbits randomized into 3 survival groups (2, 6, and 12 weeks). Implantation on the anterior rectus fascia.	No significant decrease of biomechanical properties after 12 weeks of implantation.	50% decrease in surface area.
Hilger et al., 2006 [20]	Autologous rectus fascia implanted in 20 rabbits randomized into 2 survival groups (6 and 12 weeks). Half implanted on the rectus fascia and half on the posterior vagina fascia.	No significant decrease of biomechanical properties after 12 weeks of implantation.	(i) Collagen remodeling by moderate collagen infiltration but encapsulation as well. (ii) Minimal inflammatory response. (iii) Minimal neovascularization.
Krambeck et al., 2006 [26]	Autologous rectus fascia implanted subcutaneously on the anterior rectus fascia of 10 rabbits randomized into 2 survival groups (6 and 12 weeks).		(i) Moderate fibrosis. (ii) High degree of scarring. (iii) High degree of inflammatory infiltrate.
de Almeida et al., 2007 [29]	Adult female rats incontinence model. Marlex, autologous sling, SIS, polypropylene mesh, and sham at 30 and 60 days.		Reduced inflammatory response and collagen production around autologous grafts, in comparison with synthetic materials and xenografts.
Woodruff et al., 2008 [27]	Autologous fascia grafts explanted after sling revision from 5 women, due to different complications, between 2 and 65 months after implantation.		(i) Moderate and uniform infiltration of host fibroblasts and little neovascularization. (ii) Collagen remodeling by new collagen fibers organized longitudinally. (iii) No evidence of encapsulation or gross infection.
de Rezende Pinna et al., 2011 [28]	Autologous fascia lata implanted in 14 rabbits randomized into 2 survival groups (30 and 60 days). Implantation into the right voice muscle.		(i) No significant inflammatory reaction. (ii) No significant fibrosis or scarring.

Table 3: Allografts.

Author	Sample	Biomechanical properties	Host response
Sclafani et al., 2000 [37]	Human cadaveric dermis (AlloDerm) disk implanted subdermally behind a patient's ear. Micronized human cadaveric dermis (AlloDerm) injected intradermally and subdermally in 2 different locations behind a patient's ear. Both implants were examined 3 months and 1 month after implantation, respectively.		(i) Both materials extensively invaded by host fibroblasts. (ii) Both materials present new collagen ingrowth.
Kim et al., 2001 [22]	Human cadaveric fascia implanted in 20 rats randomized into 2 survival groups (2 and 4 months).	No significant decrease of the fracture toughness calculated by the trouser tear test.	
Walter et al., 2003 [34]	Freeze-dried and gamma-irradiated human cadaveric lata fascia implanted in 18 rabbits and excised 12 weeks after implantation.	Significant decrease of biomechanical properties after 12 weeks of implantation.	
Spiess et al., 2004 [35]	Human cadaveric fascia lata implanted subcutaneously on the abdominal wall of 20 rats randomized into 2 survival groups (6 and 12 weeks).	No significant decrease of tensile strength with time.	
Yildirim et al., 2005 [38]	Human cadaveric lata fascia implanted subcutaneously on the abdominal wall in 20 rabbits randomized into 4 survival groups (2, 7, 15, and 30 days).		(i) Acute inflammation by high cell infiltration predominantly of polymorphous granulocytes. (ii) Integration in host tissue by moderate fibrotic process and muscle infiltration on day 30, with persistent inflammatory response.
Krambeck et al., 2006 [26]	Cadaveric fascia lata implanted subcutaneously on the anterior rectus fascia of 10 rabbits randomized into 2 survival groups (6 and 12 weeks).		(i) Moderate to high focal fibrosis. (ii) Minimal to moderate degree of scar. (iii) High degree of inflammatory infiltrate.
Hilger et al., 2006 [20]	Human cadaveric dermis and lata fascia implanted in 20 rabbits randomized into 2 survival groups (6 and 12 weeks). Half implanted on the rectus fascia and half on the posterior vagina fascia.	Very significant decrease of biomechanical properties after 12 weeks of implantation.	(i) Two missing or fragmented materials implanted on the vagina after 12 weeks. (ii) Moderate inflammatory response. (iii) Minimal neovascularization. (iv) Minimal collagen ingrowth without significant cell infiltration.
Woodruff et al., 2008 [27]	Human cadaveric dermis slings explanted after revision from 2 women, due to different complications, between 2 and 65 months after implantation.		(i) Moderate levels of encapsulation. (ii) High levels of degradation. (iii) Peripheries of the grafts invaded by fibroblasts but central portions remained acellular.
VandeVord et al., 2010 [39]	Human cadaveric dermis and fascia lata implanted in 16 rats, respectively, and both randomized into 4 survival groups (2, 4, 8, and 12 weeks). Implantation around the bladder neck, anchored to the surrounding tissues.		(i) Thin fibrous capsule formation. (ii) Moderate cell infiltration and angiogenesis.
Rice et al., 2010 [36]	Human cadaveric dermis (AlloDerm) implanted in 18 rats randomized into 2 survival groups (30 and 60 days). Subcutaneous implantation on abdominis rectus muscle defect.	Increase of tensile strength after 30 days and, again, increase of tensile strength after 60 days, respectively, to 30 days.	(i) Moderate amounts of collagen deposition well organized. (ii) Abundant revascularization.

Table 3: Continued.

Author	Sample	Biomechanical properties	Host response
Kolb et al., 2012 [40]	Human cadaveric dermis (AlloDerm) implanted subcutaneously in 5 pigs randomized into 4 survival groups (7, 21, 90, and 180 days).		(i) Robust inflammatory response after 7 days of implantation, which achieved maximal level at 21 days, with formation of granulomas and areas of necrosis noted within the graft. (ii) Moderate fibroblast infiltration, collagen ingrowth, and neovascularisation. (iii) Moderate levels of encapsulation.

Mersilene was found to induce a higher inflammatory response compared to Prolene, which triggered a minimal inflammatory reaction [89].

Pierce et al. reported a long term study comparing biological and synthetic grafts implanted in rabbits. Polypropylene caused a milder inflammatory reaction with more long term, better host tissue incorporation compared to natural grafts [65]. Also Bazi et al. evaluated biopsies on the basis of inflammatory infiltrate, fibrosis, mast cell presence, muscular infiltration, and collagen filling of the mesh on an arbitrary scale described as low, moderate, or extensive based on H&E, periodic acid-Schiff, and toluidine blue staining of tissue. They agreed that all of the materials (Advantage, IVS, SPARC, and TVT) induced inflammation and collagen production, with SPARC being the one with the mildest response and TVT the one with the highest inflammatory response [76]. Elmer et al. reported an increase in macrophages and mast cell counts and a mild but persistent foreign body response to polypropylene meshes [91]. This study is consistent with other reported investigations where the polypropylene meshes are invaded with both macrophages and leukocytes, signs of inflammation, resulting in collagen production [27, 38, 65, 76, 83, 85].

In summary the studies agree that polypropylene meshes provoke a fairly pronounced inflammation, leading to a massive cell infiltration into the scaffold and ultimately to collagen production [27, 29, 48, 76, 83, 84, 86, 90–92].

4. Relating Postimplantation Changes to Clinical Outcomes

4.1. Biomechanics. In general, when biological materials fail this is due to enzymatic degradation after implantation, leading to a loss of mechanical support and weakening of the repair. This appears to apply particularly to the non-cross-linked xenogenic matrices. Chemically cross-linking appears to prevent this degradation and improve the mechanical outcomes. Unfortunately there is a lack of clinical evidence on how these mechanical outcomes translate into patient outcomes. Autologous grafts are the most successful biological material used in contemporary practice and the studies reviewed appear to support the long term mechanical integrity of these grafts. Nevertheless, they present several important limitations that are related to the need to harvest from a donor site. However use of cadaveric tissues avoids these limitations; however their quality depends on the age and comorbidities of the donor and this is maybe the reason for the mixed results in mechanical properties. This is consistent with the available clinical studies which suggest that allografts have poorer cure rates than autologous grafts.

We have found that polypropylene maintains its morphology and strength after implantation for up to 24 weeks [35, 74, 76]. However there was evidence that stiffness increases [77, 93]. This is consistent with durable cure rates particularly in SUI surgery (there is still some question regarding efficacy of transvaginal POP repair, compared with native tissue repair). The major issue with polypropylene meshes is the associated serious complications, in particular vaginal or urinary tract exposure (up to 10–14%). There is some evidence that meshes with greater stiffness cause the surrounding tissue to weaken, an effect termed stress shielding [94]. This can be compared to the effect of metal implants on the surrounding bone after orthopedic surgery. This effect could lead to thinning of the surrounding vaginal tissues as predisposing to erosion.

4.2. Host Response. Biomaterials implanted into the body will always attract the attention of the immune system. With some materials there is an M1 macrophage response of constructive remodeling; this appears to be the case with some biological matrices, SIS in particular. With materials which the body cannot remodel or integrate such as polypropylene meshes, the macrophage response is much more aggressive, an M2 macrophage response [95, 96].

It appears that a state of constant inflammation can be generated by some patients in response to some of these nondegradable materials. Constant inflammation leads to an upregulation of degradative enzymes; although these enzymes cannot degrade the material, they may damage the surrounding extracellular matrix and contribute to tissue thinning and mesh exposure. Moreover perpetuation of the inflammatory response can also result in activated fibroblasts, which produce excessive collagen laid down in a disorganized fashion around the implant (i.e., fibrosis), encapsulating the material. A small amount of fibrosis is arguably advantageous to the repair in SUI, providing a stable back stop allowing urethral compression. However excessive fibrosis may lead to mesh contraction resulting in increased pull on the adjacent tissues leading to complications such as voiding dysfunction, pain, and painful intercourse. In POP this excessive fibrotic response can lead to mesh exposure which presents a major reconstructive surgical challenge, often necessitating repeat

Table 4: Xenografts.

Author	Sample	Biomechanical properties	Host response
Badylak et al., 2001 [52]	Abdominal wall defect repaired with SIS in 40 dogs randomized into 8 survival groups (1, 4, 7, and 10 days and 1, 3, 6, and 24 months).	Strength was decreased from day 1 to day 10 after implantation, followed by a progressive increase, until reaching double of the original strength 24 months after implantation.	Rapid degradation with associated and subsequent host remodeling.
Badylak et al., 2002 [55]	Abdominal wall defect repaired with SIS in 10 dogs and 30 rats, both randomized into 4 survival groups (1 week, 1 month, 3 months, 6 months, and 2 years).		(i) No shrinkage or expansion of the graft site over the 2-year period of the study. (ii) One week after implantation, abundant levels of polymorphonuclear leukocytes diminished to negligible after 1 month. (iii) Moderate neovascularization. (iv) By 3 months, graft material was not recognizable and was replaced by moderately well-organized host tissues including collagenous connective tissue, adipose tissue, and skeletal muscle.
Cole et al., 2003 [60]	SIS removed from a 42-year-old female patient 4 months after pubovaginal implantation of the sling due to severe obstruction.		(i) Completely intact acellular sling. (ii) Well defined fibrous capsule. (iii) Chronic inflammatory response.
Zhang et al., 2003 [51]	SIS implanted in the abdominal wall of rats for up to 2 months.	SIS together with the abdominal wall has increased strength.	Levels of interleukin 2 and interleukin 6 were high straight after the operation but they become normal after 2 months.
Wiedemann and Otto, 2004 [56]	Biopsies taken from the implantation site of the SIS band under the vaginal mucosa from 3 patients during reoperation, at a mean of 12.7 months, after pubourethral sling procedures due to recurrent urinary stress incontinence.		(i) Focal residues of SIS implant. (ii) No evidence of a specific tissue reaction that might point to a foreign body reaction. (iii) No evidence of any significant immunological reaction and in particular no evidence of any chronic inflammatory reaction.
Konstantinovic et al., 2005 [50]	Abdominal wall defect repaired with SIS in 24 Wistar rats randomized into 4 survival groups (7, 14, 30, and 90 days).	Significant increase of biomechanical properties after 90 days of implantation.	(i) Moderate acute inflammatory response at day 7, decreased to minimal after 90 days. (ii) Moderate neovascularization. (iii) Abundant collagen deposition well organized after 90 days.
Macleod et al., 2005 [62]	SIS and cross-linked porcine dermis (Permacol) implanted subcutaneously on the anterior rectus fascia of 18 rats each randomized into 5 survival groups (1, 2, 4, 10, and 20 weeks).		For both grafts: (i) absent acute inflammatory response, (ii) from moderate chronic inflammation after 1 week of implantation to minimal after 20 weeks, (iii) absent eosinophilic infiltration and stromal fibroblastic reaction over the entire implantation, (iv) from moderate fibrosis and vascularity around the grafts after 1 week of implantation to minimal after 20 weeks.
Poulose et al., 2005 [57]	12 female pigs were implanted with SIS intraperitoneally for up to 6 weeks.		(i) Cell infiltration. (ii) Vascularization. (iii) Collagen deposition and remodelling.
Thiel et al., 2005 [58]	SIS implanted subcutaneously on the abdominal wall of 30 rats randomized into 3 survival groups (7, 30, and 90 days).		(i) Moderate inflammatory reaction increased to severe after 90 days. (ii) 86% of the graft was replaced by new collagen fibers.

Table 4: Continued.

Author	Sample	Biomechanical properties	Host response
Krambeck et al., 2006 [26]	SIS and porcine dermis implanted subcutaneously on the anterior rectus fascia of 10 rabbits randomized into 2 survival groups (6 and 12 weeks).		(i) Porcine dermis presented moderate fibrosis which was minimal for SIS. (ii) Minimal degree of scar for both grafts and high degree of inflammatory infiltrate.
Ko et al., 2006 [54]	Abdominal wall defect repaired with 8-layer SIS in 20 domestic pigs randomized into 2 survival groups (1 and 4 months).	No significant changes of biomechanical properties after 4 months of implantation.	(i) Dense fibrous connective tissue ingrowth. (ii) Minimal to mild mononuclear inflammatory cell infiltrate throughout the connective tissue.
Hilger et al., 2006 [20]	Porcine dermis implanted in 20 rabbits randomized into 2 survival groups (6 and 12 weeks). Half implanted on the rectus fascia and half on the posterior vagina fascia.	Very significant decrease of biomechanical properties after 12 weeks of implantation.	(i) Two missing or fragmented materials 12 weeks after being implanted on the vagina. (ii) Moderate to strong inflammatory response. (iii) Minimal collagen ingrowth without significant cell infiltration. (iv) Minimal neovascularization.
Kim et al., 2007 [59]	SIS implanted in the subcutaneous dorsum of 3 rats sacrificed after 2 weeks.		(i) Prominent infiltration and ingrowth of host cells. (ii) Few macrophages infiltrated or accumulated around the grafts.
Rauth et al., 2007 [63]	SIS implanted on the peritoneal surface of the abdominal wall of 6 pigs sacrificed 8 weeks after implantation.		(i) 80% of contraction from original surface area. (ii) Moderate neovascularization. (iii) Densely populated by host cells with moderate amounts of new disorganized collagen deposition.
Woodruff et al., 2008 [27]	Porcine dermis slings explanted after revision from 4 women, due to different complications, between 2 and 65 months after implantation.		(i) Severe encapsulation. (ii) No degradation. (iii) No fibroblasts infiltration and neovascularization.
Sandor et al., 2008 [64]	Abdominal wall defect repaired with SIS and cross-linked porcine dermis (Permacol) in 33 primates randomized into 3 survival groups (1, 3, and 6 months).		(i) Considerable contraction after 1 month for both materials, but not significant change over the next 5 months. (ii) Better integration of both materials at late stage by scar formation. (iii) Inflammatory cells infiltration 3 months after implantation for SIS associated with formation of few blood vessels. (iv) Acellular porcine dermis over the entire course implantation with substantial inflammation surrounding their perimeter. (v) Partial resorption for both materials after 6 months.
Pierce et al., 2009 [65]	Cross-linked porcine dermis implanted on the abdominal wall and posterior vagina of 18 rabbits sacrificed 9 months after implantation.	11 grafts remained intact without significant changes of biomechanical properties compared to the baseline values. They were just thicker and tolerated with less elongation at failure. Seven grafts were partially degraded but thicker again and with significant decrease of all biomechanical properties.	(i) Host connective tissue incorporation between fibers. (ii) Intense foreign body reaction in degraded grafts.

Table 4: Continued.

Author	Sample	Biomechanical properties	Host response
VandeVord et al., 2010 [39]	SIS and porcine dermis implanted in 16 rats, respectively, and both randomized into 4 survival groups (2, 4, 8, and 12 weeks). Implantation around the bladder neck, anchored to the surrounding tissues.		(i) Thin fibrous capsule formation. (ii) Moderate cell infiltration and angiogenesis for SIS and minimal for porcine dermis.
Rice et al., 2010 [36]	Abdominal wall defect repair with SIS (Surgisis) in 18 rats randomized into 2 survival groups (30 and 60 days).	Increase of tensile strength after 30 days and, increase of tensile strength after 60 days, respectively, to 30 days.	(i) Moderate amounts of collagen deposition well organized. (ii) Abundant revascularization.
Deprest et al., 2010 [61]	13 patients underwent secondary sacrocolpopexy because of a graft related complication after the initial sacrocolpopexy with porcine dermal collagen (Pelvicol) (9) or SIS (Surgisis) (4).		(i) Pelvicol presented high degradation rates associated with no foreign body reaction. (ii) Pelvicol remnants were integrated into collagen rich connective tissue with limited neovascularization (scar host tissue). (iii) No significant body foreign reaction to Surgisis grafts. (iv) Surgisis no longer recognizable replaced by irregularly organized connective tissue and fat tissue.
Liu et al., 2011 [49]	Abdominal wall defect repaired with SIS and acellular porcine dermal matrix in 50 Sprague Dawley rats randomized into 5 survival groups (1, 2, 4, 8, and 12 weeks).	After initial decrease of biomechanical properties at week 2, these were increased over the next 10 weeks reaching similar values to week 1.	(i) Pronounced inflammatory response 1 to 4 weeks after implantation for SIS compared with porcine dermis, but falling to similar negligible values for both after 12 weeks. (ii) Large neovascularization and collagen deposition, which was higher for SIS group. (iii) SIS implants degraded more quickly and were almost totally replaced by organized collagenous tissues. (iv) Contraction at the first weeks leading to significant lower surface area in both materials.
Jenkins et al., 2011 [53]	Abdominal wall defect repaired with porcine dermal matrix in 24 Yucatan minipigs randomized into 2 survival groups (1 and 6 months).	Significantly greater incorporation strengths after 6 months compared with 1 month.	(i) Moderate cell infiltration. (ii) Moderate extracellular matrix deposition. (iii) Moderate neovascularisation. (iv) Partial degradation and from widely to mild fibrous encapsulation.
Kolb et al., 2012 [40]	Cross-linked porcine dermis (Permacol) implanted subcutaneously in 5 pigs randomized into 4 survival groups (7, 21, 90, and 180 days).		(i) Mild inflammatory response decreased to minimal from day 7 to day 180 after implantation. (ii) None to minimal neovascularization after 180 days. (iii) Small amount of residual SIS remained surrounded by mild to moderate chronic inflammation. (iv) Moderate levels of encapsulation.
Daly et al., 2012 [66]	Abdominal wall defect repaired with porcine dermis in rats randomized into 3 survival groups (1, 3, and 35 days).		(i) Cell infiltrates into all grafts by day 35. (ii) Degradation of the scaffold most pronounced at the periphery with fibrous tissue, angiogenesis, and foreign body giant cells noted. (iii) Grafts surrounded by a dense and circumferentially organized connective tissue. (iv) Mononuclear cells decreased in number compared with earlier time points.

Table 5: Polypropylene meshes.

Author	Sample	Biomechanical properties	Host response
Falconer et al., 2001 [89]	16 women were implanted with TVT for up to 2 years: 6 with Mersilene and 10 with Prolene.		Mersilene induces higher inflammatory response than Prolene. Mersilene is easier to extract than Prolene.
Klinge et al., 2002 [80]	Heavy weight monofilament with small pore size (HWM) and low weight with large pore size multifilament (LWM) on the posterior abdominal wall of rats for 7, 14, 21, and 90 days.		(i) HWM: intense inflammation, embedded in connective tissue. (ii) LWM: less pronounced inflammatory response and fibrotic capsule, with collagen distributed within the mesh.
Wang et al., 2004 [90]	17 women with sling erosion and 7 women with voiding difficulties implanted with TVT and SPARC.		Pronounced fibrosis around the fibers—erosion and voiding difficulty as a result.
Rabah et al., 2004 [84]	Implantation of Surgipro and cadaveric fascia lata in rabbit's bladder neck for 6 and 12 weeks.		(i) Cadaveric fascia lata group: the implant was incorporated in a plate of fibrous tissue. (ii) Polypropylene mesh: inflammation localized on the graft.
Spiess et al., 2004 [35]	TVT and cadaveric fascia lata implanted in abdominal wall of rats for 6 and 12 weeks.	TVT has the greater break load and the maximum average load compared to cadaveric fascia lata.	
Zheng et al., 2004 [81]	Prolene and Pelvicol implanted in full thickness abdominal wall defects in rats for 7, 14, 30, and 90 days.		Prolene prosthesis shows the presence of leukocytes in the activated state.
Konstantinovic et al., 2005 [50]	Marlex and non-cross-linked Surgisis implanted on the anterior abdominal wall of rats for 7, 14, 30, and 90 days.		(i) Marlex: more pronounced inflammatory reaction and vascularization throughout the graft than Surgisis (ii) Surgisis: milder inflammatory reaction.
Yildirim et al., 2005 [38]	Gynecare TVT, SPARC, polypropylene mesh, and IVS implanted in contact with the rats rectus muscle for up to 30 days.		Inflammation and fibrosis are decreased in large pore meshes.
Thiel et al., 2005 [58]	Monofilament polypropylene mesh, silicone mesh, SIS, and PLA were implanted subcutaneously on the abdomen of rats for 7, 30, and 90 days.		Polypropylene induces the mildest inflammatory response among the samples.
Bogusiewicz et al., 2006 [83]	Monofilament TVT and multifilament IVS were implanted in rats rectus fascia for 42 days.		(i) They induce production of similar amount of collagen. (ii) Differences in the arrangement of collagen and inflammation intensity.
Boulanger et al., 2006 [87]	Vicryl, Vypro, Prolene, Prolene Soft, and Mersuture were implanted in pigs peritoneum for 10 weeks.		(i) Vicryl: low level of inflammation and completely absorbed. (ii) Vypro: intense inflammation and strong fibrotic response. (iii) Prolene and Prolene Soft: well integrated, weak inflammatory response. (iv) Mersuture: no good integration.
Krambeck et al., 2006 [26]	SPARC mesh, human cadaveric fascia, porcine dermis, SIS, and autologous fascia were implanted in rabbits rectus fascia for 12 weeks.		(i) Polypropylene mesh has the greatest scar formation. (ii) Polypropylene has the mildest inflammatory response.
Boukerrou et al., 2007 [75]	Preperitoneal implantation of Vicryl, Vypro, Prolene, Prolene Soft, and Mersuture mesh for 2 months in pigs.	Nonabsorbable, monofilamentous, macroporous materials (type I) seem more resistant, retract less, and have the best tolerance.	.

Table 5: Continued.

Author	Sample	Biomechanical properties	Host response
Spelzini et al., 2007 [82]	Polypropylene type I mesh and macroporous silk construct were implanted in rat fascial defects for 7, 14, 30, and 90 days.		Polypropylene meshes induce a moderate inflammatory response and not architectural degradation.
Zorn et al., 2007 [74]	Rat abdominal wall was implanted with SPARC, TVT, and SIS for 6 weeks and 9, 6, 9, and 12 months.	TVT has tensile properties similar to SPARC and they are superior to Stratasis.	
Bazi et al., 2007 [76]	Rats rectus fascia was implanted with Advantage, IVS, SPARC, and TVT for up to 24 weeks.	They all show similar mechanical properties after removal.	They induce different host responses due to different porosity.
Tayrac et al., 2007	Ewes vaginas were implanted with a noncoated LW polypropylene mesh (Soft Prolene) and a coated one (Ugytex) from 1 to 12 weeks.		Similar inflammatory response between the two materials.
Huffaker et al., 2008 [86]	Rabbits vaginas were implanted with Pelvitex (collagen-coated) and Gynemesh (uncoated polypropylene meshes) for up to 12 weeks.		Both materials induce a mild foreign body reaction with minimal fibrosis.
Woodruff et al., 2008 [27]	24 grafts were explanted in women undergoing sling revision after 2–34 months. Grafts were polypropylene meshes, autologous fascia, porcine dermis, and cadaveric dermis.		No evidence of degradation or encapsulation, abundant host infiltration. Neovascularisation was visible.
Elmer et al., 2009 [91]	Prolift was implanted in humans for 1 year.		(i) Increase in macrophages and mast cells count. (ii) Mild but persistent foreign body response.
Pierce et al., 2009 [65]	Polypropylene mesh versus cross-linked porcine dermis implanted in rabbits vagina and abdomen for 9 months.		Polypropylene caused milder inflammatory reaction, more long term, good host tissue incorporation.
Melman et al., 2011 [77]	Bard mesh (HWPP), Ultrapro (LWPP), and GORE INFINIT Mesh (ePTFE) in minipigs hernia repair for 1, 3, and 5 months.	Their maximum tensile strength decreases for all of them.	(i) Inflammation decreases with time. (ii) Cell infiltration increases with time.
Pascual et al., 2012 [85]	Surgipro, Optilene, and GORE INFINIT Mesh (ePTFE) were implanted in rabbits abdominal wall defect for 14 days.	LWPP implants might be improved by the newly formed tissue around it.	(i) PTFE induces an increased macrophage response when compared to polypropylene. (ii) Increase in collagen deposition in high porosity meshes.
Manodoro et al., 2013 [78]	Gynemesh in two sizes (50 × 50 mm and 35 × 35 mm) implanted in 20 adult ewes for 60 and 90 days, both on the abdominal and vaginal walls.	Implants were contracting more when implanted on the vaginal wall, compared to abdominal wall. Grafts implanted on the vaginal wall are stiffer than the ones implanted on the abdominal wall, after retrieval.	(i) 30% of the 50 × 50 meshes caused vaginal erosion and exposure. (ii) 60% of the 35 × 35 meshes had reduced surface (i.e., contracting after 90 days.)

HWPP: heavy weight polypropylene.
LWPP: lightweight polypropylene (also called *soft*); ePTFE: expanded polytetrafluoroethylene; PLGA: polylactide-co-glycolide acid; PLA: polylactide acid; PGA: polyglycolide acid.

procedures with no guarantee of symptom resolution. Nevertheless with the observation that the vast majority of patients do well with mesh, it can be concluded that some degree of fibrosis is helpful to the surgical management whereas clearly excessive fibrosis is detrimental.

Implantation of autologous fascia in general showed good integration within host tissues, associated with a low inflammatory response, compared to polypropylene meshes and degree of graft remodelling in the available human studies [50, 84]. It must be borne in mind that the human studies were all reoperative cases for clinical failure. It is difficult to speculate on whether all successful outcomes result in fully integrated and remodelled graft. Non-cross-linked xenografts are associated with clinical failure due to rapid degradation which is presumably too soon for the regeneration of strong tissues in its place [20, 24, 29]. The cross-linked grafts avoid this but rather similar to the synthetic mesh are associated with a perpetuated inflammatory response as the body is unable to integrate and remodel them. This ultimately leads to encapsulation of the graft. It would therefore seem appropriate that there should be a proper balance of degradation and replacement by new host tissue with xenografts. SIS appears to fulfill this.

This relationship between grafts and host tissues will vary for different materials and with different individuals. Here it is worth noting that as many as 15% of the population are allergic to nickel and more than 80% can become sensitized to nickel on sustained exposure [97] and that there are very successful studies involving muscle regeneration using decellularized ECM [98]. Therefore, it is clear that the immune response to any foreign material is complex, dynamic, and patient specific. The fact that polypropylene meshes provoke little adverse reaction when implanted in the abdominal wall for hernia repair but are associated with complications in the pelvic floor may also suggest a site-specific host response notwithstanding the differences in biomechanical aspects [99]. This contrasting response has been confirmed in ewes [78], therefore the need for relevant animal models for longer studies [100].

