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The biology behind fascial defects and the use of implants in pelvic organ prolapse repair

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Abstract Implant materials are increasingly being used in an effort to reduce recurrence after prolapse repair with native tissues. Surgeons should be aware of the biology behind both the disease as well as the host response to various implants. We will discuss insights into the biology behind hernia and abdominal fascial defects. Those lessons from "herniology" will, wherever possible, be applied to pelvic organ prolapse (POP) problems. Then we will deal with available animal models, for both the underlying disease and surgical repair. Then we will go over the features of implants and describe how the host responds to implantation. Methodology of such experiments will be briefly explained for the clinician not involved in experimentation. As we discuss the different materials available on the market, we will summarize some results of recent experiments by our group.

Keywords Graft biology · Vaginal prolapse · Biologic implant · Synthetic implant · Surgical repair

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Parallels to herniology

Although the patient presents with a single and precisely located symptom (protrusion of organs through a *locus minoris resistentiae*), this is usually a sign of a more systemic change in the host's connective tissues. This concept is now widely accepted by general surgeons dealing with inguinal hernia. Hernia patients have a different fibroblast phenotype, who qualitatively and quantitatively synthesizes abnormal collagen [1]. Collagen is normally nearly completely made up of type I and type III collagen, in a ratio of about 4:1. Hernia patients now have an altered collagen I/III ratio. Friedman described over-expression of collagen III by fibroblasts from hernia patients. This leads to an excess of non-polymeric, extractable collagen, by inhibiting cross-linking of, and with, predominant type I [2]. The resulting fibers are inherently thinner and weaker, and more susceptible to lysis. This phenomenon affects different tissue types, including fascias, but also those at distance from the defect [3]. Collagen normally protects fibroblasts from apoptosis; conversely abnormal collagen does the opposite [4]. Read also described enhanced elastolytic activity and reduced anti-protease capacity [5]. Those proteases are increasingly released by leukocytes primed by smoke, linking this to another recognized co-factor in herniation. Matrix metalloproteinases (MMP) that can break down extracellular matrix proteins are over-expressed in hernia patients as well, although this was first shown by Jackson et al. in vaginal tissue of women with prolapse [6, 7]. A subpopulation of hernia patients may be affected by other signs of connective tissue abnormalities, such as joint hypermobility or aneurysmata [8, 9], and their lesions show the same molecular alterations as described above. Obviously, some genetic conditions, among which is Marfan's or Ehlers–Danlos syndrome, directly affect collagen metabolism, hence, predispose to hernia.

In summary, hernia patients have a systemic diminished collagen synthesis, a protease–antiprotease imbalance, an increased MMP activity, and reduced collagen I/III ratio. Unfortunately, this problem persists also in the postoper-

ative phase, and it has been shown that after surgical correction they, expectedly, display failing wound healing [10]. However, in certain life events, acquired or co-morbidity factors may be the decisive factor rendering patients with the above changes symptomatic. The mechanisms through which this happens in hernia patients are well-identified. Smoking was one of the first factors to be recognized. Its effects on collagen metabolism are systemic as decreased oxygen levels preclude normal cross-linking activity all over. Nicotine has on itself an inhibitory effect on fibroblast proliferation. Women who smoke are at higher risk than men [11]. Later, it was even shown that heavily smoking women increase the risk for congenital hernia in their offspring; however, this might be an indirect effect by an increased risk for preterm birth [12]. Aging contributes in different ways to the development of inguinal herniation: there is muscle wasting, the composition of connective as well as fat tissue changes, and age may directly affect collagen metabolism, e.g., by increased or prolonged MMP activity. Even some drugs, like the antihypertensive angiotensin-converting enzyme (ACE) inhibitors also directly interfere with collagen metabolism.

Much of these "herniology" insights applies to patients with pelvic floor disorders as well. Those patients also have a certain predisposition, with increasingly better defined molecular and biochemical alterations. The latter were recently excellently summarized in the proceedings of a meeting on pelvic floor disorders sponsored by the National Institutes of Health, and this is beyond the scope of the talk [13]. Anyway, to the underlying changes additional co-factors may add. All those earlier described in hernia patients may apply. One additional typical life event is usually named to be causative for POP and incontinence, i.e., pregnancy and childbirth injury. Claimed mechanisms include direct injury to pelvic floor muscle and/or their attachments, nerve injury due to stretch or compression, but this is beyond the scope of this talk. Available epidemiologic data as to a causal relationship are at present controversial, as the effect of birth on pelvic floor problems disappears in the elder population, as shown in the EPINCONT study [14].

Animal models in the study of fascial defects

Tissue remodeling processes can be studied in culture or in in vitro conditions. In vivo evaluation is, however, an additional important research tool. Animal models are convenient as they allow for complex experimental design or discounting an abundance of interfering co-factors as in the clinical situation. Moreover, their use reduces risks to patients, and saves time and money in understanding the problem. There are limitations to their applications in the study of POP, like anatomical ones: nearly all animals are quadrupeds, with a different pelvic floor musculature including a functional tail, and they have a different birth process. It is difficult, if not impossible, to evaluate functional problems correctly, and it is complex to mimick known co-factors, such as smoking, obesity, chronic lung disease, etc.

Rodents are cheap and widely available. (Immuno) histologic as well as molecular techniques are generally applicable, and transgenic mice, which become increasingly important, will eventually show up in this field as well. Lower urinary tract problems can already be reproduced in rodents. They have been used as models for pudendal neuropathy induced by trauma, toxic substances, or diabetes [15]. Sophisticated experiments were conducted to mimick hypoestrogenism, the effect from birth using prolonged vaginal distention and inducing pudendal nerve damage [16, 17]. More recently, the structural properties of the rat vagina and supportive structures were documented [18]. Other models include dogs because certain breeds spontaneously develop stress incontinence as they age [19]. An effect of body weight or birth has been shown and they were used to study therapeutic interventions. Rhesus and squirrel monkeys can be used to study prolapse, but their shorter lifespan is a limitation, next to limited access due to economical and ethical restrictions. In rhesus monkeys the direct influence of estrogens on vaginal smooth muscle density, biomechanical strength and collagen content was shown [20]. Squirrel monkeys develop age- and parity dependent spontaneous vaginal prolapse and pelvic floor innervation is very comparable to that in humans [21, 22]. This was not so in baboons, although they are anatomically closer to humans [23].

Physical properties required for implant materials

Clinicians need to become familiar with some relevant features when describing prosthetic materials. Products are first discriminated on the basis of the source they are derived from (Fig. 1). Synthetic materials have long been known and