5. Perspective on the Ideal Material

Whilst authors have previously described paradigms of the ideal material, we suggest that these have been unrealistic [101]. Ultimately a permanent material will always cause complications in some patients due to variation in individual immune responses. Conversely degradable materials will fail in some patients. The question is which is least desirable? Whilst recurrent symptoms can always be treated by corrective surgery, the complications of polypropylene mesh such as chronic pain have proven resistant to treatment in many cases. Thus we suggest that materials for this application should be degradable based on the principle of least harm. With this in mind, it is essential that the degradability is tuned so that it allows enough time for the development of a neotissue that is able to mechanically support the pelvic organs. A material that does not cause any inflammation is unrealistic and probably undesirable as an initial inflammatory response is required to promote angiogenesis and collagen ingrowth, integrating the material. This is essentially an M1 macrophage response. For this to happen, the material should be readily permeable to host cells. On a practical level any material for this application needs to be robust to withstand surgical handling and provide support at the point of insertion. We suggest that a more realistic material for this application would be the one that

(i) is degradable,

(ii) provokes an acute inflammatory response,

(iii) undergoes tissue remodeling,

(iv) is permeable to cells,

(v) is mechanically robust at point of implantation.

6. Conclusion and Future Perspective

The clinical experience suggests that both synthetic and biological materials can provide successful outcomes when used in the surgical management of pelvic floor disorders. However, it has become clear that there is an incidence of significant complications of polypropylene meshes and that many surgeons do not consider the complication rate acceptable. Both the host response and the mechanical properties of the materials need to be taken into consideration to predict success of the implants, in addition to their response to dynamic loading. There has clearly been a lack of adequate preclinical evaluation with polypropylene mesh and we suggest several steps which may make the development for new materials an altogether safer endeavor:

(i) a better understanding of the forces within the pelvic floor, whose materials need to cope with when implanted;

(ii) computational modeling of how materials might perform under load for many years (this can be achieved using *in virtuo* models once established);

(iii) the investigation of immune responses in patients in whom materials perform well over many years versus patients in whom they cause severe complications (using biochemical markers, genomic markers, and non-invasive imaging);

(iv) the development of better animal models that develop the complications associated with vaginal mesh use such as exposure;

(v) establishment of standardized criteria to evaluate the performance of materials in *in vivo* and *in vitro* studies so that they can be accurately compared.

There are several other factors which require urgent attention but are beyond the scope of this review. Surgical expertise based on training and experience in reconstructive surgery is a key factor in outcomes of pelvic floor procedures and there is a need to ensure that surgeons are adequately trained. Patient specific issues, such as individual anatomy and tissue strength, could also impact outcomes and further investigation remains necessary to assess these aspects and their role in determining outcome [102]. Although databases

to track complication rates exist, such as MAUDE and Postmarket Surveillance Studies, the medical community needs to participate more fully in these databases in order to more critically audit patient outcomes and move forward.

Ultimately to develop new effective and safe materials there is a need for a multidisciplinary approach that combines the efforts of those working in regenerative medicine, biomaterials, and surgery.

Disclosure

Professor Chris Chapple is a consultant for AMS, Allergan, Astellas, Lilly, ONO, Pfizer, and Recordati. He is also a researcher, speaker, and trial participant for Allergan, Astellas, Pfizer, and Recordati. All the other authors have nothing to disclose.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Complications following Tension-Free Vaginal Tapes: Accurate Diagnosis and Complications Management

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The sling procedures are the gold standard for SUI treatment. They are highly effective but not free from complications. The most common adverse effect for the surgery with the implant insertion is: overactive bladder occurring de novo after the surgery, voiding dysfunctions, urine retention, and unsatisfactory treatment outcome. The most important question that arises after 20 years of sling procedures is how to manage the complications and what can be offered to complicated patients. The above review summarises the ultrasound findings in complicated cases and shows the scheme of management of the clinical problems concerning the tape location in suburethral region.

1. Introduction

Ultrasound examination of the lower urinary tract has been established within urogynaecology as a simple, prompt, reproducible, and dynamic diagnostic procedure [1–5]. Compared to other methods, ultrasound imaging provides more accurate and perfect visualisation of both anatomy of lower urinary tract and dynamic changes in bladder neck mobility during functional tests (Valsalva manoeuvre, cough test) as well as visualisation of synthetic implants. Without radiation exposure, it offers images that are comparable with X-ray methods [6, 7]. Compared with the time and cost consuming functional MRI, ultrasound examination offers advantages because of the simple demonstration in previously mentioned areas. Moreover, the costs and learning curve are the arguments for choosing this method for the first line diagnosis in urogynaecology [8].

Nowadays ultrasound has become one of the most essential diagnostic methods in urogynaecology [4]. Perineal and introitus ultrasonography are two standardised methods, which have been available for years and are already well established [4, 5].

The above methods differ from each other by transducer and probe placement.

The linear or curved array probe is used in perineal sonography and is placed on the perineal and vaginal area [4, 7]. The advantage of perineal ultrasound examination is the short learning curve. With low ultrasound frequency and a large angle of reflection it provides a wide view of the pelvis. Without a doubt, this device setup allows a view that at the beginning often confirms the initial preliminary diagnosis. The large angle of reflection is however coherent with a lower image frequency. This can be problematic when addressing specific issues such as transient, short-term funneling of the urethra.

In the introitus ultrasound examination used for diagnostic of bladder function, a vaginal transducer is positioned in the introitus area over the meatus urethrae externus, thereby ensuring that the direction of the probe axis is strictly orthograde to the patient's body axis imaging performed in both the resting and contraction of the pelvic muscles. The probe should not be inserted into the vagina in order to avoid artificial dislocation of the cystourethral region. This orthograde positioning of the ultrasound transducer is

crucial for correct location of the bladder neck (level reading H and distance D), descensus type of the urethrae, and lower base of the bladder/bladder floor (vertical descensus of the urethrae, rotatory descensus of the urethrae, mixed forms of the urethra descensus, and central cystocele). The introitus ultrasonography positions itself between vaginal and perineal one [9]. Further advantages of introitus ultrasonography include the improved resolution of the high frequent vaginal transducer and the possibility to carry out an urodynamic measurement during the same examination.

Both ultrasonographic procedures are standardised and deliver reproducible results. They were developed for the anatomical analysis of the urethra-bladder region within the framework of advanced urinary incontinence diagnosis [3, 7, 9].

The urogynaecological examination must include the separate analysis of all compartments including both the incontinence and the possible incidence of pelvic organ prolapse in order to confirm a clinical suspected diagnosis. When the standard perineal and standard introitus ultrasonography is used, the anterior compartment could be clarified.

However, as we know from our daily practice, the anatomical defect of one compartment can positively or negatively influence the function of another parameter; for example, kinking of the urethra, large cystocele, or a rectoenterocele may lead to a voiding disorder, to an overflow incontinence or masked stress urinary incontinence.

The individual compartments of the pelvis must be objectively visualised with an imaging method in order to better understand the pathomorphological abnormalities of the pelvic organs and to achieve the optimal treatment approach. Furthermore the pelvic floor ultrasound examination can lead to a new ultrasound concept, whereby the introitus/vaginal/endoanal and abdominal ultrasonography in both 2D and 3D techniques can be combined in one investigation procedure [10].

In contrast with the already established standard ultrasonography techniques such as perineal and introitus ultrasonography, the two-dimensional pelvic floor ultrasound examination enables a real-time, static, and dynamic imaging with easy transition of the pelvic compartments in three views: sagittal, frontal, and axial planes.

Compared with the standard ultrasonography, the vaginal transducer probe can be used for both vaginal and consecutive introitus ultrasonography, delivering a new dimension of diagnostic possibilities.

Moreover the PF (pelvic floor) ultrasonography offers the adequate conditions to monitor the position and function of the tension-free vaginal sling [11–15].

2. Implants Visualisation in Pelvic Floor Ultrasound Examination and the Proposal of Complications Management

Four parameters can be used to evaluate a tape position.

(A) Sagittal Plane

(1) *The position (L)* of the sling is in relation to the length of the urethra (at rest).

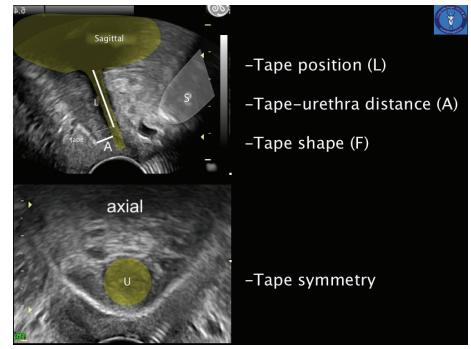

Figure 1: Pelvic floor-ultrasound images in a sagittal plane (above) and axial plane (below). S: symphysis pubis, U: urethra, L: tape position in relation to the urethra length, and A: shortest distance of the tape from the LSM complex of the urethra.

The optimal position of the tape is the distal one-third of the urethral length for TVT-procedure in the middle part of the urethra length for TOT-procedure [16].

(2) *The distance (A)* of the sling to the LSM complex (longitudinal smooth muscle complex) of the urethra is optimal between 3 and 5 mm [16].

(3) *The shape (F)* of the sling: parallel to the urethra, smoothly stretched, without the horseshoe shaped bending. During Valsalva maneuver a bending indicates a usage of the elastic reserve of the implant. The above confirms a good "tape functionality."

(B) Frontal or Axial Plane

(4) *The symmetry (S)* of the sling: no lateral contact or compression of the urethra.

Criteria to evaluate a tension-free vaginal sling and orthotropic tape position are presented in Figure 1.

We consider it particularly important to evaluate the sling position in the first postoperative days. Between the first and seventh postoperative day (*early complications*) it is possible to do the necessary corrections and in most cases it is possible to preserve the sling. Addressing a failed position of the sling at a later stage (*late complications*) results in the removal of the implant and after a successful healing period it is possible to reinsert a new sling.

2.1. Early Complications (<7 Days). The most common complications are voiding disorders or urge complaints [17–20]. The pivotal question is whether the problem results from a failed position of the implant or if there is another cause of the problem. The most common clinical presentation is cystitis, postoperative swelling of the tissues, a hematoma, or incorrect micturition.

The ultrasonography evaluation of a well-positioned sling provides certainty that a success of conservative therapy can be expected.

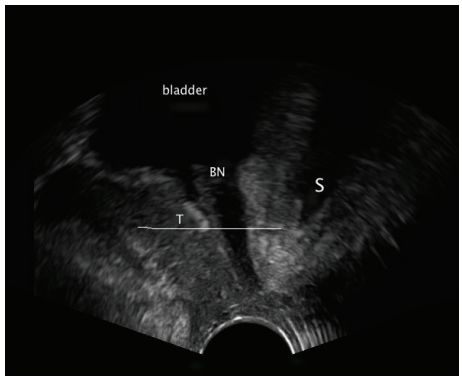

Figure 2: Pelvic floor ultrasound examination in sagittal plane. S: symphysis pubis and BN: bladder neck. The sling lies above the middle part of the urethra.

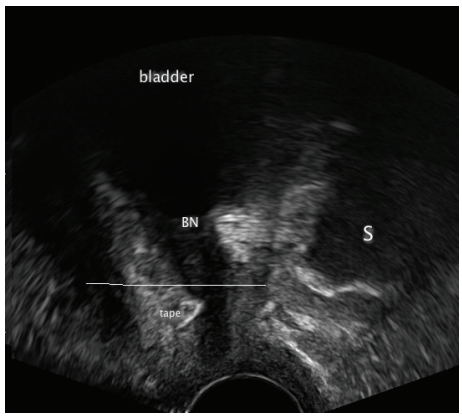

Figure 3: Pelvic floor ultrasound examination in sagittal plane. S: symphysis pubis and BN: bladder neck. The sling lies below the middle part of the urethra.

In case of a dystopic position of the implant the first step is to evaluate the sling location and to decide whether or not the band can be saved.

For teaching purposes the urethra can be halved and a dystopic sling position is divided into two groups.

(i) A high position of the implant: the middle of the sling (at rest) lies in the proximal half of the urethra. In this case there is no possibility to preserve the implant as the change of its location is impossible (Figure 2).

As it was mentioned above the implant placed in high failed position cannot be corrected; therefore it should be removed and following a healing phase, a new sling insertion may be planned and carried out.

(ii) A low position of the sling: the middle of the implant lies in the distal part of the urethra. In this case there is a possibility of sling preservation (Figure 3).

In the case of a *low faulty position*, for example, a too narrow sling position, lateral compression of the urethra, tethered tape, or dystopic position resulting from a hematoma-early correction of the sling position is usually successful.

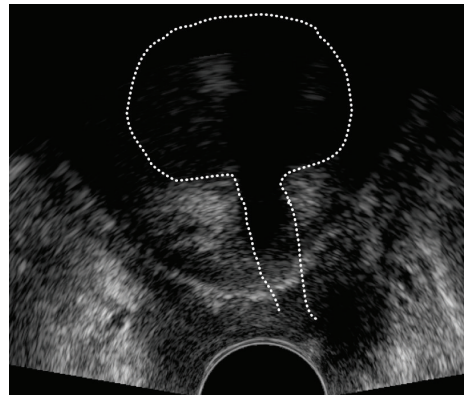

Figure 4: Pelvic floor ultrasound examination in frontal plane. Asymmetric sling position. On the right hand side of the picture the distance of the sling to the LSM complex is much shorter than on the left hand side. A loosening of the implant on the right hand side should be undertaken.

(1) If the sling is too close to the LSM complex (the distance < 3 mm) it is possible in the first seven postoperative days to loosen the implant by drawing on one of the sides preferably high with a Overholt clamp to avoid in particular suburethral damage of the band structure [21] (Figure 3).

(2) In order to decide which side to draw on, it is necessary to evaluate the symmetry of the sling on the frontal and axial plane and then to evaluate the narrow or rather the urethra proximal side and then to loosen accordingly (Figure 4).

(3) If the sling has been accidentally fixed with a vaginal suture, this presents a picture of a primary "tethered tape." With physical exertion such as coughing the patient remains continent. However because the band is adhered to the vagina when the body posture is adjusted, for example, when standing up, this can result in the opening of the urethra and lead to subsequent urine loss. Appropriate plying of the sling from the adhesion will immediately solve the problem and also preserve the implant [22] (Figure 5).

(4) If a hematoma is displacing the sling or compromising the urethra conservative treatment will be successful (Figure 6).

2.2. Late Complications (>7 Days). In case of late complications occurring due to high faulty location of the sling, the vaginal part of the implant should be removed. A suburethral splitting alone is not sufficient.

In a narrow sling position, where the implant is close to the musculus sphincter urethrae externus, a suburethral sling splitting will loosen the sling but the continued fixed urethral muscle to the lateral sling ends can still irritate the urethra even at rest. OAB or draw on the urethra when the body is under strain can lead to urge or urine loss (Figure 7).

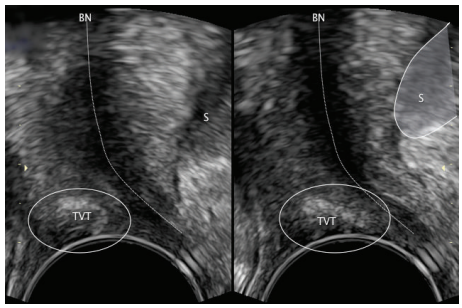

Figure 5: Pelvic floor ultrasound examination in sagittal plane. Shape changes of the sling with a vaginal probe, a typical pathognomonic ultrasound sign for tethered tape. S: symphysis pubis, BH: bladder neck, and TVT: band.

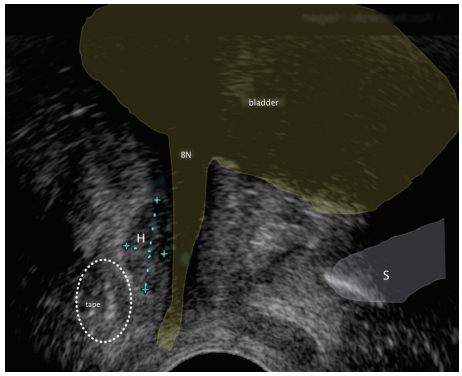

Figure 6: Pelvic floor ultrasound examination in sagittal plane. A small hematoma between TVT and the urethra leads to compression of the urethra and to transient voiding problems. No operative intervention is required. S: symphysis pubis, BN: bladder neck, and H: hematoma.

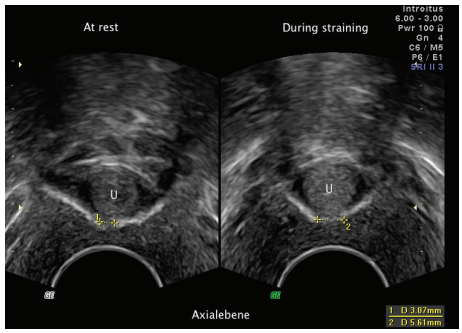

Figure 7: Pelvic floor ultrasound examination in axial plane. The sling was suburethrally split. Left: distance between both sling ends at rest. Right: during Valsalva manoeuvre.

The primary suburethral split and laterally suppressed implant ends are difficult to locate even with the help of an ultrasound. The removal is extremely difficult.

In *low faulty position of the sling*, loosening at a later stage as mentioned above is not an option. In most cases a partial implant removal should be performed vaginally (*collision phenomenon*) (Figure 8).

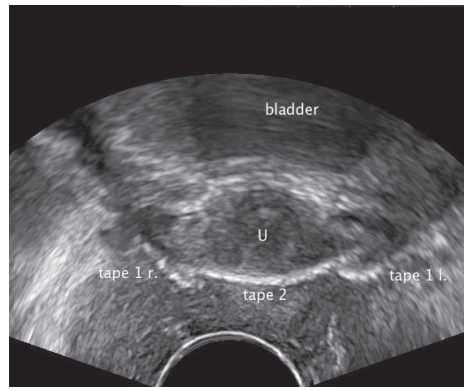

Figure 8: Pelvic floor ultrasound examination in axial plane. The sling was minimally removed vaginally. Both ends however lie still close to the urethra and disturb the second sling in its function: the so-called collision phenomenon. The patient is incontinent. Tape 1 r.: the right end of the first sling. Tape 1 l.: the left end of the first sling. Tape 2: the second sling.

Over 60% of patients have recurrent incontinence following a vaginal suburethral splitting. Removal of the sling ends at a later stage is almost impossible even with the support of interoperative PF-ultrasound examination. This is due to the fact that the implant can no longer be put under tension [23].

An exception is the repair of a low faulty positioned band, the so-called secondary "tethered tape." The overtime adhered sling to the vagina can be made responsible for the recurrent incontinence. A vaginal adhesiolysis with or without gathering of the implant can improve the function of a vaginal sling and make continence possible [22].

3. Conclusions

Therapy failure after tension-free sling insertion is rare due to the method. Almost always it is possible to identify, with PF-ultrasound examination, the cause and also to solve the problem. With these investigation techniques and the described guidelines for the management of complications we would like to encourage the search for sling failure and in doing so, we actively provide the affected patients with an improvement of their problem.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

High Structural Stability of Textile Implants Prevents Pore Collapse and Preserves Effective Porosity at Strain

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Reinforcement of tissues by use of textiles is encouraged by the reduced rate of recurrent tissue dehiscence but for the price of an inflammatory and fibrotic tissue reaction to the implant. The latter mainly is affected by the size of the pores, whereas only sufficiently large pores are effective in preventing a complete scar entrapment. Comparing two different sling implants (TVT and SIS), which are used for the treatment of urinary incontinence, we can demonstrate that the measurement of the effective porosity reveals considerable differences in the textile construction. Furthermore the changes of porosity after application of a tensile load can indicate a structural instability, favouring pore collapse at stress and questioning the use for purposes that are not "tension-free."

1. Introduction

Reinforcement of tissues by use of textile implants is increasingly used to improve the recurrence rates compared to unification of tissues just by sutures. However, at the occasion of revision operations it becomes apparent that the textile gets integrated into a tissue with more or less scar reaction. Whereas sometimes the implant is hardly palpable due to soft tissue reaction in other cases it was embedded in a thick and stiff scar plate. It is this excessive scar with consecutive contraction and thereby shrinkage of the mesh area that is related with most serious complications such as severe vaginal pain, dyspareunia, vaginal shortening, urethral obstruction, and SUI recurrence. Surgical intervention is often required to alleviate symptoms.

Scar formation can be stimulated by the trauma of surgery or by the presence of bacterial infection in the wound, but it can be stimulated by the implant as foreign body itself, even in the absence of excessive tissue damage or an infection. The local intensity of inflammatory and fibrotic tissue is significantly influenced by the configuration of the textile. In numerous studies it could be proven that the presence of large pores is mostly decisive for the quality of the tissue reaction [1].

The pore of a textile can be grasped as the area between filaments. Taking the area of the mesh fibre in comparison to the entire mesh area this results in a measurement for the "textile" porosity. However this measurement does not consider the geometry of the pores. High textile porosity can be achieved by many tiny pores (e.g., fleece) as well as few large pores. Whereas the textile porosity may be comparable the tissue reaction is not, as the latter is affected by the different contact surface and the different pore geometry. Only pores with a sufficient distance between the mesh fibres in all directions provide an area for recovery and local tissue regeneration in the centre. Correspondingly, small pore textiles even with less material but enhanced surface and lacking areas with sufficient distance to mesh fibres induce more inflammation than large pore materials made of more material of thicker monofilaments [2].

Small distances between fibres will result in linkage of foreign body reaction of opposite fibres and will promote filling the entire pore by scar, the so-called bridging. Experimental data showed that a critical minimum of a pore to

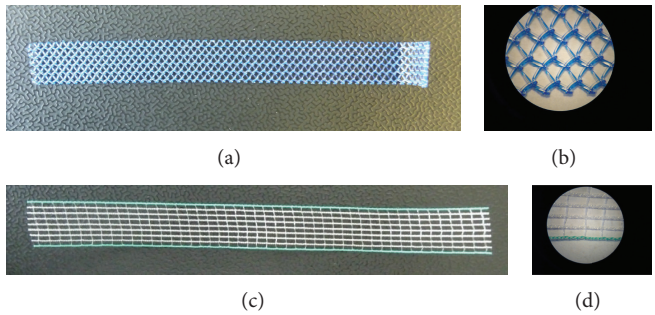


Figure 1: Sling device with the section being cut off for analysis. (a) TVT device textile part, (b) polypropylene filament and pore structure, (c) DynaMesh SIS soft textile part, and (d) PVDF filament and pore structure.

diameter to prevent bridging is about 1 mm [3]. The area of a textile with pores with a diameter of less than 1 mm is supposed to show bridging, whereas the pores with a diameter of more than 1 mm, the so-called effective pores, are supposed to not show scar tissue within the pores but fat tissue. Thus the "effective porosity" of a mesh reflects its risk to get entrapped into scar and thus reflects biocompatibility in regard to tissue integration [4, 5]. In case of substantial attenuation of the inflammatory stimulus of the polymer surface it is conceivable that even smaller pores may be filled by local physiological tissues instead of getting filled up just by scar fibrosis.

In the 60s textiles have been introduced as being used "tension-free" compared to the tension that results from sutures, without considering any subsequent deformation by mechanical stress. The concept of "tension free" may still be reasonable for many procedures and in many parts of the abdominal wall or the groin. But meanwhile textiles are used to reinforce muscle plates of the diaphragm or the pelvic floor in areas that are suspected to put considerable mechanical stress on the textile implants [6, 7]. Correspondingly the tensile load leads to an elongation of the textile, which mainly results from deformation of the pore geometry. At mechanical stress the pores become elongated and narrowed, thereby reducing the distance between filaments and the effective porosity and increasing the risk for scar entrapment.

Since the remarkable studies by Petros et al. in the 90s pelvic floor prolapse as well as urinary incontinence is treated by stabilizing the pelvic floor with textile implants, often configured as slings to reinforce or replace defective ligaments [8, 9].

In the following study we analysed at two textile implants currently used as reinforcement of the pubourethral ligament for treatment of stress urinary incontinence in women whether mechanical strain changes the textile and effective porosity and thereby the predicted risk for scar entrapment after tissue integration.

2. Material/Methods

The mesh used was either a TVT from Ethicon (810041BL), which is cut off from large meshes (Prolene mesh in the version before 1998) that are made as textile hosiery of polypropylene monofilaments, or a DynaMesh SIS soft made of PVDF by the FEG Textiltechnik, Aachen (Figure 1).

Figure 2: Experimental stand for the measurement of the effective porosity.

The porosity measurement system as described in [4] includes mesh fixing, position control, mesh illumination, camera system, control and evaluation unit, mechanical strain by weights, and evaluation software (Figure 2). For measurements without mechanical strain the mesh is fixed with magnets on an iron plate; for measurements with mechanical strain the mesh is fixed with clamps on both sides. The position control in two axes via step motors allows the selection of the measured part of the mesh. The mesh is illuminated from the back by a plane LED array with a diffusion glass. The camera system takes images from the top. Pixel resolution is $10\,\mu m \times 10\,\mu m$. During each measurement 6 images are taken. They are combined to one large image of the mesh. The evaluation is done by dedicated software named BKV-Standard, which is based on standard image processing tools. The image is converted into a black and white image via adaptive thresholds. Edge sharpening and noise reduction are done via digital filtering. Pores are detected and evaluated and finally the textile porosity and effective porosity of the mesh are determined. Due to the published experimental data a minimum distance between

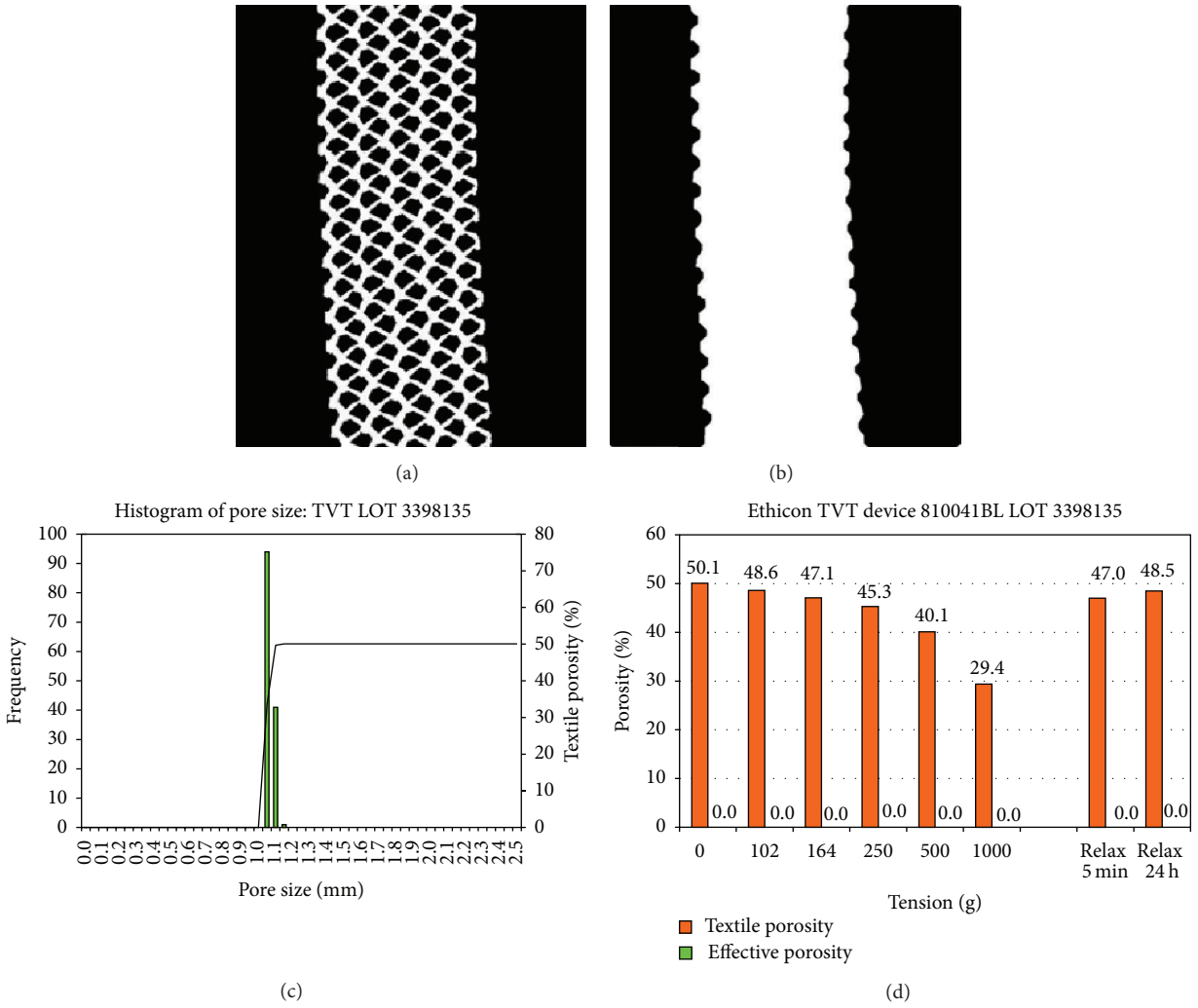


FIGURE 3: Image of TVT with (a) all pores, (b) effective pores, (c) pore frequency in dependency of pore size (estimated by simple square root of the pore area), and (d) textile and effective porosity at mechanical strain of up to 1000 g (8.9 N/cm).

filaments of 1000 μm for polypropylene and of 600 μm for PVDF meshes is set for the calculation of the effective pore areas and the effective porosity [3].

The results of the porosity evaluation are as follows:

(i) *textile* porosity (percentage of area not covered by fibres in relation to the mesh area, irrespective of the geometric form),

(ii) effective porosity (percentage of area that is filled only by sufficiently large (effective) pores in relation to the total mesh area),

(iii) histogram of pore sizes (derived from square root of the pore area),

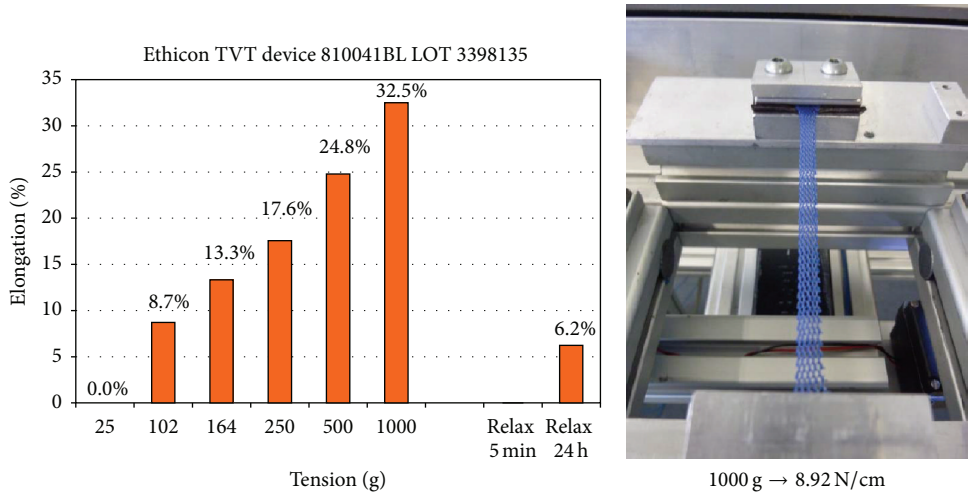
(iv) histogram of *effective* pore sizes (derived from square root of the effective pore area, which is the area of the pore that is big enough to contain a sphere with a diameter larger than the critical limit).

Additional result is the measured total length of the mesh between the clamps for the determination of the elongation under force.

The measurement system is periodically calibrated with a perforated metal plate and the results are compared with mechanical measurements to ensure reproducible and reliable results.

3. Results

3.1. Polypropylene Sling (TVT). The meshes are fixed with magnets on a metal plate without any forces applied. The textile porosity of the TVT is 50.1% whereas the effective porosity considering only large pores with a diameter of >1 mm to all sides is 0% (Figure 3). Due to the fact that several pores are just at the limit of 1000 μm distance between filaments, the determined value for the effective porosity could be dependent on the area, where the sample is measured, and is sensible to smaller changes in mesh production and sample handling.



(a) (b)

Figure 4: Elongation of the TVT at mechanical load as percent of original length (a) with macroscopic image (b).

Repetition of the measurements 5 times resulted in a mean value of 50.2% ± 0.24% for the textile porosity and 0.0% ± 0.0% for effective porosity and confirmed the reproducibility of the procedure. 24 h after release of the strain textile porosity recovers to 48.5%, but a slight elongation of 6.8% still persists.

Measurements with application of tensile forces of 0.9 to 8.9 N/cm at the TVT sling with the width of 11 mm led to a reduction of the textile porosity to 29.4% at a load of 8.9 N/cm, whereas the effective porosity always was 0%. This corresponds to an elongation of up to 32.5% due to deformation of pore geometry (Figure 4).

3.2. PVDF Sling (SIS). The textile porosity of the TVT is 66.7% whereas the effective porosity considering only large pores with a diameter of >0.6 mm to all sides is 62.9% (Figure 5). Repetition of the measurements 5 times resulted in textile porosity in a mean value of 66.4% ± 0.22% and confirmed the reproducibility of the procedure. 24 h after release of the strain textile porosity was still constant with 66.9% and only a very little elongation of 0.4%.

Measurements with application of tensile forces of 0.9 to 8.9 N/cm at the SIS sling with the width of 11 mm led to a slight increase of the textile porosity to 68.0% at a load of 8.9 N/cm and of the effective porosity to 64.0%. This corresponds to an elongation of 6.7% due to deformation of pore geometry (Figure 6).

4. Discussion

Measurement of the effective porosity at mechanical strain reveals differences of the textile construction with important consequences for the risk of scar entrapment after tissue integration. Measurement of the textile porosity obviously at rest is not sufficient to predict the changes of pore geometry at tensile load.

The TVT sling implant shows acceptable textile porosity but an absence of large or effective pores, indicating for most of the mesh area a high risk for getting completely surrounded by fibrotic scar tissue. Although already without application of any forces the mesh showed an insufficient pore size, the pore sizes are dramatically reduced further when mechanically stressed. Due to the collapse of the pores the mesh showed a considerable elongation with a narrowing in width leading to roping and curling of the textile. Similar stress may occur during implantation or as a consequence of the mobility of the pelvic floor.

In contrast the alternative design of the SIS sling showed a higher textile porosity, which is not compromised at tensile load. Almost all pores fulfil the criteria of effective pores resulting in a high effective porosity of more than 60% even at a strain of 1000 g! Correspondingly the device shows a restricted elongation reflecting the enormous structural stability.

As a result of the missing effective porosity the TVT has a higher risk for scar formation at the entire area of the mesh. Furthermore scar usually showed a contraction of at least 20%, and thus an implant being incorporated mainly in scar tissue will show an increased shrinkage of the mesh area with an implant getting folded and wrinkled. Indeed at numerous explanted slings from humans we could confirm the predominance of scar tissue around the TVT with shrinkage and folding in almost all specimens (unpublished data).

As demonstrated with the SIS, structural stability with high resistance to mechanical loads can be realised by choosing an adequate textile construction with tight binding and fibres running in line with the mechanical load. The present study with measurements of effective porosity under strain confirms the conclusion of Petros and Papadimitriou of a nonstretch tape to minimize obstruction and urethral damage [8]. And it provides a reasonable explanation that inelastic slings can be used with a lowered risk for mesh

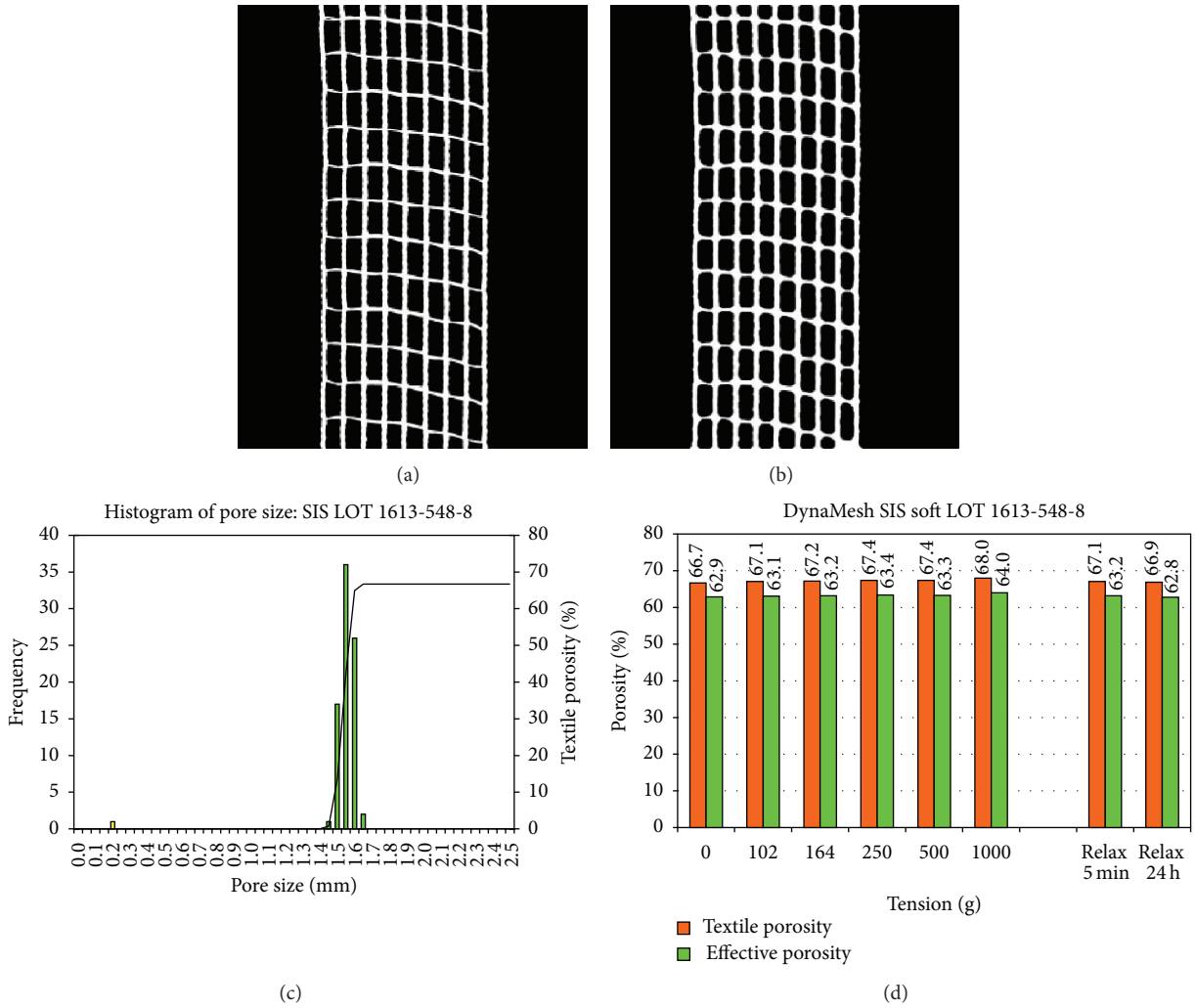


Figure 5: Image of SIS with (a) all pores, (b) effective pores, (c) pore frequency in dependency of pore size (estimated by simple square root of the pore area), and (d) textile and effective porosity at mechanical strain of up to 1000 g (8.9 N/cm).

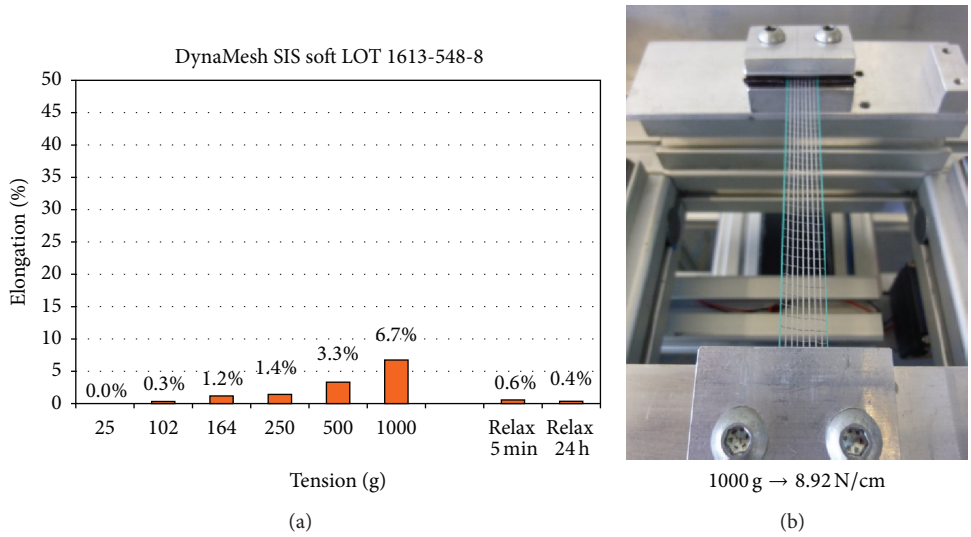


Figure 6: Elongation of the SIS at mechanical load as percent of original length (a) with macroscopic image (b).

exposure [10]. Considering the considerable similarity of the textile structure of the slings from BARD, Gynecare, Caldera, AMS, and Boston Scientific it is not surprising that all these devices are subject to litigations for comparable problems [11]. Only the sling from Mentor shows a construction like the SIS sling, though with smaller pores.

In this study the maximum physiological strain for the abdominal wall was estimated to be less than 16 N/cm [12]. Tensile measurements of tissues revealed that the layers will hardly keep more than this before disintegration [13–15]. Thus for the area of the pelvic floor both theoretical calculations of the strain to be assumed as well as the maximum holding capacity of the tissues will put a limit of <10 N/cm to any mechanical strain. Janda even found that a membrane tension of 2 to 5 N/cm as strain should be expected in the pelvic floor, even only 1 N/cm in nonprolapsed tissues [16]. The tensile strain in the pelvic floor is expected to lead to an elongation of the textile. An elongation of up to 20% is considered to form the comfort zone, and elongation of 40% defines the safety zone [17]. Thus in regard to both force and elongation, our setting should widely reflect the physiological range. However for other indications for other devices in other areas of the body the mechanical strain should be adapted correspondingly.

In the current study the mechanical strain was applied as uniaxial testing. In this specific case it reflects an application of the textile intended to support or replace a ligament, for example, the pubourethral ligaments in case of slings for treatment of stress urinary incontinence. In this setting uniaxial testing should be regarded as acceptable. However looking at the properties of bigger mesh areas in a two-dimensional setting the compliance of the textile differs considerably in dependency of the mesh orientation [18–20]. In line with the fibres (machine direction) the stretchability is more restricted than perpendicular to this. Overall, uniaxial testing thus cannot be compared to the results of a multiaxial testing or a test pressing through the stamp.

Unfortunately multiaxial testing as with the ball burst test or the test pressing through a stamp is strongly influenced by the size of the sample. But even more for this testing the mesh is fixed at its borders so that any elasticity is restricted to the little elongation that is permitted by stretching of the fibres in the binding. Any huge deformation of the pore is inhibited by this fixation, and the resulting tension forces are significantly higher compared to the uniaxial testing and thus not comparable. Maybe in the future computer simulation by use of finite elements may help to grasp the anisotropic characteristics of textile implants. The current experimental measurements do not. Therefore testing conditions have to be clearly outlined if textiles are compared.

The in vitro investigation of the pore sizes and its changes at mechanical load helps to predict tissue response after implantation, in particular the extent of scar formation and whether this scar entraps the entire implant [5, 18]. The increased risk for fibrotic bridging has been confirmed for small pore devices used in the abdominal wall as well as in the pelvic floor. However, though superior tissue integration of textiles with large pores has been proven for the abdominal wall in many clinical studies, due to the lack of explanted slings from humans the specific tissue reaction to SIS still has to be shown.

Conflict of Interests

The TVT and SIS measurements are used in parts for litigation in the US. Uwe Klinge has been involved in development of textile mesh constructions for Ethicon and FEG Textiltechnik, Aachen.

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Review Article

Global Convergence on the Bioethics of Surgical Implants

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The increasing globalization of mankind with pluralistic belief systems necessitates physicians by virtue of their profession to partner with bioethics for soundly applying emerging knowledge and technologies *for the best use of the patient*. A subfield within medicine in which this need is acutely felt is that of surgical implants. Within this subfield such recent promising ethics and medicine partnerships include the International Tissue Engineering Research Association and UNESCO Chair in Bioethics and Human Rights' International Code of Ethics. In this paper, we provide an overview of the emerging human rights framework from bioethics and international law, discussion of key framework principles, their application to the current surgical challenge of implantation of surgical mesh for prolapse, and conclusions and recommendations. Such discussions are meant to facilitate true quality improvement in patient care by ensuring the exciting technologies and medical practices emerging new daily are accompanied by an equal commitment of physicians to ethically provide their services for the chief end of the patient's good.

1. Introduction

> "The art [of medicine] consists of three things: the disease, the patient, and the physician. The physician is the servant of the art, and the patient must combat the disease along with the physician."—Hippocrates, De morbis popularibus 1.2.

Since the codification of medicine as a science and an art by the Greek Hippocrates in 4th century BC, the increasing globalization of mankind with pluralistic belief systems has enriched, and complicated, this discipline. True to modern medicine's earliest principles articulated by the Hippocrates Oath [1]—justice, patient confidentiality, respect for teachers, and solidarity with peers—this diverse international environment necessitates physicians by virtue of their profession to partner with bioethics for soundly applying emerging knowledge and technologies *for the best use of the patient.* A subfield within medicine in which this need is acutely needed is that of surgical implants. Few fields are as rapidly growing in technical complexity and ethical challenges as surgery, in which advances in genomic and bioengineering (including nanotechnology) daily push the boundaries of human possibility. Professor Mueller notes how professional ethics runs through this field as noted with The European Board of Urology (EBU) European Curriculum for Urology [2]. He highlights how this curriculum highlights the technical limitation of medicine as it can teach the information for emergency and elective cases, but the "need to act at all times in an ethical and professional manner" is required to understand how to pragmatically apply this information. Such dual competencies of physicians in the technical aspect of medicine with the art of its application amplify the "importance and understanding of evidence-based medicine," particularly with the correlate that limited evidence for a new innovation of various surgical implants should bid practitioners caution. In this paper, we provide (Section 2) an overview of the emerging human rights framework from bioethics and international law, (Section 3) discussion of key framework principles, (Section 4) their application to the current surgical challenge of implantation of surgical mesh for prolapse, and (Section 5) conclusions and recommendations.

2. Human Rights Framework from Bioethics and International Law

A promising bioethics resource for surgeons is the growing global consensus of human rights not only as commonly beliefs supported by diverse belief structures, but also as core bioethics tenants and international law, since the Universal Declaration of Human Rights adoption in 1948 by the United Nations (UN) in the World War II aftermath [3]. The United Nations Educational, Scientific, and Cultural Organization (UNESCO) Declaration on Bioethics and Human Rights (DBHR) in 2005 built on this worldwide consensus by its historic commitment through its 193 UN member states to apply 15 defined bioethical principles within and across countries [4]. Following such international human rights violations in the 1990s as the US-led placebo-control HIV study in Africa [5], the UNESCO Declaration emerged as an attempt to synthesize human rights and bioethics through its approach, both flexible enough to allow specific situation application and yet broad enough to allow pluralistic consensus, particularly in almost half of UN states without national bioethics committees to advise their governments [6].

We thus propose the following directly relevant principles from this approach as an ethically robust and pragmatically useful framework for exploring and converging on protocols for the optimal patient application of surgical implants: (I) human dignity and human rights, (II) benefit and harm, (III) autonomy and consent, and (IV) justice. Unless such an interdisciplinary approach with a global scope to medicine is adopted, then the shared expertise of physicians (including those from multiple disciplines), scientists, lawyers, philosophers, and patients from varied belief backgrounds cannot reach concrete and substantive protocols. And without such protocols, as the operationalized products of the internationally supported bioethical principles, medicine cannot realize its end as a science and art at service of the patient. "Fostering the art of convergence and cooperation in global ethics" as the mission statement of the UNESCO Chair in Bioethics and Human Rights [7] can thus become the necessary complementary art to medicine in the modern world.

3. Bioethics Principles in a Human Rights Framework

(I) *Human dignity and human rights* as the first DBHR principle provides a foundation for the remainder by asserting the primacy of the individual's interests and welfare over the interests of the society or scientific community. This prioritization is based up on the human dignity of each individual and his or her derivative rights and freedoms flowing from it. Though the DBHR excludes any defined justification of this first principle and its normative nature dictating right and wrong actions toward any individual, this omission allows for the substantive convergence of different peoples to acknowledge and anchor this fundamental principle from within their own belief systems.

(II) *Benefit and harm* describes how the operationalization of the first principle entails seeking the preferred balance between benefit and harm for the individual. Similar to the original Hippocratic Oath with its insistence to "do no harm," DBHR asserts that the minimization of harm and the maximization of direct and indirect benefits for individual much be sought during the advancement of scientific knowledge and its medical practice and technologies.

(III) *Autonomy and consent* are the related principles that define the parameters necessary for physicians' right relationships with patients. Physicians according to the autonomy principle thus respect a patient with adequate capacities and conditions (i.e., maturity and freedom from external or internal coercion) to make decisions and respond with responsibility to their effects. Consent is the derivative duty for physicians and researchers in light of patient's autonomy to provide them the information and absence of coercion to make a free and prior decision for any medical intervention or research project to be provided to them (or withdrawn from them at a later time).

(IV) *Justice* describes the social dimension of the fundamental principle of human rights by emphasizing the equality among all individuals by virtue of the equivalence of their dignity and rights. The correlate duty for physicians and researchers is to thus treat them equally. This principle of justice is further elaborated as distributive justice by the associated principles of nondiscrimination, respect for cultural diversity and pluralism, solidarity, and sharing of benefits of scientific research.

4. Application for Surgical Mesh Bioethics Analysis

4.1. Clinical Background. Pelvic organ prolapse (POP) occurs in women when such pelvic organs as the bowel, rectum, uterus, or bladder fall against the vaginal wall from their usual anatomical positions, when the internal walls that hold these organs are compromised. Quality of life can decrease with this condition, along with altered sexual and urinary function. Urogynecologic surgical mesh is a medical device for transvaginal repair of POP by strengthening these damaged or weakened internal structures [8]. In April of 2014, the United States Food and Drug Administration (FDA) proposed two orders to require mesh manufacturers to submit to the FDA a premarket approval application providing clinical data supporting the device's effectiveness and safety, in addition to reclassifying mesh from a class II device (moderate-risk) to class III (high-risk) [9].

These orders followed a multiyear FDA investigation and independent removal of such particular mesh products as Protogen-Sling from the market after increasing complication rates, including vaginal mesh erosions in 10% of cases that can then lead to infections, nerve lesion-based chronic pain, sepsis, perforated organs, and death. This American government regulatory agency approved this product without clinical testing [10] and thus allowed multiple POP meshes to be approved and applied for human patients based on the original 1997 Protogen-Sling approval. From 2008 to 2010, there were 1503 POP complication reports submitted to the FDA, and the first patient settlement made in July of 2012

totaled $5.5 million in the multidistrict litigation (MDL)-2187 against the device company, Bard [11].

4.2. Dangers of Lawsuit and Market-Based Patient Care Improvement. The necessity for the institutionalization of bioethics and medicine's partnership, and thus the timely application of bioethics analysis of the above principles for optimal patient care, is demonstrated in the legal and regulatory failure for POP patients. This can be seen with the time delays and resulting unnecessary patient suffering (and economic loss from ethically suspect device companies) with the first market withdrawal of the Protogen-Sling in 1999, bending to market pressures from the escalating complication rates. Yet a decade lapsed before the FDA in September of 2011 mandated 34 POP mesh manufacturers to conduct clinical retrospective studies for product evaluation, one year before the first patient lawsuit settlements began. The urgent question arising from this unfortunate situation is not only were the manufacturing companies or physicians unethically promoting untested and unsafe products for patients, but why did it require over 10 years of legal and market pressures to improve patient care? Thus the following bioethics analysis is provided not simply as an academic exercise for select experts, but rather as a needed *first and ongoing step* in the medical science development and clinical settings.

4.3. Bioethics Analysis as True Quality Improvement. To have ensured the true quality improvement in POP care, the following bioethics analysis could have (and should for future products) be applied in light of the human rights-framework of bioethics principles: (I) human dignity and human rights, (II) benefit and harm, (III) autonomy and consent, and (IV) justice. Beginning with the first principle, the (I) human dignity and thus rights of POP patients would have implicated the FDA and early physician adopters of POP mesh in the required systematic and detailed scientific and clinical analysis of the new products to ensure their safety and clinical effectiveness. The medical community and its regulatory bodies including the FDA owe their patients a commitment to prioritizing their health over industries who can capitalize at worst, or fail to adequately consider at best, patients' distress stemming from their disease states that can drive them to seemingly quick medical solutions. Dr. Pellegrino, the father of modern bioethics, discusses the patients' exploitable state by asserting that the three aspects of medicine are a natural conclusion from the fundamental assumption of each patient's dignity [12]. Namely, (i) the disease makes the patient vulnerable, (ii) the physician by his or her nonproprietary medical knowledge must use such knowledge to respond competently and compassionately to the patient's vulnerable state, and (iii) the oath-based professional and public commitment of the physician binds them to honor the patient-physician relationship with faithfulness to its goal of the patient's health above all other interests.

From this ethical starting point, the next bioethics principle of (II) benefit and harm highlights the medical community and regulatory agencies' duty—as the logical consequence of patients' dignity—to make unbiased judgments from the scientific and clinical analysis of the POP devices. These judgments must seriously question if implanting a semipermanent or permanent device into a patient should be done with regulatory agency approval without such implantation ever being done before in a human. The judgment of the FDA and early physician adopters of the Protogen device, for instance, appeared to be that the benefits of putting this device on the market for patients outweighed the potential harms that were not adequately analyzed or understood before their use was begun [9]. Due to the complex and ever-evolving nature of medical treatment and devices' developments, the limited knowledge of POP patients (and patients in general) to make their own judgment on benefits and harms is thus compromised if physicians and scientists fail in this duty.

Physicians in response to the next bioethics principle of (III) autonomy and consent therefore are bound by the patient-physician relationship with its roots in the patients' fundamental dignity to properly assess, understand, and communicate in an unbiased and nondirective way the benefits and harms for a patient's consent to validly be given. Patients with adequate capacities and necessary conditions (i.e., reasonably free of pressure from significant others) thus must have their autonomy respected by physicians to have open, free, and understandable discussions about POP meshes to determine if their consent should be given or delayed until more proven devices are demonstrated. Because POP is not a life-threatening condition, it is questionable if physicians can claim inadequate time exists for them to critically review the state of knowledge regarding the emerging devices, consult with regulatory agencies and professional medical societies, and make recommendations for their patients to allow them truly informed consent.

Finally, application of the bioethics principle of (IV) justice emphasizes the importance of ethical device development and its application across social strata. For a mesh to require over 9 operative revisions as noted in the American lawsuits [10], the medical care costs for such repeated mesh surgeries can be prohibitive and thus only available to higher socioeconomic populations. Smarter drug and device design on the part of the manufacturers may ensure a more equitable distribution of these treatments. On the part of the physicians applying the devices, adherence to this justice principle may provide the ethical argument needed to motivate the medical community to cost efficiently assist patients in the preventive management of their diseases or disease risks such that more costly surgeries such as POP mesh implementation may be more justly applied for the conditions necessitating them. Societal resources thus may be freed up for more just distribution more on a need-basis rather than a wealth-basis. Physicians cannot expect legal or market pressures to do their jobs for them—namely, advocating for the health of the patient by caring justly and competently for them, rather than leaving them to seek recourse through the courts or shopping around for different medical treatments.

5. Conclusions and Recommendations

Our world's globalization and rapid medical technology development must catalyze a global ethics and medicine. Amid diverse belief systems, convergence as well as cooperation is not only possible across patients, physicians, regulatory agencies, and industries as seen in the growing body of international law and human rights declarations with multinational support—they are necessary. The case of surgical mesh for pelvic organ prolapse typifies the failure of regulatory agencies and physicians to honor their identity as servants of the science and art of medicine, at service of their patients, if they fail to discharge their duty for the art of ethical convergence throughout device and drug development and their deployment to patients.

We have proposed the international consensus-based human rights approach to bioethics to facilitate optimal medical technology and practice evolution through the partnership between science and ethics. Since being the world's medical expert in surgical mesh does not make one an ethical expert in their development or use, collaboration is a necessary dimension of medicine to ensure that patients do not bear the harmful consequences of poorly tested technologies. Such ethical partnership from the beginning of technology development and ongoing through its practice in medicine is thus an integral aspect of quality improvement to ensure that evidence-based medicine includes the ethical base as well. The fear of stifling medical innovation or market growth is thus invalid as there are no shortcuts to patient care, including skipping bioethics steps that must accompany the development of the science and art of medicine.

Such recent ethics and medicine partnerships as the International Tissue Engineering Research Association and UNESCO Chair in Bioethics and Human Rights' International Code of Ethics [13] suggest a promising route forward. Such partnerships may help ensure the patient's case be resolved in their exam room, not in a legal court or stock market. Therefore, the exciting technologies and medical practices emerging new daily must be accompanied by an equal commitment of physicians to ethically provide their services for the chief concern of the patient's good. Hearkening to Hippocrates, physicians must combat the disease with their patients through ongoing and rigorous medical and bioethical reflection—lest the physician or patient, rather than the disease, become the enemy the other must combat.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Management of Mesh Complications after SUI and POP Repair: Review and Analysis of the Current Literature

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Purpose. To evaluate the surgical treatment concepts for the complications related to the implantation of mesh material for urogynecological indications. *Materials and Methods.* A review of the current literature on PubMed was performed. *Results.* Only retrospective studies were detected. The rate of mesh-related complications is about 15–25% and mesh erosion is up to 10% for POP and SUI repair. Mesh explantation is necessary in about 1-2% of patients due to complications. The initial approach appears to be an early surgical treatment with partial or complete mesh resection. Vaginal and endoscopic access for mesh resection is favored. Prior to recurrent surgeries, a careful examination and planning for the operation strategy are crucial. *Conclusions.* The data on the management of mesh complication is scarce. Revisions should be performed by an experienced surgeon and a proper follow-up with prospective documentation is essential for a good outcome.

1. Introduction

Pelvic organ prolapse (POP) affects about 50% of parous women. Approximately, 11% of these women will need surgical correction due to symptoms, like incontinence, voiding dysfunction, and discomfort from vaginal bulge. In the USA, more than 300,000 women undergo surgery for POP annually [1]. Repair with native tissue showed a high recurrence rate up to 30%, especially in the anterior compartment [2]. To reduce the risk of recurrence, transvaginal mesh has been applied in the treatment of POP since the 1990s. In the last decade, the number of mesh operations and various presumed easy-to-use mesh kits from various manufacturers grew exponentially. This development led to a widespread application of this outpatient surgical method. Less attention was paid to possible new complications and only a few clinical trials were available prior to product approval and application. Meshes or grafts potentially add to the complication profile. These include the trauma of insertion, foreign body reaction to the implant in terms of inflammation, infection and/or rejection, contraction of the mesh causing pain, and the stability of the prosthesis over time [3]. In 2008, the U.S. Food and Drug Administration (FDA) issued a warning in dealing with foreign materials for incontinence and POP repair, based on the report of more than 1000 serious side effects by Manufacturer and User Device Experience (MAUDE). Following a systematic review of the literature, the FDA pronounced further examinations on benefits and risks of surgical mesh for SUI (stress urinary incontinence) and POP repair. In September 2011, the FDA organized a scientific advisory board and made 34 manufacturers of POP meshes and 7 manufacturers of SUI meshes perform clinical retrospective studies on their products [4]. Currently, over 30.000 cases due to mesh-related complications and law suits on several manufacturers are brought before the US courts. Reacting to this, several products have been withdrawn from the market by the manufacturers. Despite these developments, in Germany, there are relatively few reactions to the alerts. The changes in the supervision of the medical device approval are currently under debate for the coming EU regulation. In addition to comprehensive education and information of patients on specific mesh-related complications, a special surgical skills training in dealing with foreign materials and the management of possible complications is recommended [5–7].

2. Methods

A systematic review was performed for English language articles published in the last five years from January 2009 to June 2014 in PubMed and the Cochrane Library Database. Search items included the following keywords and phrases: "pelvic organ prolapse and POP," "incontinence," "vaginal surgery," "sacrocolpopexy," "vaginal mesh or implant," "abdominal mesh or implant," "alloplastic material," "Prolift," "Apogee," "Perigee," "Gynemesh," "Gore-Tex," "complications," "vaginal or endoscopic or laparoscopic or abdominal resection," and "explantation." Keywords appeared in the title, abstract, or both. Studies with more than 10 reported complications after mesh application for POP or SUI were included. Studies with lacking information on primary surgery, complications, and management were excluded. Classification, risk factors, and treatment concepts of complications after mesh implantation were analyzed. The primary outcomes assessed were the subjective (patient-reported) and objective cure/improvement rates. Secondary outcomes included reoperations for complications and recurrent incontinence after the initial treatment. Data were analysed using RevMan v.5.3 (Cochrane Collaboration, Oxford, UK) and GraphPad Prism v.6 (Graphpad Software, Inc.). Quantitative synthesis was done when more than one eligible study was identified. The outcome results were expressed as weighted means difference (WMD), standard deviations (SDs), and risk ratio (RRs) with 95% confidence intervals (CIs) for dichotomous variables using the Mantel-Haenszel method [8]. Methodological heterogeneity was assessed during selection, and statistical heterogeneity was measured using the chi-square test and I^2 scores. A random effects model was used throughout to reduce the effect of statistical heterogeneity [9]. Treatment failure risk was defined as reoperation after the initial treatment.

3. Results and Discussion

No randomized trials on the surgical treatment of mesh complications were detected. Only one was a partly prospective trial on mesh resection [10]. A total of 17 retrospective studies were included in the review (Table 1). Different conservative approaches and surgical techniques for the resection of alloplastic materials after the treatment of pelvic organ prolapse and stress urinary incontinence are presented. Initial surgeries were midurethral sling (MUS), transvaginal mesh, and abdominal colposacropexy. Only alloplastic polypropylene materials were used.

3.1. Classification of Complications. To analyze the mesh-related complications, a Clavien-Dindo classification of surgical operations is often used in the literature [11]. The advantages hereby are a clear correlation to the management of complications and broad acceptance. However, the information on the site and timing of complications is missing. In addition, the classification is not always adequate; for example, the clinically less severe intraoperative bladder injuries must be classified as Grade III complications and distort the analysis. International Continence Society (ICS) and International Urogynecologic Association (IUGA) introduced in 2010 a consensus-based standardized terminology and classification for the description and documentation of specific complications after the use of implants in pelvic floor surgery of women [3]. The classification is based on the information on the category, time, and location of complications. Because of high complexity and low concordance in different trials, the ICS/IUGA classification is currently rarely used [6, 12]. However, the classification could be valuable for the reporting of long-term data in registries.

3.2. Complications and Risk Factors. Polypropylene meshes are usually used for vaginal repair of POP and SUI. The overall rate of mesh-related complications after transvaginal mesh application for POP is about 15–25% and mesh erosion is up to 10% for these indications [6, 13]. The most common complications (retrospective review of 388 cases with complications) after implantation of midurethral sling (MUS) are overactive bladder (52%), obstructive micturition (45%), SUI (26%), vaginal mesh exposure (18%), chronic pelvic pain (14%), local infection (12%), dyspareunia (6%), and vesicovaginal fistula (4%) ([14], Table 2). Kasyan et al. analyzed the biggest series of 152 complications (22.5%) following Prolift transvaginal mesh for POP. The following complications were detected: erosions (21%), dyspareunia (11%), mesh shrinkage (4.4%), pelvic abscess (2.7%), and fistula (1.3%). Younger age, less prominent prolapse, hematomas, and concomitant hysterectomies were associated with higher risk of complications [15]. As part of the abdominal sacrocolpopexy where nonabsorbable synthetic materials (Mersilene, Prolene, Polypropylene, Gore-Tex) are applied, the risk for mesh erosion is between 0 and 12% (medium risk 4%). Causes of complications were primarily surgical techniques, concomitant surgeries, non-type 1 meshes, and previous surgery in the field [6, 7, 16]. Most complications occur in a time range of one to five years after the operation [12]. Median time to revision in selected trials was 19.2 mos (5.8–59). The complications are attributed to a considerable extent to the wrong indication, faulty surgical techniques (tape positioning and overcorrection), and material properties (biocompatibility and contraction of the mesh material). New developments in material optimization are currently expected. Other risk factors retrieved from multivariate analysis were previous anti-incontinence procedure, obesity, and estrogen status [5, 6, 15]. Reasons for vaginal mesh exposure of the mesh material are categorized into tissue causes and biomechanical mesh properties. Tissue causes include superficial placement, traumatic dissection, tissue healing, and thin and atrophic vaginal mucosa, especially in postmenopausal women [16].

3.3. Management Strategies for Mesh Complications. The current retrospective data on mesh excision for complications is presented in Table 1. 12 trials reported on complications after MUS, 8 trials on complications after transvaginal mesh for POP repair, and 3 trials on abdominal colposacropexy. Median patient number in the studies was 42 patients (8–347). Mean follow-up after the treatment of mesh-related complications was 22.6 mos (6 weeks–65 mos). Many authors propagate an initial conservative approach with antibiotics

Table 1: Studies on management of mesh related complications after incontinence and prolapse surgeries.

Author	Trial	Number of patients	Mesh	Complications	Median time to revision	Management	Concomitant procedure	Follow-up
Abbot et al. 2014 [17]	RT	347 (49.9% MUS; 25.6% TVM or CSP; 24.2% combination)	Various	30% dyspareunia 42.7% mesh erosion 34.6% pelvic pain 77% grade 3 or 4 (reoperation) complication	5.8 mos (0–65.2 mos)	(1) Trimming of mesh/partial excision (50.9%) (2) Release of mesh arms (18.1%) (3) Complete intravaginal mesh excision (26.9%) (4) Recurrent prolapse treatment (23.2%) (5) Recurrent incontinence treatment (14.8%) (6) Other surgeries (20.1%) (7) Initial conservative treatment (23%) 60% ≥2 interventions	MUS	
Agnew et al. 2012 [18]	RT	63 MUS	Various synthetics (67% monofilament TVT, 17% TOT)	100% voiding dysfunction	12.4 mos (1 week–8 yrs)	(1) Simple sling division (73%) (2) Partial excision of sling (21%) (3) Concomitant procedure to prevent Re-SUI (4/63)	Burch, MUS	Persistent voiding dysfunction (1) 10.9%; (2) 7.7%; (3) 50% ($P = 0.09$) Subsequent surgery for recurrent SUI (1) 2.2%; (2) 23.1%; (3) 0% ($P = 0.04$) De novo urgency (1) 10.9%; (2) 15.4%; (3) 25% ($P = 0.51$)
Blaivas et al. 2013 [19]	RT	47 MUS	Type 1 76% Types 2–3 23%	OAB (70%) SUI (55%) Recurrent UTI (21%) Pelvic pain/dysuria (34%) Obstructive symptoms (9%) Vaginal extrusion (9%)	2 yrs (1 mos–8 yrs)	(1) Sling excision + urethrolysis (34%) (2) Sling excision + urethral reconstruction (including fistula repair) + autologous fascial sling (30%) (3) Sling incision (21%) (4) Partial cystectomy (10%) (5) Ureteroneocystostomy (4%)	MUS	2 yrs (0.25–12 yrs) Successful treatment 72% 28% recurrent surgery refractory pain (19%), mesh extrusion (17%), and OAB (8%)
Costantini et al. 2011 [20]	RT	12 (12/179, 6.7%) mesh erosion after abdominal CSP	11 PP, 1 Gore-Tex	100% mesh erosion 41% vaginal bleeding 33% asymptomatic 17% dyspareunia 17% infection (1x Gore-Tex)	22.9 mos (2–66 mos)	(1) Antibiotics and local estrogen (100%) (2) Vaginal (partial) mesh resection (83%) (3) Abdominal resection (17%) (4) Endoscopic (8%)		57 mos (18–120 mos) (1) All needed surgery (3) Recurrent cystocele (4) Fistula, abdominal revision
Davis et al. 2012 [21]	RT	12 TVT	PP	100% mesh erosion	59 mos (7–144 mos)	Endoscopic holmium: YAG laser excision (100%)		65.5 mos (6–134 mos) 33% second laser excision 17% surgery for recurrent SUI 8% (1 patient) abdominal mesh resection
Firoozi et al. 2012 [22]	RT	23 TVM for POP	Various PP	Vaginal/pelvic pain (39%), dyspareunia (39%), vaginal mesh extrusion/exposure (26%), urinary incontinence (35%), recurrent pelvic organ prolapse (22%), bladder mesh perforation (22%), rectal mesh perforation (4%), ureteral perforation injury (4%), and vesicovaginal fistula (9%)	10 mos (1–27 mos)	(1) Transvaginal excision (90%) (2) Transvaginal/endoscopic (5%) (3) Transrectal/transperineal (5%) (4) Concomitant POP/SUI repair (45%)	TVM, MUS	3 mos 14% UTI 4.3% collagen injection for Re-SUI 4.3% PFT for perineal pain
Greiman and Kielb 2012 [23]	RT	28 (28/118, 23%) MUS	PP	Intravesical sling (4%), extruded vaginal mesh (93%), obstructive voiding symptoms (78%), dyspareunia (42%), and vaginal bleeding (21%)	15 mos	(1) Sling loosening, incision in the midline (2) If mesh erosion >1 cm a resection		11% reoperation for mesh extrusion, no other complications
Hammett et al. 2014 [24]	RT	57 patients (26 MUS, 23 TVM, and 9 intraperitoneal prolapse CSP)	Various PP	100% mesh erosion with pelvic pain (55.9%), dyspareunia (54.4%), and vaginal discharge (30.9%).		(1) Vaginal mesh excision (91%) (2) Abdominal resection (all CSP, $n = 9/15$, 40%)		6 weeks 57% symptoms completely resolved 12% required more than 1 surgery for mesh excision (1) 9% UTI (2) 4.5% cardiopulmonal complications; 18% sepsis; 45% wound infection

Table 1: Continued.

Author	Trial	Number of patients	Mesh	Complications	Median time to revision	Management	Concomitant procedure	Follow-up
Hampel et al. 2009 [25]	RT	48 MUS (44 TVT, 4 TOT)	Various PP	De novo urge (65%), mesh erosion (21%), dyspareunia (19%), UTI (35%), and fistula (6%)		(1) Partial mesh resection (trans-/suburethral, 23%) (2) Self-catheterisation (23%) (3) Botox/neuromodulation (27%) (4) Fascia plastic (10%) (5) Complete abdominal-vaginal mesh resection (8%) (6) Urinary diversion (2%) (7) Fistula repair (6%) (8) Conservative treatment (25%)		42% symptoms completely resolved
Kasyan et al. 2014 [15]	RT	152 TVM	Prolift (Gynecare), PP	Erosions (21%), dyspareunia (11%), mesh shrinkage (4.4%), pelvic abscess (2.7%), and fistula (1.3%)		(1) Conservative treatment with local oestrogen (2) Partial/total mesh excision		
Nguyen et al. 2012 [26]	RT	82 MUS (2.2%)	Various			(1) Sling loosening or transaction for voiding dysfunction (60%) (2) Excision for vaginal mesh exposure 30 (36%) (3) Excision for pain (1.2%) (4) Excision for urethral erosion (1.2%) (5) Drainage of retropubic hematoma (1.2%)	MUS, colporrhaphy, and CSP	
Abdel-Fattah et al. 2006 [16]	RT	34 TVM (2.2%)	Various			(1) Excision for vaginal mesh exposure (85%) (2) Excision of vaginal suture (6%) (3) Biologic graft reoperation (12%) (4) Drainage hematoma/abscess (6%) (5) Bowel resection for obstruction (3%)		
Padmanabhan et al. 2012 [27]	RT	85 (MUS, TVM)	Various PP	Perforation of urethra (14%), bladder (36%), and vagina (50%)		(1) Vaginal excision (14%) (2) Lower urinary tract excision (47%) (3) Partial cystectomy (21%) (4) Urethroplasty (21%)		Subjective cure in 75% and improvement in 21% SUI (6.6–12.5%)
Renezeder et al. 2011 [28]	RT	118 (80% MUS, 20% TVM)	Various PP (88% type 1)	De novo urgency (46.6%), dyspareunia (41.5%), recurrent UTI (39.0%), mesh erosion (37%), and vaginal bleeding (9.3%)	27 mos (1–89 mos)	(1) Tissue patch covering (17.8%) (2) Partial removal (65.3%) (3) Complete removal per laparotomy (12.7%) (4) Bone stabilization (0.8%) (5) Excision of granulation tissue (3.4%)		8 weeks 45.5% urgency
Ridgeway et al. 2008 [29]	RT	19 TVM	Monofilament PP	Chronic pain (31%), dyspareunia (31%), recurrent pelvic organ prolapse (42%), mesh erosion (63%), and vesicovaginal fistula (16%)		Partial tailored vaginal mesh resection with concomitant procedures	Burch, MUS	33 weeks (16–75 weeks) 16% UTI 5% hematoma 21% persistent symptoms
Rouprêt et al. 2010 [30]	RT	38 TVT	PP	Mesh erosion/extrusion (42%), pelvic pain (39%), and obstruction (18%)		(1) Laparoscopic (97%) (2) Laparoscopic + vaginal (3%)		38 mos (2–80) Healing and pain release (100%) Recurrent SUI (66%)
Shah et al. 2013 [31]	RT	21 MUS	Polypropylene, type I	Urethral perforation (67%), bladder perforation (33%), fistula (19%), vaginal pain (67%), urgency (29%), incontinence (38%), obstruction (33%), dyspareunia (19%), and hematuria (24%)	15.5 mos (1–60 mos)	(near) Total mesh excision, urinary tract reconstruction, and concomitant pubovaginal sling with autologous rectus fascia	MUS, urethroplasty	22 mos (6–98 mos) Continence (81%) Incisional seroma (9.5%) Additional procedures (36%) UTI (9.5%) Pelvic pain (9.5%) dyspareunia 9.5%

RT: retrospective trial; PT: prospective trial; MUS: midurethral sling; TVM: transvaginal mesh; TVT: tension-free vaginal tape; TOT: transobturator tape; CSP: colposacropexy; PP: polypropylene.

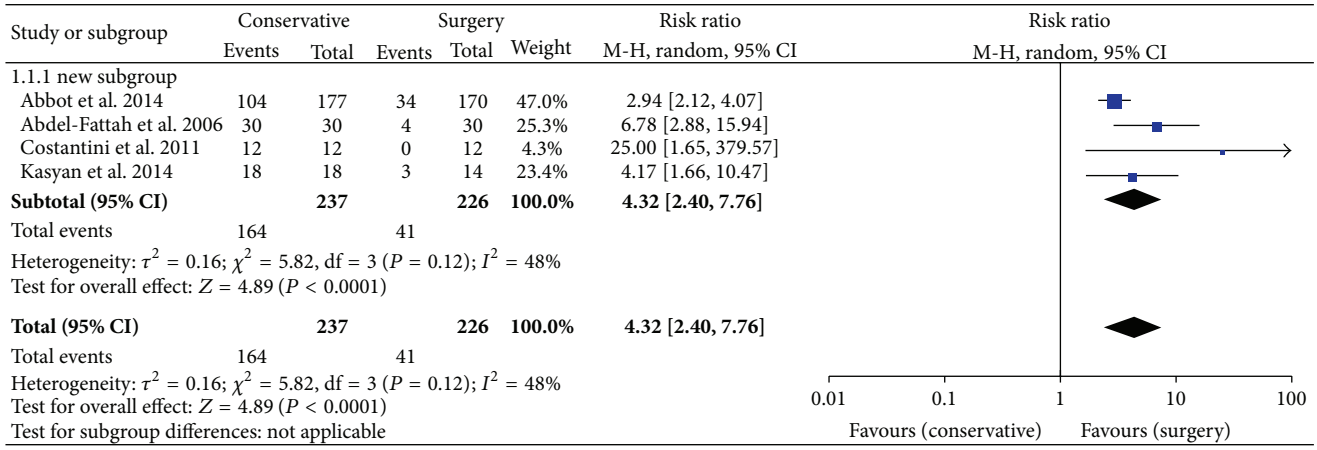

Figure 1: Treatment failure risk for mesh-related complication after conservative treatment versus mesh excision. CI: confidence interval; M-H: Mantel-Haenszel [15–17, 20].

Table 2: Complications of midurethral slings (total number: 388 women sent for revision) [14].

Complications	Number	Percentage
Overactive bladder	201	51.8%
Lower urinary tract obstruction	173	44.58%
Recurrence of SUI	101	26.03%
Vaginal exposure	68	17.52%
Pain	54	13.91%
Infective complications	48	12.37%
Dyspareunia	22	5.67%
Vesicovaginal fistula	14	3.6%
Inrolled sling or contraction of material	18	4.63%
Intraoperative bladder injury	11	2.83%
Groin/upper thigh pain	11	2.83%
Postoperative hematoma	10	2.57%
Bladder/urethral penetration	18	4.63%
Foreign body sensation in vagina	6	1.54%
Husband's penis laceration	6	1.54%
Groin infection	4	1.03%
Necrotizing fasciitis	3	0.77%
Retropubic abscess	3	0.77%
Urethrovaginal fistula	2	0.51%
Intraoperative bowel injury	1	0.25%

and local estrogen application in cases of mesh erosion. However, new studies show an advantage of the timely revision surgery to relieve the symptoms. The analysis of trials comparing conservative treatment with surgery for mesh erosions showed a 4.32-fold risk ratio for treatment failure after the conservative approach (Figure 1). Abbott and colleagues showed that 60% of the initially conservatively treated patients required surgical intervention and 60% of the total cohort were operated on at least twice [17]. Erosions in the vagina or internal organs with consecutive infection, pain, dys- or hispareunia, voiding dysfunction due to obstruction, and urge incontinence often require surgical revision [25]. In

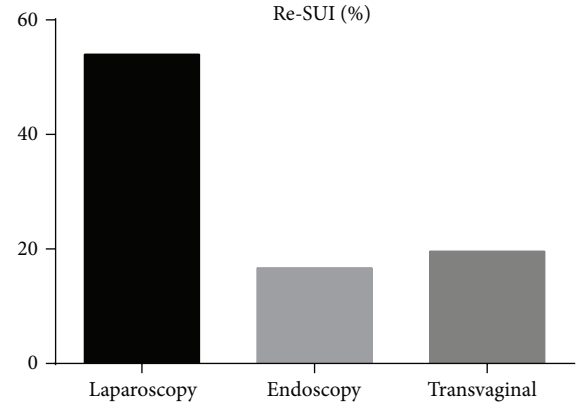

Figure 2: Recurrent incontinence after MUS-mesh excision (mean), $P < 0.05$.

the current US-American and European studies with long-term observation, the rate of postoperative mesh explantations was about 1% after a midurethral sling (MUS) and about 3% after a vaginal mesh for POP repair [26, 32]. The complications can be often corrected by mesh resection, but, in some cases, further surgeries for de novo incontinence (10–25%) or POP (7–47%) were necessary [17]. Figure 2 shows the percentage of recurrent stress incontinence depending on different MUS-excision techniques. Laparoscopic abdominal resection causes a 3-fold higher risk of Re-SUI probably due to a complete incision and excision of the mesh arms [30]. The result was however not significant due to a small trial number. There are a few data on the effect of mesh explantation on dyspareunia and chronic pelvic pain. Previous studies suggest that the pain due to the scarring and foreign body reaction may persist even after the mesh removal [33].

A comprehensive diagnosis of symptoms and localization of erosion by cystoscopy, vaginal examination, imaging and urodynamics, education of patients on possible irreversible damage, and careful planning of the operation steps are required prior to revision surgery. A careful clinical examination and determination of the pain location by trigger

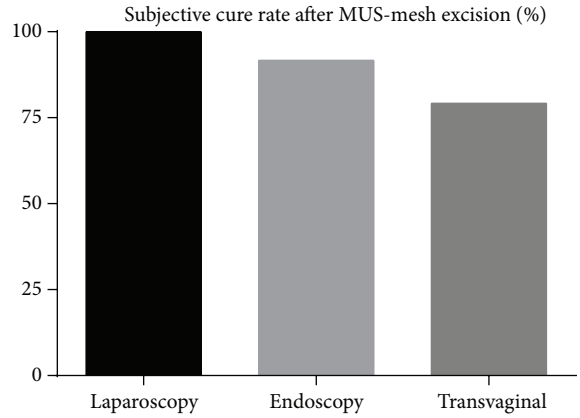

Figure 3: Subjective cure rate after MUS-mesh excision (mean), $P < 0.05$.

points are excellent markers for planning of the site and extent of mesh resection [20, 33]. However, a standardized surgical procedure and access do not exist up to date. The analysis of the available studies showed a similar subjective cure rate of 79–100% for different techniques (Figure 3). The rate of reoperations was higher if an endoscopic or transvaginal access were chosen [18, 19, 21, 22, 24, 30]. However, the hospital stay, operation time, and postoperative pain were higher in the case of laparoscopic mesh excision [30]. Generally, a vaginal access with partial or complete resection of the infected foreign material is favored in most trials (88% of the analysed studies). Non-type 1 alloplastic materials according to Amid classification (e.g., polytetrafluoroethylene and Gore-Tex) have to be removed completely in case of erosion or infection in order to achieve symptom relief [34]. A complete mesh excision can be very difficult especially for abdominal access. Complications such as bleeding, fistula, neuropathies, and prolapse recurrence are frequent [20]. Different transvaginal techniques like sling loosening, mesh incision, and partial or complete excision were described in included studies but no clear strategy or algorithm could be found (Table 1). Costantini and colleagues propose the following intraoperative management of mesh exposure: closure of the vaginal defect with double-layer suture to avoid a direct mesh contact with the mucous membranes, flush with antibiotic solution, no stitching of the full thickness of the vaginal wall, atraumatic preparation, use of nonwoven, nonabsorbable suture and polypropylene meshes, avoidance of concomitant hysterectomy, and long-term follow-up after the revision [20]. Similar vaginal techniques with optional excision of the alloplastic material and two-layer closure of a vesicovaginal fistula are described by other authors [22]. The German group from Mainz University reported on the urogynecological management of complications based on 259 patients after implantation of MUS [25]. In the case of de novo OAB, the symptoms improved only after the resection of the portion of the sling which was in contact with the urethra. The wrong position of the sling could be detected by pelvic floor sonography (PFS). PFS is an important tool to assess the tape position, form, and distance from urethra. The reasons for the complications and sling failure can be identified and corrected. The ultrasonography evaluation of a well-positioned sling provides certainty that a success of conservative therapy can be expected. In case of a dystopic position of the sling, the first step is to evaluate the sling location and to decide whether or not the band can be saved [34]. The removal of the foreign material was more difficult if the initial operation has been long ago. Particularly difficult and traumatic for the pelvic floor were the excisions of transobturator tapes [25]. Infections of the alloplastic material in the obturator fossa are especially dangerous for the development of abscesses or necrotising fasciitis and require careful debridement and follow-up. If a significant erosion of the mesh was diagnosed, partial vaginal material removal has been usually performed. In case of vaginal mesh exposure (small erosions under 1 cm without infection), the defect could be closed by a suture. In case of mesh shrinkage, a resection of the fibrotic band in the paravaginal sulci was proposed. In some cases, infection of TOT required extensive debridement with opening of the deep tissues of the groin and adductor compartment, removal of the complete tape, antibiotics, and sometimes hyperbaric oxygen therapy [15]. Agnew and colleagues reviewed 63 women with voiding dysfunction (>150 mL residual volume) after MUS (67% TVT). Three different surgical procedures were analysed (simple sling division, partial resection, and concomitant SUI procedure). Taking into account the results of the findings (Table 1), the authors changed their strategy to divide synthetic midurethral slings lateral to the urethra and then carefully perform cystourethroscopy to ensure that no urinary tract injury has occurred [18].

A tertiary center in the US presented retrospective data on 47 women after salvage operation following at least one revision on mesh-related complications. Different operative strategies and approaches were applied, depending on the intraoperative findings. The median follow-up was 2 years. Patients presented with various symptoms and 72% could be treated successfully (QoL questionnaire) by the first salvage operation. However, 14 women needed a reconstruction of the urethra, 5 women a continent stoma, and 2 women a partial cystectomy. The treatment of patients with symptoms of chronic pain was difficult; only 28% reported a relief of symptoms postoperatively. The authors assume 3 potential causes of mesh-related urethral complications; namely, (1) the surgeon simply pulls the sling too tight at surgery, (2) a correctly placed sling contracts with time due to tissue ingrowth, and (3) faulty surgical technique results in placement of the sling directly into the urinary tract [19].

Other case reports showed good postoperative results after covering the exposed alloplastic material with vulvar fat without resection [35]. In case of sling erosion into the bladder with consecutive infections, stone formation, and pain, transurethral resection or laser excision (holmium and thulium) techniques have been successful [21, 36]. Other groups reported successful individual cases with laparoscopic and robot-assisted excision and transvesical reconstructions to treat the mesh erosions after MUS implantation [30, 37, 38].

4. Conclusion

Mesh-related complications are a current emerging problem, which confronts all urologists and gynecologists in their daily practice. The previous findings from retrospective studies

show that early surgical treatment of these complications is advantageous. There is no profound evidence based algorithm on the access and surgical procedure up to date. However, transurethral and vaginal mesh excision techniques were demonstrated to be safe and successful in present studies. It is important to ensure a gentle tissue dissection and continuous follow-up after the surgery. The revision operations belong in the hands of experts and should be documented prospectively in trials and registries.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

An Open Multicenter Study of Clinical Efficacy and Safety of Urolastic, an Injectable Implant for the Treatment of Stress Urinary Incontinence: One-Year Observation

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The prevalence of stress urinary incontinence rises and affects up to 30% of women after 50 years of age. Midurethral slings are currently the mainstay of surgical anti-incontinence therapy. Some patients experience recurrent SUI (RSUI) which is defined as a failure of anti-incontinence surgery after a period of time or persistence of SUI after the procedure aimed at correcting it. The urethral bulking agent application decreases invasiveness of treatment and meets patients requirements. The objective of this study was to assess the safety and clinical efficacy of Urolastic injection. One hundred and five patients with SUI (including 91 patients with RSUI) were treated with Urolastic in three tertiary gynecological clinics. The efficacy of the procedure was assessed objectively at each follow-up visit by means of cough test and a standard 1-hour pad test. Objective success rate after 12 months after primary procedure in RSUI patients was found in 59.3% of patients. In 14 patients with primary SUI improvement after 1 year was found in 71.4% of patients. Although cure rates after MUS are up to 90% there is still place for less invasive treatment option like periurethral injection of bulking agents, especially in patients with previous SUI surgical management.

1. Introduction

Stress urinary incontinence (SUI) becomes social disease and affects up to 30% of women after 50 years of age [1, 2]. In addition the prevalence of SUI is increasing, because of rising prevalence of obesity and diabetes mellitus in demographically aging populations of Western world [3]. Although midurethral slings (MUS) are currently the mainstay of surgical anti-incontinence therapy, some patients experience its failures, indicating the need for an appropriate salvage therapy [4, 5]. Moreover, incontinent women expect more and more to be treated with a minimally invasive surgery. The periurethral application of urethral bulking agent (UBA) in local anesthesia decreases invasiveness of treatment and meets patients' requirements [6]. This method should also be developed in order to make treatment possible in people with varied, often live threatening comorbidities, which makes general anesthesia contraindicated. In ageing population it is very important issue to look for future therapies suitable for more demanding patients from medical point of view. The ideal bulking agent should be easily injectable under local anesthesia, non-absorbable, hypoallergenic, nonimmunogenic and it should maintain its shape, volume, and flexibility in order to exert long-lasting clinical effect [6, 7]. Many different bulking materials had been used as bulking agents in the treatment of SUI with long term (2.8 years) improvement rate up to 80% and cure rate up to 40% [8]. Recurrent SUI (RSUI) is defined as a failure of anti-incontinence surgery after a period of time or persistence of SUI after a procedure aimed at correcting it.

Moreover, the complication of particular concern after primary or secondary sling is the incidence of voiding dysfunction resulting usually from improper tape positioning or its excessive tension [9, 10]. One has to remember that repeating procedures performed on vaginal skin could cause scarred vagina syndrome. This condition markedly decreases every next vaginal procedure's efficacy in the treatment of stress urinary incontinence and causes periurethral pain syndrome [11]. Urolastic is a new bulking agent used in SUI treatment with success rate up to 68% after one year of follow-up and 30% of minor complications related to the injection [12]. Urolastic is composed of following chemical substances: vinyldimethyl terminated polydimethylsiloxane (PDMS) polymer, tetrapropoxysilane cross-linking agent, platinum divinyltetramethyl siloxane complex as catalyst, and titanium dioxide as a radio-pacifying component. It is used since the 1970s as hysteroscopic tubal plugging in women seeking nonhormonal contraception [13]. Urolastic is injected into the periurethral, submucosal tissue around the bladder neck close to the midurethra. The injection creates increased tissue bulk and subsequent coaptation of the bladder neck and urethra, to achieve a better anatomy, closure of the bladder neck and urethra, thus preventing leakage of urine. The primary objective of the present study was to assess the safety and clinical efficacy of Urolastic injection using Stamey incontinence scale grade [14]. The secondary objective was to evaluate the frequency and severity of any foreseeable complications related to Urolastic.

2. Materials and Methods

The study was conducted in accordance with the Declaration of Helsinki, local laws, and regulations relevant to the use of therapeutic agents. Prior to start of the study the protocol was approved by the medical ethics review committee at one of the participating institutions (Warsaw). Between February 2012 and March 2013 one hundred and five patients with SUI (including 91 patients with RSUI) were treated with Urolastic (Urogyn BV, Nijmegen, The Netherlands) in three Polish tertiary referral gynecologic departments. Inclusion criteria for this study were as follows: women with SUI or RSUI as confirmed by medical history and cough test, with at least 2nd grade of incontinence according to Stamey scale, the bladder capacity at least 300 mL or more, and postvoid residual urine of less than 100 mL. Exclusion criteria were detrusor overactivity (DO) or predominately urgency incontinence, pelvic organ prolapse (POP), and suspicion of neurogenic bladder. In RSUI group 77 (85%) of patients had at least one previous midurethral sling surgery, 36 (40%) of them had two previous slings, 9 (10%) had Burch colposuspension, and 5 (5,5%) had anterior colporrhaphy. Mean time from previous surgery in the sling and colposuspension group was 12 months, whereas in colporrhaphy group it was 6 years. Eligible patients were fully informed about the study. The patient received an information sheet and had the opportunity to ask any questions before signing informed consent to participate in the study. Urolastic device consists of a dual container 5 (2 × 2.5) mL syringe. Both ingredients are mixed by means of a static mixer connected to the syringe just before the injection. The bulking material was injected through 18G needle. During injection the syringe is placed in specially designed gun-like injecting device, with ability to inject same amount of Urolastic at each trigger pushing. After injection it becomes permanent and solid. Urolastic was injected, under local anesthesia with 1% lignocaine according to the manufacturer's instructions, at 10, 2, 4, and 8 o'clock positions with 0.5 to 1.25 ccm per spot. If the second injection was needed it was performed 6 weeks after primary procedure and Urolastic was injected only at 4 and 8 o'clock with 0.75 ccm per spot. All injections were performed only by one investigator at each center (KF, JD, and MJ). Immediately after the injection cough test was performed with bladder filled with 200 ccm. Routinely, ciprofloxacin 500 mg bid for 5 days in order to minimize the risk of infection was prescribed. Follow-up visits were scheduled two weeks, six weeks, and 3, 6, and 12 months after primary procedure. The efficacy of the procedure was assessed objectively at each follow-up visit by means of cough test in the supine and standing positions with a comfortably full bladder and a standard 1-hour pad test. A pad weight increase or decrease, when compared to baseline, was then calculated for each patient. Patients were considered completely cured when they were free of all objective SUI symptoms; cough tests as well as a pad test were negative. The procedure was considered as a failure if the patient still reported urine leakage during increases of intra-abdominal pressure, or if the cough tests or pad test was positive. In the improvement group the cough test was negative but patients still reported occasional urinary leakage or the pad test was negative, though the increase in pad weight was minimal: approximately less than 1 gram. Additionally, subjective cure rate was assessed by means of visual analog scale (VAS). Patients had to mark their satisfaction on scaled line with 0–100 endpoints. Stamey incontinence scale was evaluated according to description of the symptoms severity. Statistical analyses were performed with Statistica package version 8.0 (StatSoft Inc., Tulsa, OK, USA). A P value < 0.05 was considered statistically significant. Wilcoxon rank test was carried out to test the difference between outcomes of follow-up visits versus baseline characteristics. Intention to treat (ITT) analysis was taken into account when calculating final results of Urolastic efficacy.

3. Results

Demographic and clinical data of all patients are given in Table 1. Eighty-six patients with RSUI and all treatment-naive patients ($n = 14$) were available for 12-month follow-up, respectively. Eleven RSUI patients and seven treatment-naïve patients required second injection. Objective success rate in patients with RSUI (cured and improved) was found in 54 patients (59.3%) including 45 (49.5%) patients completely dry 12 months after primary procedure. After 1 year, of 14 patients with primary SUI, only 3 patients were totally dry (21.4%), and improvement was found in 10 patients (71.4%). In 10 patients, bladder outlet obstruction (BOO) was observed after injection requiring catheterization for a maximum of 7 days, four of which (40%) required partial removal of the Urolastic material with BOO resolved in all of them. In 4

Table 1: Patients' demographic and clinical data.

Parameter	RSUI ($n = 91$)	SUI ($n = 14$)	P value
Age at surgery (years ± SD)	63.6 ± 9.4	63.3 ± 14.1	NS
Parity n (range)	2.8 (0–6)	2.8 (1–4)	NS
BMI (kg/m^2 ± SD)	30.1 ± 5.7	30.7 ± 6.7	NS
Stamey Score 2° n (%)	45 (49.5)	6 (42.8)	NS
Stamey Score 3° n (%)	46 (50.5)	8 (57.2)	NS
Previous anti-incontinence surgeries (mean)	1.41	NA	NA

other patients, some bulking material had to be removed due to its displacement under the urethra which caused pain and dyspareunia. Urolastic was removed during the following surgery (spiral sling). It was very easy to remove as the implants were oval shaped, silicone-like spheres, and we did not observe any incorporation of thematerial into the surrounding tissues. In case when Urolastic was removed from the bladder in other centers we did not hear about any problems with removing the material during cystoscopy from the bladder wall. Three patients experienced recurrent urinary tract infections and were admitted at urology department where some injected material was removed from the bladder during cystoscopy. We did not observe any type of fistula in these patients. No other serious complications including hemorrhage, periurethral abscess, or vaginal wall erosion were observed. Overall, complications in both groups were observed in 17 patients (16.2%). Stamey incontinence grade was significantly decreased compared to baseline, at 6 and 12 months of follow-up after procedure (both $P < 0.01$). Decrease in Stamey incontinence scale by one grade or more was found in 54 (59.3%) RSUI patients and in 10 patients (71.4%) with genuine SUI. Other results after 6 and 12 months are given in Figures 1, 2, and 3.

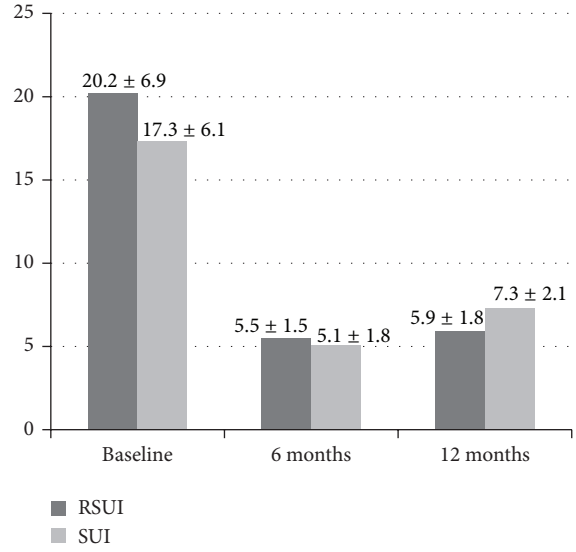

Figure 1: Pad weight test results (g). Change in the pad weight test results: baseline versus 6 months: $P < 0.01$; baseline versus 12 months: $P < 0.01$; and 6 versus 12 months: $P > 0.07$. Wilcoxon rank test, data are presented as a mean ± SD.

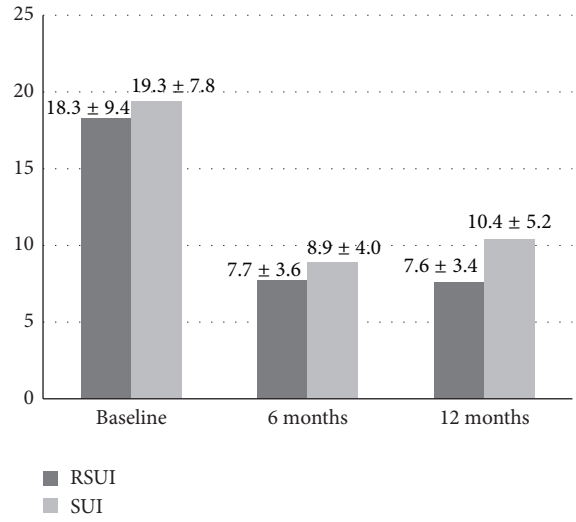

Figure 2: Frequency of incontinence episodes per week (n). Mean numbers of total incontinence episodes: baseline versus 6 months: $P < 0.01$; baseline versus 12 months: $P < 0.01$; and 6 versus 12 months: $P > 0.05$; Wilcoxon rank test, data are presented as a mean ± SD.

4. Discussion

Published to date clinical results after treatment with UBA are difficult to compare because, first of all, they vary in the bulking agent material, second in patient eligibility criteria, and finally in route of injection [15]. There are few other products on the market today, used to treat female SUI. Most of them are resorbable and thus have ephemeral effect. The first popular product that was used as a UBA was Contigen—collagen material, injected under the urethral or bladder neck mucosa (inside lining) to treat incontinence in men and women. No randomized trials comparing Contigen to conservative therapy or placebo were identified. A randomized clinical trial by Corcos and colleagues compared the efficacy of collagen injections with surgery (Burch colposuspension, needle bladder neck suspensions, and slings) in 133 women [16]. Eligibility criteria included stress incontinence for at least 6 months, or one year after delivery. The twelve-month success rate for collagen treatment was lower than for surgery (53% versus 72%). There were also significantly fewer adverse events in the collagen-treated group (36% versus 63%). Results from this study show superiority of surgery against resorbable bulking agent. In 1999 Durasphere was introduced into the market. A double-blind randomized study comparing carbon-coated beads of zirconium to cross-linked collagen was reported as part of the FDA-approval process. The study showed no difference in efficacy or in the number of treatments between

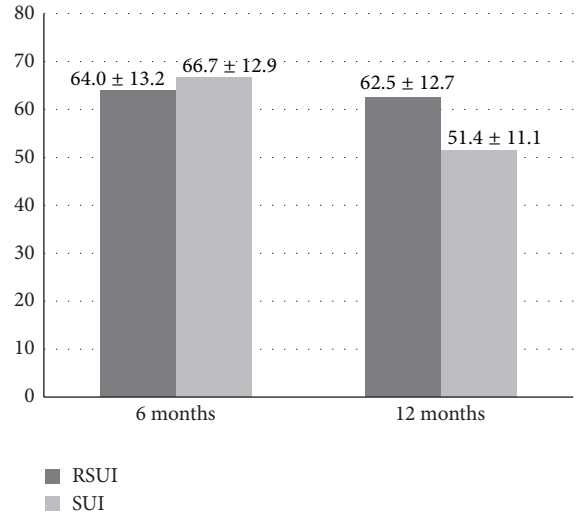

Figure 3: Subjective cure rate as assessed by means of a visual analog scale (VAS), compared to baseline. Subjective cure rate after 6 months: $P < 0.01$ and after 12 months: $P < 0.001$. Wilcoxon rank test, data are presented as a mean ± SD.

the groups, although the trial length of 12 months may not have been long enough to assess comparative durability [17]. The other study performed to compare the efficacy of calcium hydroxylapatite (Coaptite) with collagen in treatment of SUI showed slight advantage of nonabsorbable material. After the 12 months of follow-up 63% of patients treated with hydroxylapatite and 57% of control patients treated with collagen showed improvement by one grade or more on the four-grade Stamey Urinary Incontinence Scale. Similar results were obtained when ITT analysis was done (58% versus 51%, resp.) and decrease in urine loss by 50% or more in pad weight (51% versus 38%, resp.) was considered [18]. Investigation performed by Ghoniem and coworkers comparing the efficacy of Macroplastique with collagen in women with SUI also showed that nonabsorbable material has higher clinical efficacy compared to absorbable collagen (61.2% versus 48%, resp., $P < 0.001$) [19]. There were no serious treatment-related adverse events reported. The rates of treatment related adverse events are similar between the Macroplastique and the Contigen group, but one exception: the occurrence of postprocedure bladder catheterization is significantly higher among Macroplastique treated subjects (43.4% Macroplastique versus 24.0% Contigen). Two-year data on 67 of 75 women who responded to treatment with Macroplastique were further published in 2010. Fifty-six of the 67 (84%) patients had sustained treatment success at 24 months, defined as an improvement by at least one Stamey Score grade compared to baseline. Forty-five of the 67 (67%) patients evaluated at 24 months were still dry (Stamey grade 0). The interpretation of this long-term outcome is somewhat limited because the analysis included 67 (55%) of 122 patients originally randomized to receiving Macroplastique and did not provide data for the patients in the comparison group [20]. There is limited data about UBA in patients with RSUI. Lee and colleagues published results concerning patients treated with UBA after failed MUS [21]. The cure rate was 34.8% for a median follow-up of 10 months. Surprisingly, 92% of the patients reported a benefit and 77% were satisfied with the treatment. Results of our multicenter study are very promising as they concern the minimally invasive SUI treatment method in patients with a history of failed anti-incontinence surgery history. We need to remember that we had to deal with previously treated patients and each additional procedure in such patients may be not so effective as first one. Although the treatment-naive SUI group was substantially smaller than RSUI group, apparent disproportions in results among the groups can be seen. Improvement was much higher in patients with primary incontinence (71.4% versus 59.3%; $P = 0.02$) but full recovery rate was much higher in the RSUI group compared to treatment-naïve patients (49.5% versus 21.4%; $P = 0.005$). According to the presented data, there is a place for Urolastic—minimally invasive UBA—in the treatment of SUI.

Further research should be conducted to verify the long-term efficacy of this novel and promising bulking agent.

5. Conclusions

Although cure rates after MUS are up to 90%, there is still place for less invasive treatment options. Only a carefully selected number of patients will be able to benefit from the periurethral injection of bulking agents, especially patients with previous anti-incontinence surgery. In our opinion the most eligible patients for such therapy are those with low urethral mobility. Higher effectiveness of BA in RSUI patients is probably due to scarred tissue surrounding the urethra which decreases the possibility of injected material displacement over time. The advantage of this method is minimal invasiveness and safety of the procedure.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

A Novel Operative Procedure for Pelvic Organ Prolapse Utilizing a MRI-Visible Mesh Implant: Safety and Outcome of Modified Laparoscopic Bilateral Sacropexy

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Introduction. Sacropexy is a generally applied treatment of prolapse, yet there are known possible complications of it. An essential need exists for better alloplastic materials. *Methods*. Between April 2013 and June 2014, we performed a modified laparoscopic bilateral sacropexy (MLBS) in 10 patients using a MRI-visible PVDF mesh implant. Selected patients had prolapse POP-Q stages II-III and concomitant OAB. We studied surgery-related morbidity, anatomical and functional outcome, and mesh-visibility in MRI. Mean follow-up was 7.4 months. *Results*. Concomitant colporrhaphy was conducted in 1/10 patients. Anatomical success was defined as POP-Q stage 0-I. Apical success rate was 100% and remained stable. A recurrent cystocele was seen in 1/10 patients during follow-up without need for intervention. Out of 6 (6/10) patients with preoperative SUI, 5/6 were healed and 1/6 persisted. De-novo SUI was seen in 1/10 patients. Complications requiring a relaparoscopy were seen in 2/10 patients. 8/10 patients with OAB were relieved postoperatively. The first in-human magnetic resonance visualization of a prolapse mesh implant was performed and showed good quality of visualization. *Conclusion*. MLBS is a feasible and safe procedure with favorable anatomical and functional outcome and good concomitant healing rates of SUI and OAB. Prospective data and larger samples are required.

1. Introduction

Surgical treatment of pelvic organ prolapse (POP) underwent a remarkable transformation over the last decade. Starting with facilitated use of vaginal meshes through simplified mesh kits and followed by Food and Drug Administration (FDA) warnings about their safety there has been a change in practice patterns among urogynecologists. One of the observed trends seems to be a decrease of vaginal mesh use and an increase in sacropexy [1–3].

Abdominal sacropexy which represents the "gold standard" in POP surgery is associated with apical success rates of 93–99% along with low recurrence rates [4]. The laparoscopic sacropexy seems to achieve similar success rates in addition to having advantages of less blood loss, reduced morbidity, and shorter hospital stay [5].

Nevertheless it seems that postoperative dysfunction may have a negative effect upon patient's satisfaction. New onset bowel (10–50%), voiding (18%), and sexual (8%) dysfunction after sacropexy have been described [6–8]. In current literature reports on de-novo stress incontinence after sacropexy, as well as on the obstructed defecation syndrome, are to be found [9, 10]. A further possible complication after sacropexy is mesh erosion. In some recent publications the rates of mesh erosion after sacropexy showed up to be unexpectedly high [11].

Thus there is a challenge to optimize this procedure by site specific defect repair to obtain a better anatomic reconstruction.

Furthermore, the chosen alloplastic material according to its biomechanical characteristics may play a role in minimizing mesh-related complications. There are some data available about nonpolypropylene meshes [12, 13]. In an effort to increase patient's safety some of these meshes have been developed to be MRI-visible [14].

The objective of this study was, therefore, to investigate the safety and outcome of a modification of laparoscopic sacropexy in an effort to abate postoperative complications and dysfunction. In this procedure we utilized a MRI-visible mesh implant with good biomechanical characteristics.

2. Material and Methods

We report on patients who underwent modified laparoscopic bilateral sacropexy (MLBS) between April 2013 and June 2014.

The selected patients consisted of women with symptomatic uterine or vault prolapse ICS POP-Q stages II or III along with overactive bladder OAB symptoms. The OAB was diagnosed either by urodynamic, micturition diary, or both. Patients with previous vault prolapse surgery of any kind and those with contraindications for sacropexy were excluded.

In patients with previous hysterectomy we performed a sacrocolpopexy and in those without previous hysterectomy we performed a laparoscopic supracervical hysterectomy along with a sacrocervicopexy. In the latter a negative papsmear no older than 6 months was required preoperatively.

Out of 32 patients that fulfilled the mentioned criteria and who were eligible for sacropexy in terms of adherence to the guidelines only 10 patients decided to undergo MLBS after obtaining informed consent.

To ensure patients' safety we conducted a very strict and frequent follow-up program. Patients were invited to the follow-up at 1, 3, 6, and 12 months. The follow-up took place at the urogynecology department and included a gynecologic examination, a POP-Q determination, and evaluation of micturition diaries.

All patients signed up an informed consent giving permission to use their medical data.

2.1. Surgical Procedure

2.1.1. Intra-Operative Setting. The procedure is performed under general anesthesia in the dorsal lithotomy position. A 14-F catheter is inserted into the bladder and a uterus or vaginal manipulator is placed transvaginally.

After establishing a CO_2-pneumoperitoneum a 10 mm transumbilical trocar is used for the laparoscopy. Two additional 5 mm access ports are placed medial to and 3 cm superior to the anterior superior iliac spine laterally to the epigastric vessels on each side. One 12 mm access port (12 mm Versaport) is placed 3 cm superior to the symphysis pubis.

2.1.2. Dissection of the Lower Point of Mesh Attachment. In patients with previous hysterectomy we performed a dissection of the vaginal stump and in those without previous hysterectomy we performed a laparoscopic supracervical hysterectomy.

2.1.3. Dissection of a Tunnel for Mesh Placement along the Lateral Pelvic Wall at Each Side. In order to perform a site specific repair of the impaired uterine suspension dissection of a peritoneal tunnel for later mesh placement through the superficial portion of the uterosacral ligament (USL_s) is undertaken.

Identifying the USL is facilitated by ventral traction at the cervical stump or the vault via vaginal manipulator and simultaneous lifting of the rectum cranially and to the contralateral side. After the peritoneal fold overlying the USL_s is depicted blunt dissection of a subperitoneal tunnel is performed using a 5 mm overholt-clamp utilized through the contralateral lower access port.

The preparation is started on the right side and is performed strictly subperitoneally to avoid injury to nearby ureter or parts of the inferior hypogastric plexus (IHP).

The sacral end of the created tunnel corresponds to the upper insertion point of the uterosacral ligaments (USL). This point lays on the anterior surface of the sacrum 3 cm caudal to the promontory and 1.5 cm lateral to the midline. Having identified this point of insertion, the overlying peritoneum is incised and the underlying tissue is bluntly dissected: iliac vessels are bluntly pushed laterally and tissue containing parts of the IHP is pushed medially, thus revealing the periosteum of the anterior surface of S2.

On the left side the procedure is performed identically. It is important to mention that the preparation at the left side is far more difficult due to the anatomical lay of the rectosigmoid junction that must be sufficiently mobilized (Figure 1).

2.1.4. Lower Mesh Fixation/Fixation on the Descent Part. The mesh is inserted via the 12 mm port. The utilized mesh is knitted from nonabsorbable, biostable polyvinylidene fluoride (PVDF) monofilament. We used one of two meshes (DynaMesh-CESA for sacrocervicopexy and DynaMesh-VASA for sacrocolpopexy). Each consists of two thin mesh arms to be placed alongside the lateral pelvic wall with broad ends to be used for sacral fixation and a central part to be attached to the cervical stump or vaginal vault.

A nonabsorbable suture (2.0 Ethibond) is used to fix the central part of the mesh by four simple interrupted sutures.

In case of sewing the mesh to the vaginal vault the same suture can be used but attention should be paid to prevent penetrating the full thickness of the vaginal wall (Figure 2).

2.1.5. Bilateral Mesh Placement through the Created Tunnels. Now the tip of the thin right mesh arm is pulled through the formerly created tunnel. The same is done on the left side, thus achieving a reinforcement of the USL_s (Figure 3).

2.1.6. Sacral Fixation at the Level of the Upper Boarder of S2. Two interrupted nonabsorbable sutures (2.0 Ethibond) are used for the fixation of the broad end of the lateral mesh arm to the periosteum of the anterior surface of S2 at each side (Figure 4).

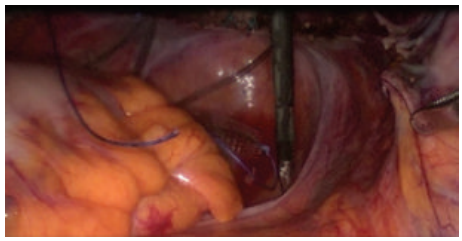

Figure 1

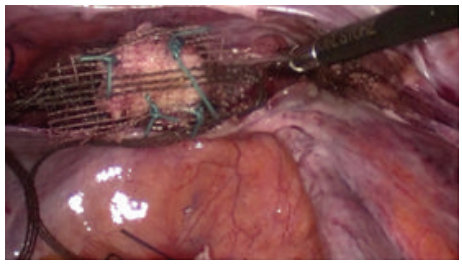

Figure 2

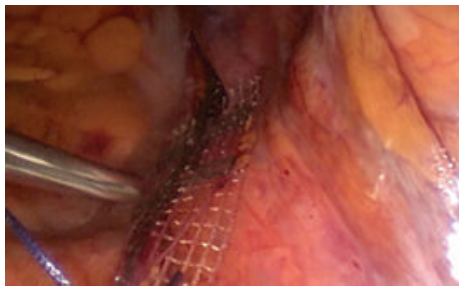

Figure 3

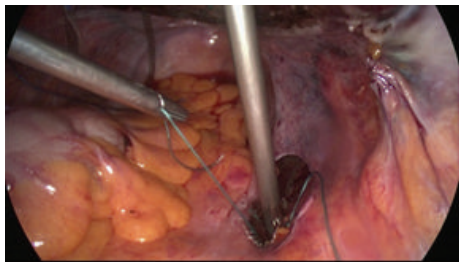

Figure 4

2.1.7. Peritoneal Closure. Closure of the peritoneum is achieved via a continuous suture with an absorbable suture (3.0 Vicryl).

2.2. Visualizing the Mesh in Magnetic Resonance Imaging (MRI). Imaging was performed on a 1.5 Tesla Magnet (Magnetom-Aera Siemens, Erlangen, Germany) using a body-array surface coil, placed over the pelvis.

Table 1: Pre-operative/baseline characteristics.

Age (yrs., mean)	62
Body mass index (kg/m^2, mean)	25.7
Parity (*n*)	
1	2/10
2	2/10
≥3	6/10
Mode of delivery (*n*)	
Spontaneous	10/10
C. section/Forceps	0/10
Other obstetric risk factors (*n*)	
Birth weight > 4,000 gr.	0/10
Birth weight > 4,500 gr.	2/10
Perineal tear grades III or IV	1/10
Menopausal status (*n*)	
Premenopausal	2/10
Postmenopausal	8/10
Hormone replacement therapy (*n*)	3/8
History of prolapse surgery (*n*)	
Anterior compartment	3/10*
Middle compartment	0/10
Posterior compartment	1/10**
History of hysterectomy (*n*)	
Vaginal	3/10
Abdominal	0
Laparoscopic	0

*One of these three patients has had an anterior colporrhaphy twice in her past medical history.
**This patient has had a posterior colporrhaphy twice in her past medical history.

Imaging protocol included both 3D and 2D T1-weighted and T2-weighted sequences. For optimal depiction of the implants, coronal minimum-intensity projections of the 3D datasets were performed.

3. Results

We had performed the MLBS on 10 patients between April 2013 and June 2014. All the operations were performed by the same surgeon at an academic university hospital in Germany.

Preoperative risk factors and morbidity data were analyzed. Table 1 shows the baseline characteristics. We noticed that all patients had given birth via spontaneous vaginal delivery and that 6 (6/10) of them have had 3 or more deliveries. Furthermore, 2 (2/10) of the patients have had a macrosomic baby weighing ≥ 4,500 grams.

In terms of previous prolapse surgery, 2 (2/10) patients have had previous anterior colporrhaphy and 1 (1/10) patient has had concomitant anterior and posterior colporrhaphy for two times in her past medical history.

Regarding the prolapse, 4 (4/10) patients were POP-Q stages II and 6 (6/10) POP-Q stage III preoperatively (Table 2). We took the mean of each POP-Q measurement in all patients to estimate the POP-Q stage resulting from the

Table 2: Pre- and postoperative quantification of the prolapse.

	POP-Q measurements (cm)					
	Aa	Ba	C	D	Ap	Bp
Preoperative						
Mean	1.2	2.1	−0.2	−1.5	−2.1	−2.1
Median	1.0	1.5	−0.5	−2.0	−2.5	−2.5
Range	0 to +3	0 to +5	−4 to +3	−4 to +1	−3 to +1	−3 to +1
n	*10*	*10*	*10*	*7*[*]	*10*	*10*
Postoperative						
Mean	−1.5	−1.1	−6.3	−8.0	−2.7	−2.7
Median	−1.0	−1.0	−6.0	−8.0	−3.0	−3.0
Range	−3 to 0	−3 to 0	−7 to −5	−7 to −9	−3 to −1	−3 to −1
n	*10*	*10*	*10*	*7*[*]	*10*	*10*
Diff. postoperative to preoperative						
Mean	2.7	3.2	6.1	6.5	0.6	0.6
Median	2	2.5	5.5	6	0.5	0.5
Range	1 to 4	1 to 6	3 to 10	4 to 10	0 to 3	0–3
n	*10*	*10*	*10*	*7*[*]	*10*	*10*

[*]3 patients had a hysterectomy in their past medical history, so that measurement D is not applicable.

Table 3: Pre- and postoperative quantification of the prolapse in respect of each compartment.

POP-Q measurement (cm) and POP-Q stage according to each compartment	Ant. compartment	Mid. compartment	Post. compartment
Preoperative			
Mean	Aa: +1.2/Ba: +2.1	C: −0.2/D: −1.5	Ap: −2.1/Bp: −2.1
Mean	Stage III	Stage II	Stage I
Median	Stage III	Stage II	Stage I
n	*10*	*10*	*10*
Postoperative			
Mean	Aa: −1.5/Ba: −1.1	C: −6.3/D: −8.0	Ap: −2.7/Bp: −2.7
Mean	Stage I	Stage 0	Stage 0
Median	Stage I	Stage 0	Stage 0
n	*10*	*10*	*10*

descent of each compartment by its own (Table 3) to facilitate later comparison with the postoperative results.

All selected patients were suffering from urgency and frequency, of whom 9 (9/10) suffered from OAB-dry and 1 (1/10) from OAB-wet. Further 6 (6/10) patients were suffering from stress urinary incontinence (SUI). The mean frequency of micturition was 13.3 mic./d. and the mean nocturia was 2.3 micturitions/night (Table 4).

Table 5 shows the perioperative data. Low blood loss is reflected by rather small change in hemoglobin levels postoperatively. Regarding concomitant operations, only 1 (1/10) patient required an anterior and posterior colporrhaphy. In the other 9 (9/10) patients the anterior and posterior compartments were sufficiently corrected after performing the MLBS.

Anatomical success was defined as POP-Q stage 0 or I. Postoperative results show that 2 (2/10) patients were POP-Q stage 0 and 8 (8/10) were POP-Q stage I.

Using the mean of each POP-Q measurement in all patients to estimate the POP-Q stage of each compartment by its own shows a mean postoperative POP-Q stage 0 for the middle and posterior compartments and a POP-Q stage I for the anterior compartment (Table 3).

The difference between the pre- and postoperative status is lined out in Figure 5.

Postoperative evaluation of urinary incontinence showed that 8 (8/10) patients did not suffer from OAB anymore, whereas 1 (1/10) patient had persistent OAB-dry. One other patient (1/10) had a reduction of her urgency and frequency that was reduced postoperatively from 11 to 7-8 mic./d. Yet she reported bothersome mild urgency despite absent proof of OAB. We regarded that as persistent OAB (Table 4).

Out of 6 (6/10) patients with preoperative SUI only 1 (1/6) patient had persistent SUI postoperatively. Additionally 1 (1/10) patient was diagnosed with de-novo SUI. The mean frequency of micturition was reduced to 8 mic./d. and the mean nocturia to 1.2 micturitions/night (Table 4).

Table 6 shows patients' adherence to the follow-up examinations conducted in our department of urogynecology. At

Table 4: Pre- and postoperative quantification of the urinary incontinence.

Incontinence	OAB-dry	OAB-wet	SUI	SUI grade		Frequency of mictur. *n*./d.*	Nocturia *n*./d.*	Pads used *n*./d.*
				1	2			
Preoperative	9/10 (90%)	1/10 (10%)	6/10 (60%)	3/10 (30%)	3/10 (30%)	13.3	2.3	2
n:	10	10	10	10		10	10	8
Postoperative	2/10** (10%)	0/10 (0%)	2/10 (20%)	0/10 (0%)	2/10 (20%)	8.6	1.2	0.4
n:	10	10	10	10		8	8	7

*n./d.: number per day.
**One other patient had no evidence of OAB in the urodynamic or micturition diary and still reported urgency.

Table 5: Intra- and perioperative data.

Concomitant surgery (*n*)	
LASH (laparoscopic supracervical hysterectomy)	7/10
Salpingectomy	2/10
Salpingooophorectomy	5/10
Ovarian cystectomy	1/10
Adhesiolysis of omentum or bowel	5/10
Anterior colporrhaphy	1/10
Posterior colporrhaphy	1/10
Haemoglobin (mean, g/dL)	
Preoperative	13.9
Postoperative day	12.0
Postoperative before discharge	12.4
Need for analgesics postoperatively (*n*, %)	
Piritramid 0–6 h.	9/10
Piritramid or other short acting opioids 6–48 h.*	1/10
NSAID in medium dose 6–48 h.	7/10
NSAID in low dose 6–48 h.	3/10
NSAID regularly in a low dose 3–5 d.	2/10
NSAID on demand in a low dose 3–5 d.	6/10
NSAID on demand in a low dose beyond 6 d.**	1/10
Hospital stay (days)	
Mean	5.9
Range	3 to 11

*Given in the intermediate care unit (ICU).
**This patient was discharged and took NSAID on demand at home.

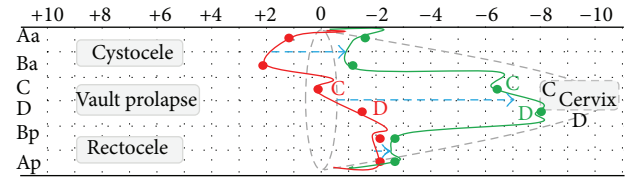

Figure 5: Correction of prolapse in each compartment. The dots correlate to the mean measurements of Aa, Ba, C, D, Ap, and Bp. Red line: lines out the preoperative status (POP-Q measurements). Green line: lines out the postoperative status (POP-Q measurements) before discharge.

times 4 (4/10) patients had completed the one-year follow-up, whereas the average follow-up for all patients was 7.4 months.

3.1. Complications. Postoperative complications were carefully analyzed and are listed in Table 7. We classified these complications by using the Clavien-Dindo grading of surgical complications [15, 16].

Furthermore, we divided the complications into early, midterm, and late complication according to the time of their occurrence.

Regarding early complications, one (1/10) patient suffered from paresthesia of the right thigh. We performed a MRI that revealed the implanted mesh in the desired lay and ruled out any neural compression or hematoma (Figures 6 and 7).

The symptoms declined after reassurance and use of NSAID for a few days and had completely resolved 1 month postoperatively. The same patient suffered from de-novo SUI, which required a placement of a TVT. Since the procedure was performed under regional anesthesia the patient was classified as suffering a complication grade III_a.

Furthermore, 1 (1/10) patient suffered from persisting SUI, which required a placement of a TVT and 2 (2/10) patients reported mild pain in the sacral region, which was treated by NSAID in a low dose on demand for 2-3 weeks. There was no need for further intervention as the pain resolved in less than 3 weeks.

One (1/10) patient required a relaparoscopy on the second day postoperatively due to a hematoma of the right pelvic wall. The bleeding showed to be from the right ovarian vein and management required a laparoscopic salpingooophorectomy. This patient additionally had a recurrent UTI that was treated with an antibiotic. Since management of this patient required general anesthesia the patient was classified as suffering a complication grade III_b.

There were no midterm complications whereas follow-up revealed one late complication comprising lower abdominal pain. Diagnostic laparoscopy revealed a 1.5 cm long opening in the peritoneum overlying the right lateral mesh arm approximately 2 cm from the cervical attachment point. Laparoscopic mobilizing of the peritoneum and closure above the underlying portion of the mesh were performed.

During the whole follow-up no vaginal mesh erosion, no chronic pelvic pain and no dyspareunia were seen. Apical success was observed in all the 10 (100%) patients and persisted throughout follow-up.

No recurrent prolapse surgery had to be performed. Only 1 (1/10) patient had a recurrence in the anterior compartment

Table 6: Follow-up examinations.

	Follow-up 1 3–6 weeks	Follow-up 2 2–4 months	Follow-up 3 6-7 months	Follow-up 4 11–14 months	Follow-up (mean/range)
Follow-up completed (*n*)	1/10	9/10	6/10	4/10	7.4 months/1 to 14 months

Table 7: Description and classification of postoperative complications according to the Clavien-Dindo grading system.

Post-operative complications	Type of complication (*n*)	Management	Classification Clavien-Dindo grading sys.
Early complications days 01 to 30	Intraperitoneal hematoma* 1/10	Relaparoscopy day 2	Grade III_b 1/10
	Recurrent UTI* 1/10	Antibiotics	Grade I 1/10
	Paraesthesia in right thigh** 1/10	MRI/spontaneous resolving	Grade I 1/10
	De-novo SUI** 1/10	Urodynamics/TVT	Grade III_a 1/10
	Persistent SUI 1/10	Urodynamics/TVT	Grade III_a 1/10
	Mild sacral pain 2/10	Reassurance/NSAID	Grade I 2/10
Midterm complications days 31 to 90	None		
Late complications >90 days	Lower abdominal pain (erosion of the peritoneum) 1/10	Relaparoscopy day 119	Grade III_b 1/10
	Recurrence of a mild cystocele	Not bothersome, no treatment.	Grade I 1/10
	Intraperitoneal Hematoma* and adhesions. 1/10	Relaparoscopy	Grade III_b 1/10

*The same patient in 3 occasions: 2 early and 1 late complications.
**The same patient in 2 occasions: 2 early complications.

at 13 months follow-up showing a mild cystocele without any discomfort. Since the patient had normal bladder function and no relevant residual volume, no correction was indicated.

Thus to summarize the early complications we say that one patient had a complication classified as Clavien-Dindo grade I (UTI) and another one classified as Clavien-Dindo grade III_b (hematoma).

Another patient had one complication classified as Clavien-Dindo grade I (spontaneous resolving paresthesia of the thigh) and another one classified as Clavien-Dindo grade III_a (de-novo SUI). A third patient had a complication classified as Clavien-Dindo grade III_a (persistent SUI).

That means that we had early complications requiring a higher pharmacologic, surgical, or radiologic intervention (Clavien-Dindo grades higher than grade I) in 3 (3/10) patients, representing the relevant early complication rate.

4. Discussion

The uterosacral and cardinal ligaments (CL) are regarded the main anatomical support of the uterus and vault [17]. In a MRI-based study DeLancey estimated the lines of action and the tension load of both USL and CL showing that thetension on these ligaments is affected by their orientations [18].

As for the anatomical lay and histologic composition the USL can be divided into a superficial (USL_s) and deep (USL_d) part. The superficial part mainly comprises smooth muscle and connective tissue, whereas the deep part is of a neurovascular composition, as is the CL.

Taking this in regard, the USL_s seem to be the best accessible and anatomically safest part of both ligaments to operate on. Thus making it the most suitable to perform a site specific prolapse repair upon.

Regarding the operative technique, the critical steps are the dissection of a tunnel along the USL_s and the dissection at the sacrum at the level of S2.

The dissection of the tunnel has to be strictly subperitoneally. In the middle part of the uterosacral ligament (and the dissected canal) the distance to the ureter is 1–1.5 cm [19, 20]. Furthermore attention is paid to perform strict superficial

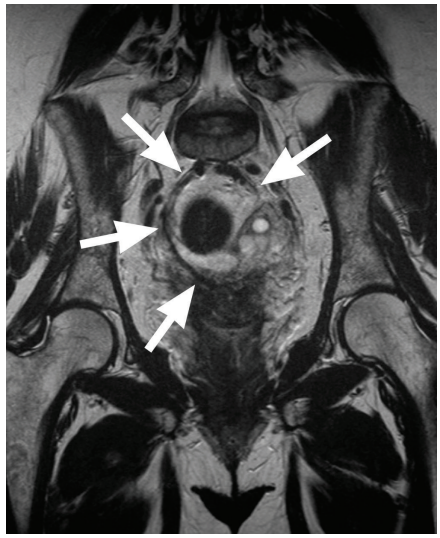

Figure 6: Coronal subvolume minimum intensity projection of a T2-weighted dataset, displaying the implant with a low signal intensity (arrows), comparable to the signal of muscle tissue.

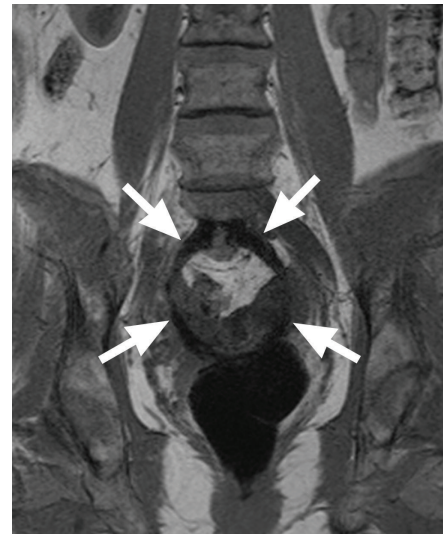

Figure 7: Same patient as in Figure 6, this time a T1-weighted dataset, again with a coronal subvolume minimum intensity projection. Using the T1-weighted images, the contrast between the implant and the surrounding tissue is even better. Due to the iron oxide particles, a signal loss in the area of the implant is obvious (arrows), which allows for exact identification of the implant.

preparation in order to keep a safe distance to the USL_d which is the neurovascular part.

Due to limited access when using a rigid laparoscopic instrument to create a curved tunnel of 5-6 cm of length, overdue tension at the peritoneum during dissection may accidently be applied. This may eventually cause a localized thinning of it. In the case of the patient who presented with a late complication of lower abdominal pain and localized opening in the peritoneum overlying part of the mesh (mentioned under 3.1 complications) this thinning may be a predisposing factor.

The complication of postoperative hematoma in the cervical region (mentioned under 3.1 complications) may be due to the supracervical hysterectomy. The later performed salpingooophorectomy was conducted because of a necrosis of the right ovary that may have been caused by a vascular shortage after hysterectomy or by electrocoagulation during hematoma revision.

Regarding the two patients who required a TVT, one had persistent SUI which means that 5/6 patients who suffered from SUI were cured after anatomical correction of the prolapse alone. On the other hand there was only 1/10 patients presenting with de-novo SUI. Due to the small sample size it is not possible to compare the apparently good results to other series, but as for this small sample results it seemed to be better than in a lot of published series [9].

This may also be related to our therapeutic protocol, since we only perform a colporrhaphy if the residual cysto- or rectocele after apical stabilization corresponds to POP-Q stage ≥ 2 (i.e., Aa, Ba, Ap, or Bp ≥ -1) to prevent undue overcorrection. In this series 1/10 patients had received a concomitant anterior and posterior colporrhaphy. Recently Leclaire found that a greater reduction in point Aa is a risk factor for de-novo SUI after sacropexy [9].

In terms of reduction of urge symptoms, we had 7/10 patients in whom OAB-dry dissolved as well as 1/10 with OAB-wet. Altogether 8/10 patients were relieved from OAB symptoms after the operation which is a good result. These results seem consistent with the results shown by abdominal mesh placement displayed in a series [21].

Summarizing, we had a 100% apical healing rate in this small sample of patients along with good anatomical results in the anterior compartment. The functional outcome seems to be favorable, yet a comparison with available data from abdominal or laparoscopic sacropexy series is not possible due to the small sample size.

In the ongoing debate on the use of meshes in prolapse surgery the choice of the material plays a critical role. The mesh we used is one with full ce-mark made up of PVDF. Many data suggest that this material has favorable properties. Comparison of PVDF and polypropylene (PP) in rodent model showed a better biocompatibility and less foreign body reaction with PVDF [22].

Furthermore it is well accepted that meshes for POP surgery should be macroporous. The used alloplastic material possesses a higher porosity under strain than most meshes do [23]. Further data are required to evaluate to what extent these properties may positively influence the postoperative outcome in patients.

The application of meshes made of PVDF is widely used in hernia repair. Berger and Bientzle reported a large prospective study in 2009 [24]. As for the application in POP-surgery, Noé et al. reported the use of this material in a prospective clinical trial [25].

The same mesh we applied was used for an abdominal procedure of abdominal sacropexy described by Jäger et al. who reported a cure rate of urge incontinence of 77% [21].

Regarding our knowledge about mesh properties after implantation it has to be stated that it is very limited in the case of sacropexy. Since the standard meshes are "invisible" for radiologic examinations or MRI the only way to evaluate them after implantation is by means of ultrasound.

Performing pelvic floor ultrasound provides valuable information about vaginal meshes but rather few information about meshes used for sacropexy because it is not capable of showing the meshes lying above the pelvis. Thus the relationship of the mesh to the sacral fixation point could not be investigated well so far.

Further on, a possible complication—like mesh detachment or compression of nerves or vessels in the presacral space—occurring above the pelvis could not be investigated through imaging so far and often required reoperation to visualize the area of concern.

In a step toward higher patients' safety effort was undertaken to enhance the visibility of meshes in radiologic examinations.

Krämer et al. first introduced a concept for MRI visualization of surgical meshes by integrating iron oxide particles into them in 2010 [14]. The first MRI visualization of an implanted mesh for inguinal hernia repair was reported in 2013 [26].

In our series we had three patients in whom we performed a MRI because of postoperative complaints. In these presented cases there was no need for surgical intervention since a complication was ruled out through MRI.

So the use of MRI comprises the only nonoperative way to visualize and evaluate the lay of an implanted mesh and may reduce the need for reoperations in case of postoperative complications. Additionally it gives the unique opportunity for the evaluation of changing mesh characteristics over time giving us new opportunities to study mesh behavior after implantation. This may be helpful in better understanding of causes for mesh related complications in POP surgery.

In this paper we presented the first in-human magnetic resonance visualization of a prolapse mesh implant. The performed MRIs showed a very good visualization of the mesh in addition to the nearby structures and were helpful in the management of postoperative complications.

5. Conclusion

Modified laparoscopic bilateral sacropexy (MLBS) is a feasible and safe operative procedure. The preliminary data are encouraging, showing favorable anatomical and functional outcome and good concomitant healing rates of SUI and OAB. The MRI-visibility of the implanted mesh has a good quality and is helpful in postoperative complication management. For further evaluation we are planning to perform a prospective study with a larger sample.

Abbreviations

CL: Cardinal ligaments
FDA: Food and Drug Administration
ICS POP-Q: International Continence Society Pelvic Organ Prolapse Quantification
IHP: Inferior hypogastric plexus
MLBS: Modified laparoscopic bilateral sacropexy
MRI: Magnetic resonance imaging
NSAID: Nonsteroidal anti-inflammatory drug
OAB: Overactive bladder
POP: Pelvic organ prolapse
PP: Polypropylene
PVDF: Polyvinylidene fluoride
SUI: Stress urinary incontinence
S2: Second sacral vertebrae
TVT: Tension-free vaginal tape
USL: Uterosacral ligaments
USL_s: Superficial portion of the uterosacral ligament
USL_d: Deep portion of the uterosacral ligament
UTI: Urinary tract infection.

Conflict of Interests

The authors declare a conflict of interests: Speaker fee in conferences in issues partially concerning the product used.

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Clinical Study

Coating of Mesh Grafts for Prolapse and Urinary Incontinence Repair with Autologous Plasma: Exploration Stage of a Surgical Innovation

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Purpose. Optimized biocompatibility is a major requirement for alloplastic materials currently applied for stress urinary incontinence (SUI) and pelvic organ prolapse (POP) repair. In the preliminary studies the mesh modification by coating with autologous plasma resulted in the increased adherence score *in vitro* and improved biocompatibility in an animal model. The first use of plasma coated meshes in human is presented. *Materials and Methods*. Between 04/2013 and 05/2014, 20 patients with the indication for SUI and POP repair were selected in a single institution. The applied meshes were modified by autologous plasma coating prior to implantation. A retrospective chart review for peri- and early postoperative complications was performed. Functional outcome and QoL were evaluated pre- and postoperatively. *Results*. The functional outcome and QoL improved significantly in all groups. Two reoperations (Grade IIIB) with the release of TVT-mesh in anesthesia due to the obstruction were needed. No other severe complications were registered. *Conclusion*. For the first time we applied a mesh modification in a human setting according to *IDEAL* criteria of surgical innovations. The procedure of mesh coating with autologous plasma is safe and a prospective randomized trial proving a positive effect of plasma coating on the biocompatibility and morbidity outcome with long-term registry is planned.

1. Introduction

Currently the approval of medical devices as surgical meshes is regulated by American Food and Drug Administration (FDA) and European guidelines according to risk classification. Clinical trials and postmarket followup were not required for the commercial approval. In a Public Health Notification (PHN), from 2008, the FDA reported more than 1000 unexpected and severe adverse events, associated with transvaginal placement of surgical mesh to treat POP and SUI. In 2011, a second FDA warning has been amended, proposing an upgrading in risk classifications for meshes, which would allow the request of premarket approval and postmarket surveillance studies [1].

Meshes or grafts potentially add to the complication profile the aspects of trauma of insertion, foreign body reaction to the implant in terms of inflammation, infection and/or rejection, and the stability of the prosthesis over time [2]. Polypropylene meshes (Type 1, Amid-classification) are usually used for vaginal repair of POP and SUI [3]. The rate of

Table 1: Material and biomechanic characteristics of selected meshes [7, 9, 10, 14, 28–31].

Mesh	Material	Biomechanic characteristics	Adhesion score (Melman)	Adhesion score after coating with plasma (Melman)
Seratim PA, Serag Wiessner	Monofilament polypropylene, polyglycol acid, and caprolacton	Partly absorbable (90–120 days) Pore size: 5800 μm (11 mm^2) Weight: 15 g/m^2 (after resorption) Thickness: 0.5 mm Tear resistance (Fmax): 80 N	2.5	Pending
Vitamesh, ProxyBiomedical	Monofilament polypropylene	Nonabsorbable Weight: 35 g/m^2 Pore size: 2410 μm Thickness: 0.25 mm Tear resistance (Fmax): 33.7 N	1.6	1.9
UltraPro, Ethicon	Monofilament polypropylene reinforced with poliglecaprone fibers (Monocryl)	Partly absorbable (90–120 days) Pore size: 3000–4000 μm Weight: 28 g/m^2 (after resorption) Thickness 0.5 mm Tear resistance (Fmax): 69 N	1.4	1.6
TVT, Johnson and Johnson	Monofilament polypropylene	Nonabsorbable Pore size: <1000 μm Weight: 105–110 g/m^2 Thickness: 0.7 mm Tear resistance (Fmax): about 10N	1	1.6

mesh-related complications after transvaginal mesh application for POP is about 15–25% and especially mesh erosion up to 10% for these indications [4, 5]. Most common complications after MUS (midurethral sling) are obstruction, *de novo* urge, chronic pain, dyspareunia, and mesh erosion [6]. The complications are attributed to a considerable extent to the wrong indication and faulty surgical techniques; material properties are the other reasons. The choice of the optimal mesh for a particular indication with the highest functionality (hold shape) as well as minimized side effects remains difficult. Mesh material (type of polymer, pore size, and material weight, etc.) and its biocompatibility were detected to be crucial parameters [7, 8]. A biocompatibility is described by the foreign body reaction (FBR) at the host-tissue/biomaterial interface. The dynamic of the FBR is given by the inflammatory host response depending on the biomaterial composition (Table 1) [7, 9, 10]. The current understanding about an optimized surgical mesh describes a material that permits the transmigration and localisation of beneficial host cells and if directly exposed to visceral organs, vessels, or nerves it strongly inhibits the adherence of the respective organs in order to avoid erosion, foreign body provoked pain, and so forth. Inert (Titan), (partly) absorbable, light-weight materials are currently under development. Sophisticated methods, like preoperative coating of meshes with a protective layer on the visceral side of the mesh, have been frequently investigated, mostly *in vivo* [11, 12]. They seem to present a potential approach to reduce foreign body reaction and improve biocompatibility and therefore have been introduced in mesh applying surgery.

In a considerably narrow time frame, reacting to the first and second FDA warnings, our international scientific collaboration group has recently developed and concluded preliminary studies in order to investigate and improve biocompatibility of surgical meshes. Our entire innovative approach has been conducted following the five-step *IDEAL* model for surgical innovations (*Innovation, Development, Exploration, Assessment, and Long-term study*) with the aim of maintaining it comparable and reproducible at every single step of development [13]. A validated *in vitro* test system to compare biocompatibility features of different meshes has been developed (*Idea*, first stage) [9]. This test system was subsequently expanded, to show that mesh modification by autologous plasma coating results in higher biocompatibility and adherence score *in vitro* [9, 10]. The predictability of these approaches, biocompatibility evaluation, and improvement by plasma coating could then be validated and confirmed in a two-year large animal study (*Development*, second stage) [14]. In particular, an early inflammation reaction seems to be influenced by the coating procedure [15]. Herewith we present a consecutive study on the first clinical assessment of meshes modified by autologous plasma coating in human (*Exploration*, third stage).

2. Materials and Methods

Patients (age > 18 y) with surgical indication for SUI (Stamey grade ≥ I) and POP (POP-Q Grades I–III and anterior and apical prolapse) repair with mesh were selected after the informed consent. In case of POP and SUI a concomitant *Burch* colposuspension was performed. All patients experienced an unsuccessful treatment with medicaments and physiotherapy prior to operation. The male patients presented a moderate SUI (grade I-II, 2–6 pads/day) after radical prostatectomy. Urodynamics and urethrocystoscopy were performed prior to the operation and a partial defect of the

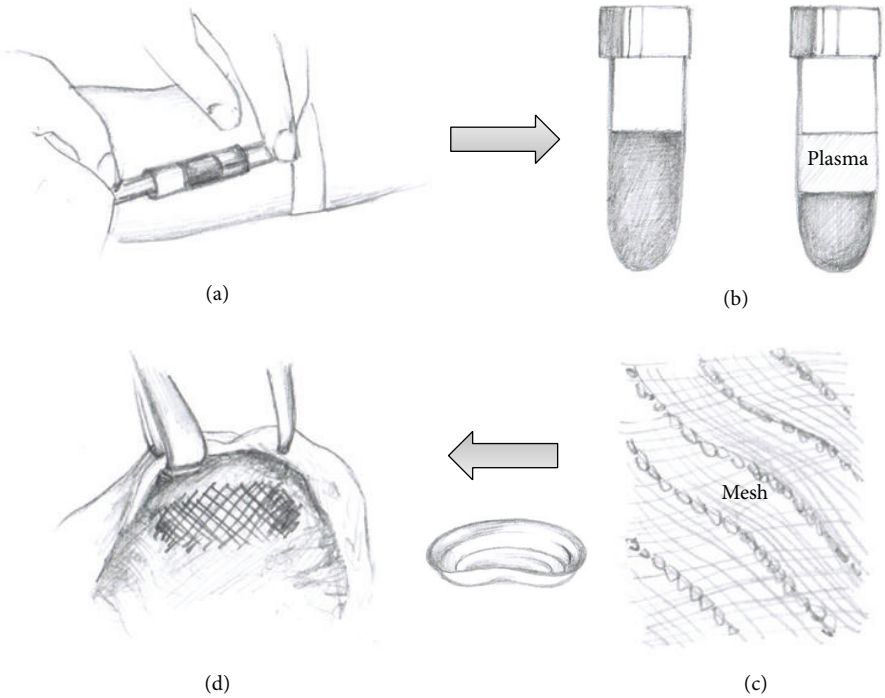

Figure 1: The technique of mesh coating with autologous plasma. (a) Vein puncture, 20–40 mL blood is obtained in EDTA-tube before anesthesia. (b) Centrifugation of blood sample in the operation room. (c) Plasma is abstracted and incubated with the mesh in a bowl. (d) The coated mesh is implanted. The rest of plasma is spilled over the implantation site.

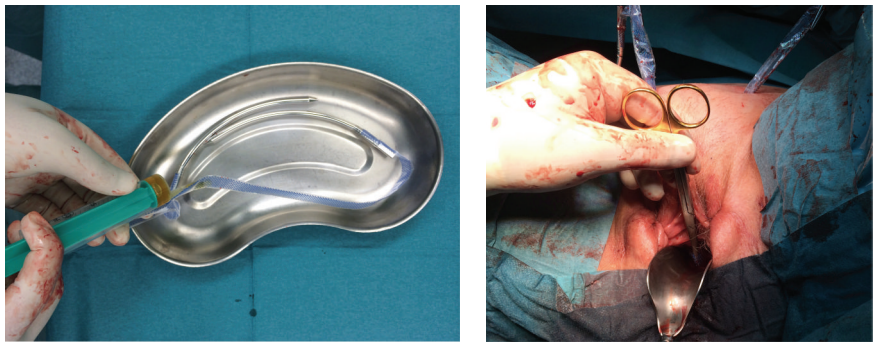

Figure 2: TVT-procedure. (a) Coating of TVT-mesh with autologous plasma. (b) Insertion of retropubic midurethral sling.

external sphincter was revealed. According to the *IDEAL* model a sophisticated, well-defined selection of patients was performed. The exclusion criteria were previous mesh implantation at the operation site, infection, chemo- or immunological therapy during the last three months, psychiatric illness or inability to answer the questionnaire, and pregnancy. Different mesh materials were used (TVT, Seratim, Ultrapro, and Vitamesh) (Table 1). 20–40 mL blood sample was obtained in the EDTA-tube (ethylenediaminetetraacetic acid) from the respective patient by vein puncture before the induction of anesthesia. The blood collection and centrifugation of blood sample (4000 rpm for 10 min) was performed in the operation room in order to prevent the contamination. The clear supernatant (plasma) after centrifugation of the precipitation was removed with sterile syringe. Before the implantation the meshes were incubated for 30 min with 10–20 mL (depending on the size of the mesh) autologous plasma in a bowl (Figures 1 and 2). The surgical technique was not altered by the application of this technology (Figure 2). The patients were examined pre- and postoperatively and interviewed before the operation and on telephone 6–8 weeks after the operation. For high grade POP (grade ≥ III) a perioperative ureteral stenting for about two weeks was performed. Ultrasound controls for residual urine volume and hydronephrosis were done after catheter removal on the third postoperative day. In cases of obstruction due to MUS (midurethral sling) a prolonged catheterisation was needed. If the voiding dysfunction persisted (residual volume >

Table 2: Patient characteristics.

Procedure	TVT	TOT	Anterior vaginal mesh	Sacrocolpopexy
Number of patients (gender)	7 (female)	4 (male)	1 (female)	8 (female)
Age, mean (yr)	67 (57–85)	71 (70–72)	58	64 (45–75)
Operation time, mean (min)	36 (31–49)	46 (42–55)	51	57 (43–71)
Followup, median (mos)	3 (2–4)	4 (2–7)	3	3 (1–4)
Concomittant procedures	1 × SSF	No	1 × SSF	8 × *Burch*, 1 × Rectopexy

SSF: sacrospinous fixation.

Table 3: Peri- and early postoperative complications.

Procedure	TVT	TOT	Anterior vaginal mesh	Sacrocolpopexy	Total	IUGA/ICS-classification
Number of patients (gender)	7 (female)	4 (male)	1 (female)	8 (female)	20	
Complications, number (%)						
Clavien-Dindo Grade I						
Prolonged pain	0	1 (25%)	0	1 (12.5%)	2 (10%)	6Be/S4
Hematoma	1 (14%)	1 (25%)	0	0	2 (10%)	7A/S3/S4
Urge *de novo*	3 (43%)	0	0	0	3 (15%)	4B/site?
Obstruction (prolonged cath.)	1 (14%)	0	1 (100%)	0	2 (10%)	4B/site?
Grade II						
UTI	2 (28%)	0	0	2 (25%)	4 (25%)	4B/site?
Grade III						
Obstruction (reoperation)	2 (28%)	0	0	0	2 (10%)	4B/S1
Bladder/bowel injury	0	0	0	0	0	4A/S3, 5A/B/S5
Fistula	0	0	0	0	0	4/5B/S1 or S2
Mesh exposure	0	0	0	0	0	2B or 3B/S1 or S2
QoL improved	6 (86%)	2 (50%)	1 (100%)	7 (87.5%)	16 (80%)	

200 mL) an endoscopic evaluation with cystoscopic release of the sling was performed. The patient charts were searched for perioperative and early postoperative complications. The safety of our technology for the patient was validated by the Clavien-Dindo classification of surgical complications and ICS/IUGA classification [2, 16]. The quality of life (QoL) was assessed by P-QOL and ICIQ-SF 2004 questionnaires [17]. In cases of explantation the immunhistochemistry analyses of the mesh are planned [7, 14].

3. Legal Requirements

The application of autologous blood plasma coating was performed according to the German Pharmaceutical Law (AMG), the Medical Product Act (MPG) and the Transfusion Act. The permission for this new experimental method was provided by local government. According to the statement of the local government, the preparation of autologous blood plasma and the modification of the mesh by the coating procedure are subject to paragraph 13, 2 b, of the AMG and no permission according to paragraph 13, 1, of the AMG is necessary.

The patients were carefully educated on the experimental technique and possible complications. Because of the retrospective data evaluation no ethical approval was necessary.

4. Results

Between 04/2013 and 05/2014, 20 patients (16 females and 4 males) with the indication for SUI and POP repair with mesh graft were selected for surgery in a single institution. The patient characteristics are described in Table 2. The mean age was 67 years (45–85) and the mean followup was 3 months [1–7]. 11 patients were treated for SUI (grades II-III, Stamey score) and 9 patients were treated for POP (POP-Q grades I–III, anterior and apical prolapse). In 50% of patients concomitant operations (*Burch* colposuspension, sacrospinous fixation, and rectopexy) were performed. No intraoperative problems or complications (transfusion reaction, etc.) associated with mesh coating with autologous plasma were observed. Two reoperations (10%, Clavien-Dindo Grade IIIB) with the cystoscopic release of TVT-mesh in anesthesia due to the obstruction were needed. No other severe complications (mesh exposure, bladder or bowel injury, and fistula) were registered. Prolonged perineal paraesthesia and hematoma were observed in 2 cases after TOT (50%) (Table 3). An 85-year female with extended usage of analgesics and antidepressant agents presented a prolonged voiding dysfunction after TVT. Prolonged catheterization and the cystoscopic release were not successful. A suprapubic tube was inserted, the antidepressants were reduced, and the medication with Ubretid was started. A 76-year female presented persisting SUI after the anterior POP repair (grade III)

with sacrocolpopexy and consecutive TVT (plasma-coated). The postoperative examination revealed a persisting Grade II-cystocele. A reoperation with colporrhaphy and plasma-coated vaginal mesh application is planned. Two of four male patients after TOT procedure complained about persisting SUI (>1 pad/day); in these cases an artificial urinary sphincter was planned. The functional outcome and QoL improved overall in all groups during the followup. No mesh resections or explantations were necessary up-to-date.

5. Discussion

The preliminary work on the principles of plasma coating were described in *in vitro* and animal studies previously [9, 10, 14, 15]. Our study illustrates the first clinical usage of the mesh modification by autologous plasma for POP and SUI repair. The observed early perioperative complications correspond to the data of current meta-analyses and studies [4, 5, 18]. Voiding dysfunction, UTI, recurrent SUI, and paraesthesia were described previously and are associated mostly with the surgical technique and not to the mesh modification. The procedure is safe and offers good functional results. The only Grade III (Clavien-Dindo) complication in the TVT-group was the obstruction with the need of reoperation. This complication is due to the operation technique and has no relation to the coating procedure. The technique of plasma coating is an easy-to-do and timely procedure. No additional complications or intraoperative problems due to this technique were observed. The complications were graduated according to Clavien-Dindo and ICS (International Continence Society)/IUGA (International Urogynecologic Association) classification. The ICS/IUGA classification is based on the information on the category, time, and location of complications. We had problems to make a precise classification for some complications due to inconsistent definitions (Table 3). Because of high complexity and low concordance in different trials ICS/IUGA-classification is currently rarely used [4, 19]. However, we consider the classification to be valuable for the report of long-term data in registries.

The current studies show the importance of acute inflammatory and immune responses for the integration of mesh into the surrounding tissue [9, 10, 15]. Foreign body reaction (FBR) often causes a fibrotic rebuilding of implants and the loss of functions (loss of flexibility, etc.). Furthermore, there is a risk of complications, like deformations (capsule fibrosis of breast implants), chronic pain, and dyspareunia, especially in a sensitive genital region. Seconds after the implantation, the biomaterials are covered by protein layer and 4–8 hours later the macrophages appear and in a few days a granuloma with fibrotic tissue appears [20]. Albumin, fibrinogen (Fg), and immune complexes, in particular IgG, can be found on many surfaces after implantation, such as polyethylene terephthalate (PET), expanded polytetrafluoroethylene (ePTFE), polydimethylsiloxane, polyurethane, and polyethylene polymers, which are all important materials in the manufacture of the implant [7]. Fibrin or fibrinogen modulation by the proteins in the inflammatory response after implantation of foreign materials in the body is particularly important. Studies show that plasma-coated surfaces accumulate significantly less inflammatory cells compared to uncoated surfaces [21, 22]. The profound understanding of the FBR plays the crucial role for optimisation of biocompatibility of alloplastic materials in order to reduce the complications.

An ideal graft material is supposed to be chemically inert, nontoxic, nonallergic, noninflammatory, resistant to infection, noncarcinogenic, solid, sterilizable, convenient, and affordable [8]. New developments in material optimization are currently tested. There are only a few groups who have investigated polypropylene mesh modifications by surface coating with collagen, titanium, or absorbable polymers in animal and *in vitro* studies [11, 12, 23, 24]. While some of these studies found higher biocompatibility (e.g., light polypropylene mesh) compared to the standard polypropylene control group, others found very similar outcomes between the two groups. Some of these meshes have been now introduced into the market as they were thought to be associated with lower complications [25]. Our study group was the first one to analyse the mesh modification according to *IDEAL* criteria of surgical innovation [13]. On the basis of the results presented in this study we are currently initiating a prospective randomised clinical trial for the optimization of implants in mesh surgery. We will compare the group of native meshes versus coated meshes for postoperative complications and functional results. The last step of *IDEAL* model with long-term surveillance of mesh grafts was successfully introduced for hernia surgery by national and European registries [26, 27]. A consecutive urogynecological registry for implants is currently under construction (unpublished data).

It is crucial that randomised controlled clinical trials should be supported in the future, in particular with regard to fundraising or industrial sponsoring. Therefore research funders need to recognise the nature of surgical innovation to encourage high-quality research approaches.

In the study presented here we could first transfer the previous *in vitro* and animal model findings on optimisation of mesh properties in human. The results of this research and the developed evaluation approach for meshes could get more important in the future evaluating processes as the method can be performed independent from manufacturers concerns, in particular after market entry [14].

6. Conclusion

Coating of meshes with autologous plasma prior to implantation is a safe procedure with no increased perioperative complications. The modification is implemented according to *IDEAL* criteria of surgical innovations (*Exploration* stage). A randomized single-blinded clinical trial proving a positive effect of plasma coating on the biocompatibility of meshes and morbidity outcome is justified and is in the progress of preparation (*Assessment stage*). A long-term surveillance of new mesh materials will be performed in national and European urogynecological registries (unpublished data, EuraHS) (*Long-Term* stage). In reaction to FDA reports on mesh associated problems, our international collaboration group presents a unique implementation of all five steps of surgical innovations for mesh graft development in urogynecology.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Acute *In Vivo* Response to an Alternative Implant for Urogynecology

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Purpose. To investigate *in vivo* the acute host response to an alternative implant designed for the treatment of stress urinary incontinence (SUI) and pelvic organ prolapse (POP). *Methods*. A biodegradable scaffold was produced from poly-L-lactic acid (PLA) using the electrospinning technique. Human and rat adipose-derived stem cells (ADSCs) were isolated and characterized by fluorescence-activated cell sorting and differentiation assays. PLA scaffolds were seeded and cultured for 2 weeks with human or rat ADSCs. Scaffolds with and without human or rat ADSCs were implanted subcutaneously on the abdominal wall of rats. After 3 and 7 days, 6 animals from each group were sacrificed. Sections from each sample were analyzed by Haematoxylin and Eosin staining, Sirius red staining, and immunohistochemistry for CD68, PECAM-1, and collagen I and III. *Results*. Animals responded to the scaffolds with an acute macrophage response. After 7 days of implantation, there was extensive host cell penetration, new blood vessel formation, and new collagen deposition throughout the full thickness of the samples without obvious differences between cell-containing and cell-free scaffolds. *Conclusions*. The acute *in vivo* response to an alternative implant (both with and without cells) for the treatment of SUI and POP showed good acute integration into the host tissues.

1. Introduction

Surgical implantation of both natural and synthetic cell-free materials is the current standard of care in many parts of the world in the treatment of stress urinary incontinence (SUI) and pelvic organ prolapse (POP) [1]. Autologous fascia, long used as a sling material for SUI, requires specialized training and is limited by the amount that can be harvested with associated donor site morbidity [2]. Nondegradable polypropylene synthetic meshes, introduced as a less invasive alternative, have been widely used over the past decade; nevertheless, increasing reports of serious complications with these materials such as vaginal or urinary tract exposure, chronic pain, and voiding dysfunction are now emerging [2–4].

Although many factors may influence the outcome of mesh surgery, including physical properties of the material and surgical and constitutional factors [1], the host response is particularly important. Nondegradable polypropylene implants cannot be remodelled and induce release of cytokines, and some patients respond to them with chronic inflammation followed by an unsuitable fibrosis which can lead to the above complications [5]. Alternatively, the outcomes of using degradable biological grafts, trialled in limited clinical studies, are mixed. Animal collagen grafts have been found to fail due to quick degradation and while chemical

cross-linking overcomes this it can result in poor graft integration [6].

We have previously shown the potential of poly-lactic acid (PLA), an FDA approved polymer synthesized into a microfiber scaffold, to develop *in vitro* into an engineered tissue when seeded with adipose derived stem cells (ADSCs) producing the key extracellular matrix (ECM) proteins [7]. In addition, we also showed *in vitro* that PLA scaffolds are more biocompatible than polypropylene meshes with mechanical properties close to those of native tissues [8].

Therefore, we aim to develop an alternative material for the treatment of SUI and POP which degrades slowly while the introduction of autologous cells to these scaffolds will produce new ECM. We hypothesise that the absorbable material is less likely to result in exposure through vaginal tissues and the cellular component will encourage tissue regeneration and good integration in the host tissues leading to better outcomes than current materials used to treat SUI and POP.

Since the acute host response elicited by any biomaterial is critical to its integration into the host tissues [9], in this study, we sought to assess this response in animals by comparing PLA scaffolds implanted with and without human ADSCs. Rat ADSCs were also included in this study as an allogeneic implantation control.

2. Materials and Methods

Scaffold production and human ADSCs isolation were performed in the Kroto Research Institute, University of Sheffield. Cells and PLA scaffolds were sent to the Laboratory of Experimental Gynaecology, University Hospital Leuven, for sample preparation. Rat ADCSs isolation and characterization of rat and human ADSCs were also carried out in this laboratory. Animal surgery was conducted in the Centre for Surgical Technologies, Katholieke Universiteit Leuven. After the sacrifice, samples were paraffin fixed in the Laboratory of Experimental Gynecology and histological analysis was conducted at the Kroto Research Institute.

2.1. PLA Scaffold Synthesis. A 10% PLA solution (Sigma-Aldrich, Dorset, UK) dissolved in dichloromethane was made (w/v). PLA scaffolds were produced aseptically by electrospinning as previously described [7]. Thereafter scaffolds were heat-annealed in a dry oven at 60°C for 3 hours.

2.2. ADSCs Isolation and Culture. ADSCs were sourced from human subcutaneous fat donated on an anonymous basis under a research tissue bank licence (number 08/H1308/39) under the Human Tissue Authority. Isolation and culture were performed as previously described from 10 mL of fat tissue [7]. Cells at passage 4 were cryopreserved in 1 mL of 10% DMSO (dimethyl sulfoxide) in fetal calf serum (FCS) (Advanced Protein Products, Brierley Hill, UK). Once in Leuven, cells were resurrected and then maintained at 37°C and 5% CO_2 with Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% FCS, 1% penicillin/streptomycin, 1% glutamine, and 0.25% fungizone (Gibco Invitrogen, Paisley, UK) (all experiments were in DMEM medium plus 10% FBS unless stated otherwise). Cells were used at passage 6 in experiments.

All animal procedures were approved by the ethical committee of the Katholieke Universiteit Leuven with the project number P163_2011.

After isoflurane anaesthesia, Sprague-Dawley rats were sacrificed by cervical dislocation. After laparotomy, subcutaneous fat was processed to isolate rat ADSCs following the above human ADSCs isolation protocol. Cells at passage 4 were used in experiments.

2.3. Fluorescence-Activated Cell Sorting (FACS). Human ADSCs were characterized using flow cytometry analysis [10]. 100,000 cells were harvested and incubated with either FITC or PE-conjugated antibodies against human CD24, CD90, CD44, CD105, CD73, HLA-ABC, HLA-DR, CD34, and CD45 (BD Bioscience, Erembodegem, Belgium) and CD29 (Acris, Herford, Germany) mouse anti-human monoclonal antibodies and appropriate isotype controls. Stained cells were analyzed using a Beckton Dickinson flow cytometer (Beckton Dickinson, Franklin Lakes, NJ, USA) using the Cell Quest software and data were analysed using the FlowJo software (Tree Star, Ashland, OR, USA).

The same analysis was performed for rat ADSCs using either FITC or PE-conjugated antibodies against rat I-E[κ] CD90, CD44, CD31, CD45, and CD11b (BD Bioscience) and CD29 (Acris) mouse anti-rat monoclonal antibodies and appropriate isotype controls.

2.4. Differentiation Assays. The multipotency potential of human and rat ADSCs was evaluated by differentiation assays as previously described [11].

After 3 weeks in culture with osteogenic or adipogenic medium, cells were fixed and stained by incubation for 30 minutes with 1 mg/mL Alizarin Red solution (Sigma-Aldrich) or filtered 0.3% Oil Red O (Sigma-Aldrich) in 60% isopropanol (Fisher Scientific, UK Ltd.) (w/v), respectively.

2.5. Scaffold Preparation and Cell Seeding. Sterile PLA scaffolds of 1.5 × 1.5 cm were seeded with 500,000 human or rat ADSCs using steel rings as a seeding well of 1 cm diameter. All samples were cultured in DMEM medium at 37°C in a 5% CO_2 atmosphere. We also included cell-free scaffolds in medium as controls.

2.6. Implantation. After 2 weeks in culture, 3 groups of samples were implanted—plain PLA scaffolds and PLA scaffolds cultured with human or rat ADSCs. Only one sample was implanted in every female Sprague-Dawley female rat with 12 rats per each of the 3 groups (36 rats in total).

Animals were placed in 100% isoflurane (Isoba) and kept under isoflurane anaesthesia via a nose cone. After the belly of the animal was shaved and disinfected, the abdominal skin was incised and flaps of the subcutaneous layer were raised (Figure 1). Samples were sutured on the abdominal wall with nonabsorbable sutures (Prolene* (4-0/RB-1 17 mm 1/2c; Ethicon, Groot Bijgaarden, Belgium)) on each corner.

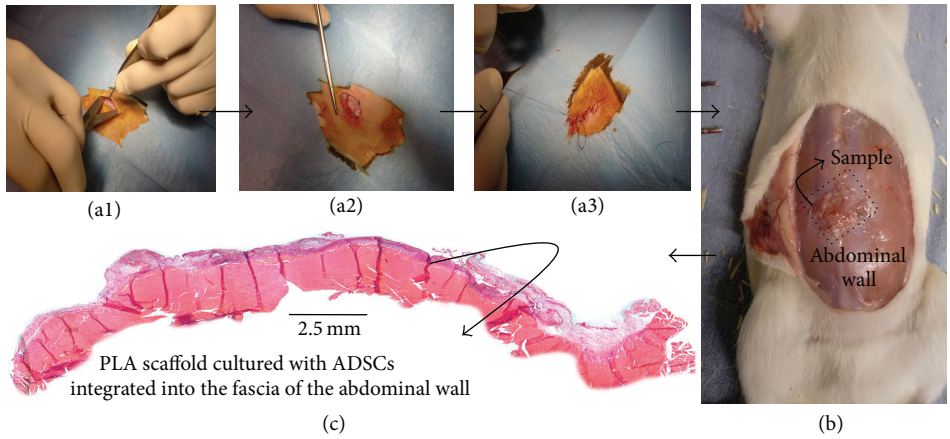


Figure 1: Animal surgical procedure. (a1) Skin incision and flaps of subcutaneous layer were raised from the top of the abdominal wall. (a2) Suture of sample at four corners. (a3) Subcutaneous and skin layers closure. (b) Animals sacrificed and appearance of sample on top of abdominal wall. (c) Representative light microscopy H&E stained panoramic image of the abdominal wall of female Sprague-Dawley rat, after 3 days of implantation of PLA scaffold on top, previously cultured with human ADSCs in DMEM medium for 2 weeks.

Subcutaneous layer and skin were closed with resorbable sutures (Vicryl* (2-0/FS-1 24 mm 3/8c, Ethicon)). Animals were weaned from anaesthesia and observed for recovery.

2.7. Sacrifice and Sample Fixation. At 3 and 7 days after implantation, 6 animals from each group were sacrificed by intracardiac injection of T-61 (embutramide 200 mg, mebenzonium iodide 50 mg, and tetracaine hydrochloride 5 mg, per mL) (Intervet, International B.V.). Abdominal wall pieces of 2 cm^2 containing implants on top were explanted (Figure 1). Samples were fixed in 10% neutral buffered formalin and paraffin embedded (Chandon CITADEL 1000, HVL).

2.8. Histology. Sections 6 μm thick were cut from the paraffin embedded samples with a microtome (Leica TP 1020 Automatic Tissue Processor) and placed on Superfrost plus slides (Menzel-Gläser, Denmark).

Conventional Haematoxylin and Eosin (H&E) staining was performed as previously described [12]. Slides were then mounted in DPX mounting medium (Fisher Scientific) with a coverslip.

For immunohistochemistry procedure sections were rehydrated, then delineated with a Dako pen, and treated with 0.05% trypsin (Sigma-Aldrich) for 20 minutes at 37°C. The samples were blocked using donkey serum (ImmunoCruz goat ABC Staining System, Santa Cruz Biotechnology, Inc.) for 1 hour. Sections were incubated with one of four monoclonal antibodies overnight: mouse anti-rat CD68 (1 : 200; Abcam, UK), goat anti-rat PECAM-1 (1 : 50; Santa Cruz Biotechnology, Inc.), goat anti-human collagen I (AbD Serotec, Oxford, UK), and goat anti-human collagen III (AbD Serotec, Oxford, UK). This was followed by 1 hour incubation with secondary antibodies: biotinylated goat anti-mouse Ig (1 : 200; BD, Pharmingen) and biotinylated anti-goat Ig (1 : 200; ImmunoCruz goat ABC Staining System, Santa Cruz Biotechnology, Inc.). After incubation with an avidin and biotinylated horseradish peroxidase, the target proteins were visualized by incubation in peroxidase substrate and DAB chromogen (ImmunoCruz goat ABC Staining System). Samples were then counterstained with Haematoxylin, dehydrated, and mounted as per H&E protocol.

Three groups of controls were performed—samples incubated without primary and secondary antibodies, or incubated only with secondary antibodies. Semiquantitative assessment of the extent of immunostaining was done on a blinded observer basis using a qualitative grading scale; absent = 0, mild presence = 1, large presence = 2, abundance = 3, and great abundance = 4. Example photographs depicting 0, 1, 2, 3, and 4 were provided for reference and the median value from these scores was used [7].

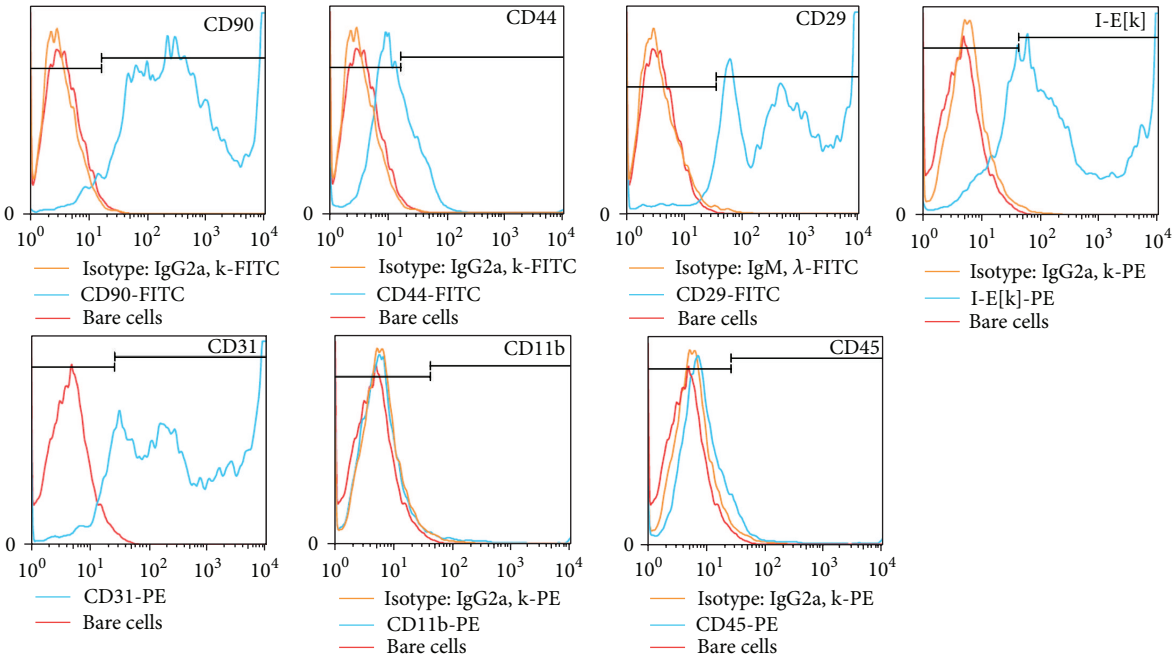
For total collagen staining, sections were rehydrated, following the same protocol as for H&E, and then incubated with Sirius red (0.1% w/v Direct Red 80 in saturated picric acid, Sigma-Aldrich) for 1 hour. Samples were then rinsed briefly in distilled water and washed in acidified water (0.5% acetic acid, VWR International Ltd.) for 1 minute. Finally samples were dehydrated and mounted as per the H&E protocol.

2.9. Statistics. Differences for the semiquantitative assessment of the extent of immunostaining were statistically tested against a null hypothesis of no difference between samples using a two-sample Student's t-test with equal variance not assumed (significance = $P < 0.05$).

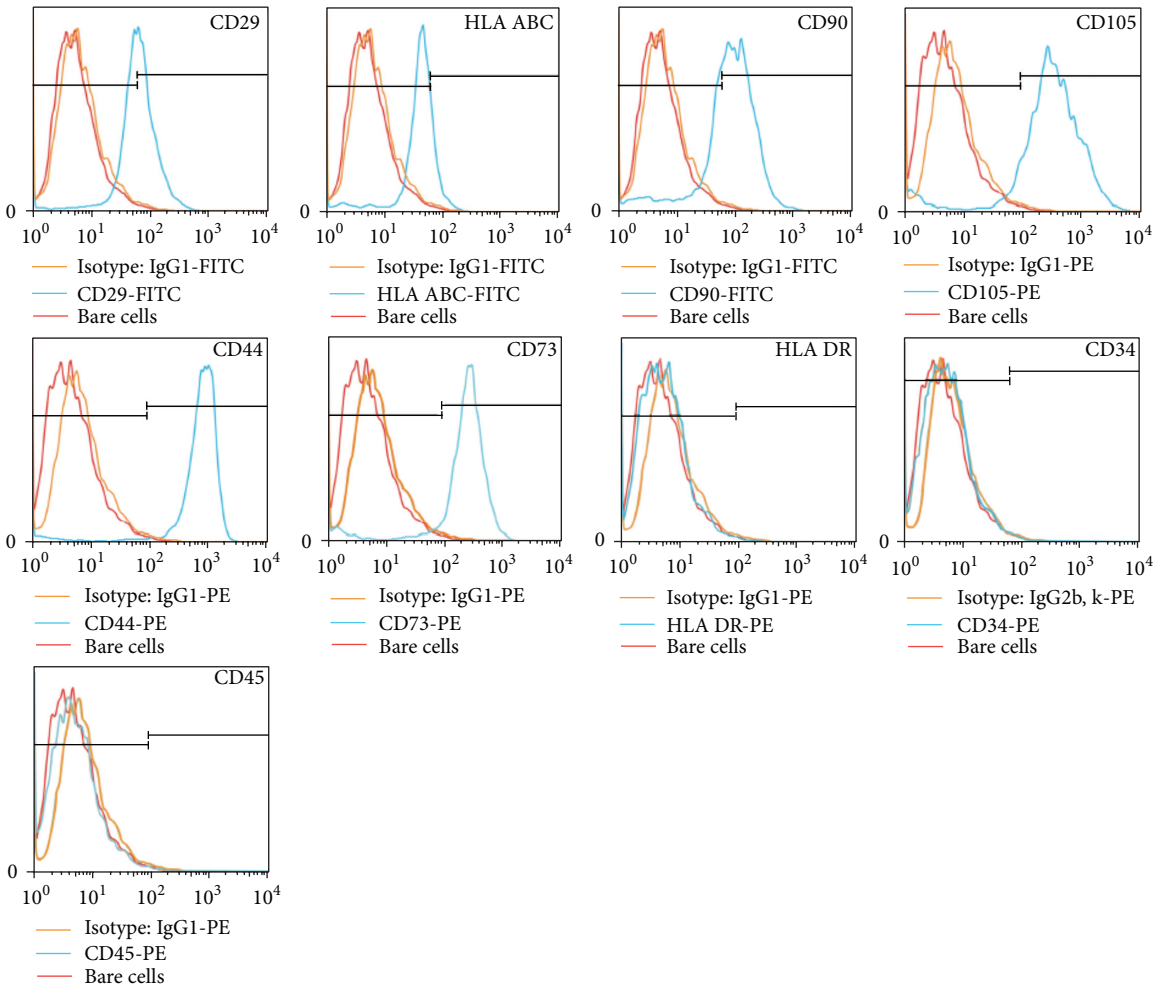
3. Results

Human and rat ADSCs were positively and negatively characterized by expression of specific cell surface antigens, as previously described [10], and by their differentiation potential (Figure 2).

All animals survived both the operation and the period of implantation without any observed alteration in their physiological functions. No signs of infection were observed



(a)



(b)

Figure 2: Continued.

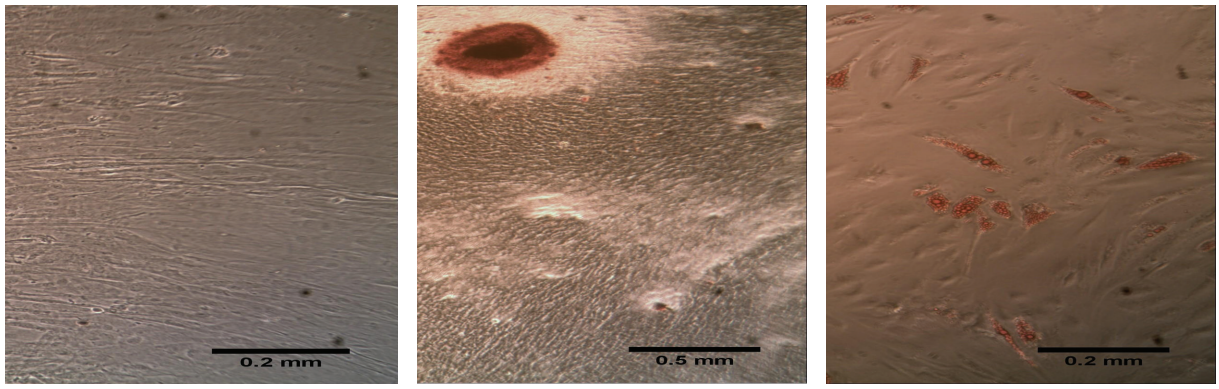


Figure 2: Characterization of ADSCs. Rat (a) and human (b) ADSCs isolated from subcutaneous adipose tissue characterized by FACS showing fluorescent intensity for bare cells in red colour, for isotypes controls in orange colour, and for each specific antigen marker in blue colour. At the bottom, differentiation assays showing potential for osteogenic (c2) and adipogenic (c3) lineages, preceded by human ADSCs cultured in DMEM medium as control (c1).

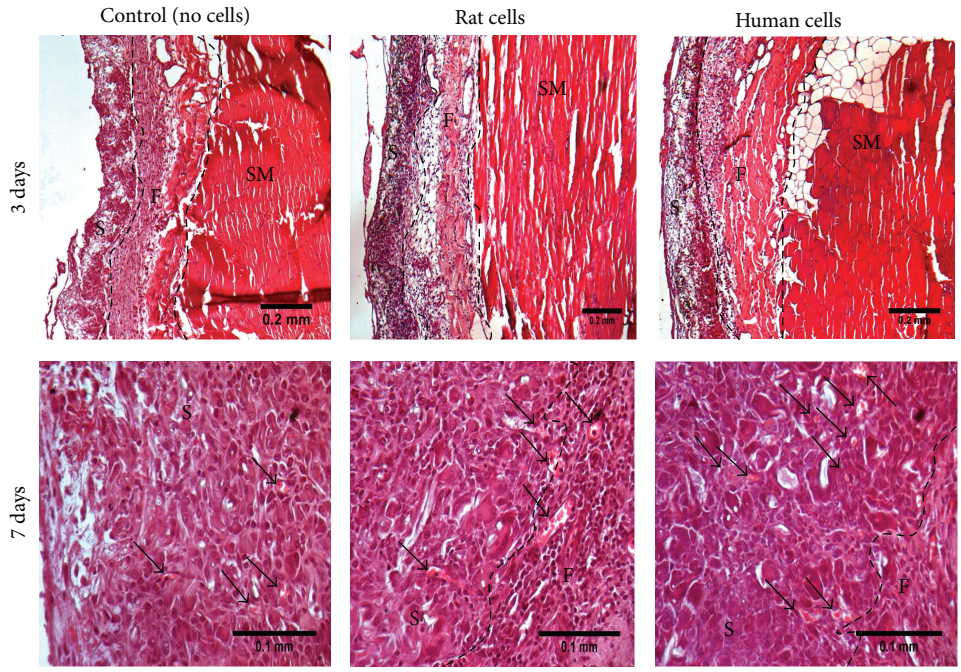


Figure 3: Morphological appearance of the implanted samples. Representative light microscopy H&E stained sections of abdominal wall of female Sprague-Dawley rat after 3 and 7 days of implantation of PLA scaffold on top, previously cultured with and without (control) rat or human ADSCs in DMEM medium for 2 weeks. At 7 days, all samples presenting several small blood vessels are identified by (↑). Scale bars of 0.2 mm for images from 3 days implantation and 0.1 mm for images from 7 days implantation. (S) Sample; (F) Fascia; and (SM) Skeletal Muscle.

when harvesting the samples and all of them (PLA scaffolds previously cultured with and without cells) were identified on the subcutaneous fascia which covers the abdominal wall muscles (Figure 1).

After 3 days of implantation, host cells infiltrated samples, as seen in samples implanted without cells for H&E staining. After 7 days the cell infiltration was increased in all samples, and new small blood vessels were visible inside the samples (Figure 3).

At day 3, CD68 positive cells were seen throughout the samples, localized inside them and not found in the surrounding tissues (Figure 4). Semiquantitative assessment of the immunohistochemistry demonstrated this staining to be moderate, becoming more intense after 7 days implantation (Figure 5).

A moderate PECAM-1 staining was identified after 3 days with no differences between groups. By 7 days, there was a similar expression between samples with rat or human

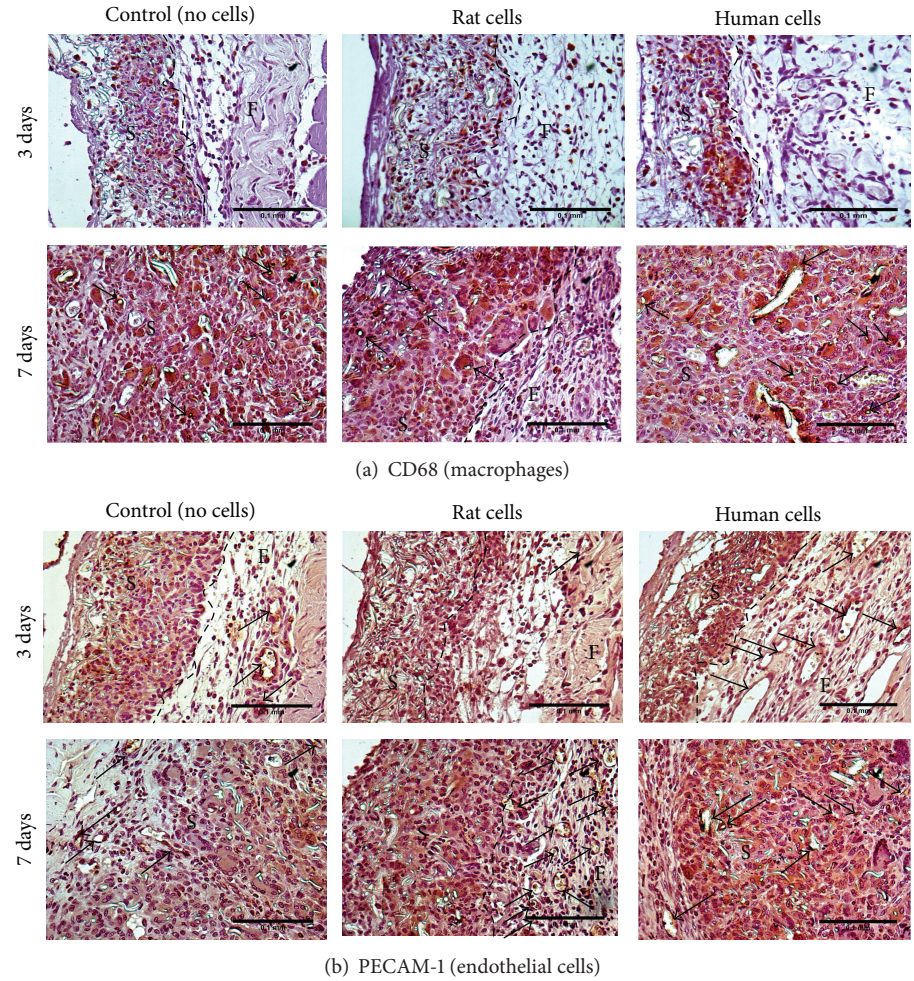


Figure 4: Assessment of the acute host response against the implanted samples. Representative light microscopy image of sections of abdominal wall of female Sprague-Dawley rats after 3 and 7 days of implantation of PLA scaffold on top, previously cultured with and without (control) rat or human ADSCs in DMEM medium for 2 weeks; following immunohistochemistry for anti-CD68 antibody (a) or anti-PECAM-1 antibody (b). (a) Macrophages surrounding individual PLA fibres are identified by (↑). (b) Endothelial cells stained for PECAM-1 around blood vessels are identified by (↑). Scale bars of 0.1 mm. (S) Sample; (F) Fascia.

ADSCs but statistically lower staining for cell-free samples (Figure 5). Although PECAM-1 stained many cells inside the samples, similarly to CD68, this was also identified around large blood vessels in the abdominal fascia at day 3; while, after 7 days of implantation, new small blood vessels inside all samples were stained (Figure 4).

After 3 days of implantation, immunohistochemistry for collagen III and Sirius red staining for total collagen revealed a thin layer of collagen production on the lower surface of all the samples, and at day 7, thin new collagen fibres were visible throughout the samples (Figure 6). Collagen I staining at day 3 was minimally found around cells inside samples and only for samples implanted with human or rat cells; although, after 7 days, this minimal staining was found inside all samples (Figure 6).

4. Discussion

Since the U.S. Food and Drug Administration announced serious complications with current surgical meshes used to treat POP and SUI [13], several studies have investigated the host response in animals to different cell-free synthetic and biological materials. This is viewed as a critical indicator in predicting their long-term outcomes [14–16].

Many animal studies show that polypropylene meshes provoke a fairly pronounced inflammation leading to a massive cell infiltration into the scaffold and ultimately to new collagen production described as a vigorous fibrotic process [17–19]. These studies also reported an increase in the stiffness of polypropylene after its implantation due to this fibrosis. Some fibrosis may be desirable for successful outcomes when treating SUI or POP. This is an area where it is currently difficult to obtain data correlating patient's responses to clinical outcome. Alternatively, irreversible plastic deformation of this material may explain why it could "cheesewire" through the patient's tissues leading to exposure in some patients.

To improve integration into native tissues, a few groups have investigated *in vitro* and in hernia repair animal models light polypropylene meshes which have been modified by surface coating with collagen, titanium, or absorbable

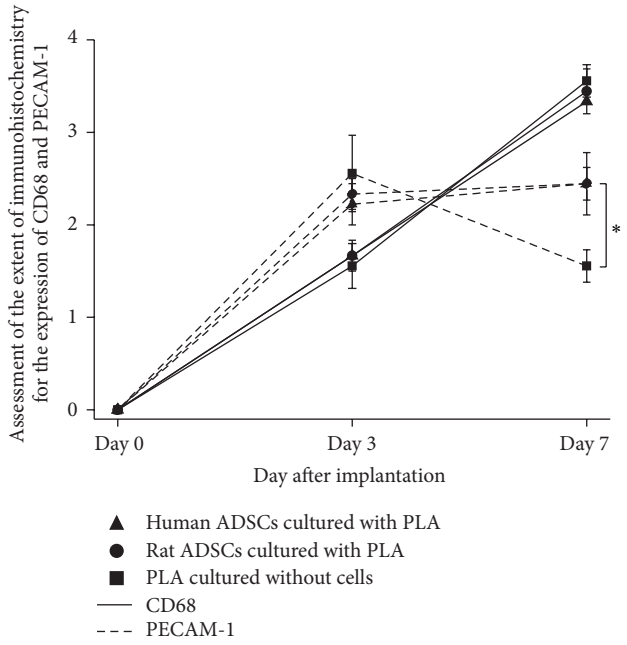


Figure 5: Semiquantitative analyses of the host response against the implanted samples. Assessment of the extent of immunohistochemistry using a blind scoring for the expression of CD68 and PECAM-1 from sections of abdominal wall of female Sprague-Dawley rat after 3 and 7 days of implantation of PLA scaffold on top, previously cultured with and without (control) rat or human ADSCs in DMEM medium for 2 weeks. Results shown as mean ± SEM ($n = 6$). Scale: 0 = absent, 1 = mild presence, 2 = large presence, 3 = abundance, and 4 = great abundance.

polymers. While some of these animal studies found higher biocompatibility for the polypropylene light meshes compared to the polypropylene control group [20, 21], others found that the outcomes were very similar between the two groups [22]. Some of these meshes have now been introduced into the market since these are thought to be associated with lower complications. However, a review of randomized controlled trials using these meshes for human hernia repair found higher recurrence rates compared to conventional polypropylene meshes [23].

On the other hand, the tissue engineering field has recently introduced new biomaterials which can be used for several clinical applications. Neural stem cells or osteoblasts have been combined with electrospun PLA scaffolds with potential for peripheral nerve repair [24] and as a bone substitute [25], respectively.

In addition, PLA monofilament meshes have been assessed *in vivo* with an incisional hernia Wistar rat model used to simulate vaginal wall repair [26]. Compared to polypropylene, the PLA scaffold retained an acceptable strength 8 months after implantation, showed a significantly lower inflammatory response, and the collagen produced was better organized. The same authors also reported PLA meshes to have less infection risk compared to other meshes in a rat infected abdominal model [27].

Similarly to our study, only two research groups have previously assessed in animals an engineered tissue for the treatment of SUI and POP which were developed from biodegradable polyglycolic acid (PGA) [28] or poly-lactic-glycolic acid (PLGA) [13] scaffolds. Both studies found good integration into host tissues with neofascia formation. However, the rate of degradation of scaffolds *in vivo* is rapid (within weeks) for PGA and proportionally slower as PLA, which is much slower to degrade, is added to the polymer solution. Our group has shown *in vivo* that electrospun scaffolds of 50% PGA and 50% PLA are degraded within 8 weeks in rats and PLGA (75/25) scaffolds last for more than 3 months whilst PLA scaffolds are present after 12 months of implantation [12]. Thus the rate of breakdown is tunable and predictable and has relevance to maintenance of mechanical properties of the implants.

The current study also aimed to explore the acute response to the use of mesenchymal stem cells which have been already used in women [29] to treat SUI by cell injection into the urethral sphincter and submucosa.

Large numbers of these cells can be quickly isolated using a minimally invasive liposuction in humans [30]. ADSCs do not differentiate when cultured in basic DMEM medium, displaying fibroblastic behavior and producing an endogenous ECM [31]; in addition to this, they have been shown to release a growth factor to stimulate fibroblast proliferation with the potential to regenerate connective tissues [32]. Furthermore, ADSCs have the potential to inhibit inflammatory responses by secretion of the inhibitor of tumor necrosis factor α [32] and a subpopulation of ADSCs expresses an endothelial surface antigen (CD34) which can promote neovascularization [33].

In our study we implanted human cells in immunocompetent Sprague-Dawley rats; however, rat cells were included as a control. All samples were implanted in different rats since interpretation of responses to different materials in the same animal is not recommended with a body wide immune response.

ADSCs were well characterized prior to implantation but they were not tracked post implantation so it is not possible to comment on any direct regenerative effect of these cells. Alternatively, after few days implantation the major aspect to assess was the host inflammatory response elicited against these implants and, actually, this was very similar for cell-free scaffolds and those seeded with human or rat ADSCs.

All PLA scaffolds, both without and with cells, were integrated into the fascia of the abdominal wall with rapid host cell infiltration and ingrowth of small blood vessels.

The macrophage response against all samples was evident, particularly 7 days after implantation as identified by CD68+ cells [9]. This response seems to be specific to the synthetic foreign material since macrophages were not found in tissues surrounding the samples and macrophages enclosed individual PLA fibres (Figure 4).

Although PECAM-1 is expressed on platelets and subsets of leukocytes, it mainly stains endothelial cells with cell adhesion, transendothelial migration of myeloid-derived cells, and angiogenesis functions; and therefore, it has been widely used to assess neovascularization [9]. Since PECAM-1 staining was higher at day 7 for cell-seeded samples compared to samples implanted without cells, this could be

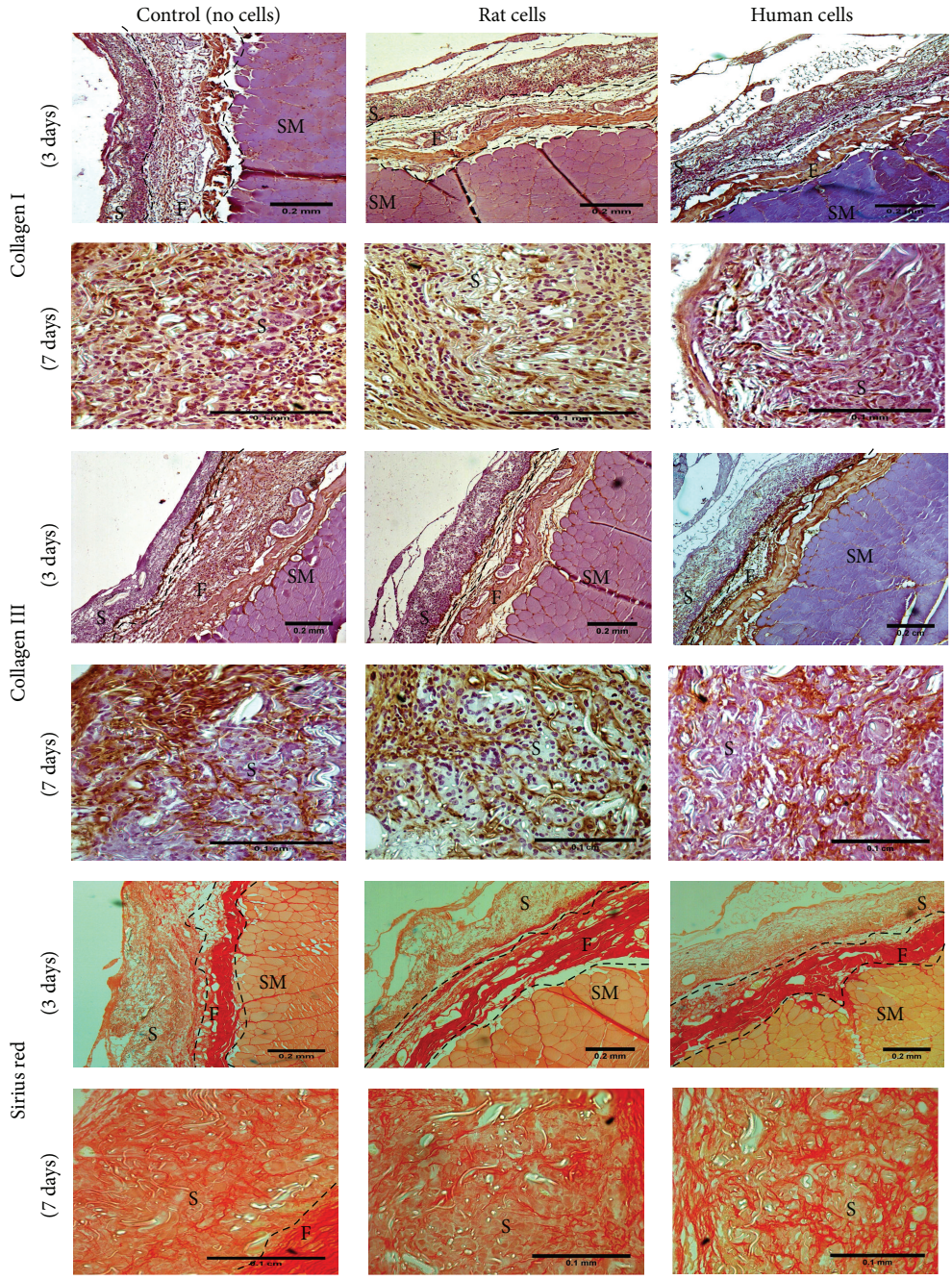


FIGURE 6: Assessment of new extracellular matrix formation in the samples implanted. Representative light microscopy of sections of abdominal wall of female Sprague-Dawley rat after 3 days of implantation of PLA scaffold on top, previously cultured with and without (control) rat or human ADSCs in DMEM medium for 2 weeks; following immunohistochemistry for anti-collagen I and anti-collagen III antibodies, or Sirius red staining. Scale bars of 0.2 mm for images from 3 days implantation and 0.1 mm for images from 7 days implantation. (S) Sample; (F) Fascia; and (SM) Skeletal Muscle.

interpreted as more myeloid-derived cell infiltrates and/or higher neovascularization as identified by small blood vessels inside cell-seeded samples.

Macroporous polypropylene mesh is said to be more favourable to permit host cell infiltration [2]. The current study shows that a microporous electrospun PLA scaffold permitted the infiltration of macrophages throughout its entire thickness which means that this scaffold is no barrier to macrophage activity so their ability to tackle bacterial infection would not be compromised. Additionally, the host cell infiltration led to ECM formation, as seen particularly for collagen III, which is indicative of remodelling of the implant leading to good integration into host tissues [9]. Alternatively, collagen I was minimally detected in all samples and, at day

3, it was only found in samples implanted with human or rat cells which may suggest production of this by the cells during the initial period of their culture *in vitro* [7].

In animal studies, the host response to materials used to treat SUI and POP is often analyzed after 7, 30, and 90 days after implantation. While acute inflammatory responses and integration into native tissues, including neovascularization and ECM production, can be assessed in the short-term by subcutaneous implantation in rats [34]; long-term implantation (30 and 90 days) usually in larger animals also allows the evaluation of chronic immune responses and the evaluation of any changes in mechanical properties after implantation [17–19].

Therefore, the major limitations of this work are its short-term nature since this model cannot be used to assess whether a chronic immune response ensues or the regenerative/angiogenesis potential of the cell-seeded scaffolds. Additionally, implanted ADSCs were not labelled, something that will be necessary in longer-term experiments to provide information on their survival or migration.

5. Conclusion

For all groups, an alternative implant designed for urogynecology showed host cell infiltration, mainly due to a macrophage response against the foreign material as a normal wound healing mechanism, which led to neotissue production with new blood vessels formation—all early indicators of constructive remodelling for long-term integration into host tissues [9].

Our future experiments will now progress to a longer term (3 months) rabbit fascial-defect model to investigate the development of any chronic immune response, the fate of the ADSCs, and, very crucial, the biomechanical properties of the implant after several months of implantation. Ultimately, our ideal approach to achieve an economical final clinical product would be to combine these scaffolds with patient's cells just before being surgically implanted on the same operation as rapid extraction of ADSCs from fresh lipoaspirate is being developed currently [35].

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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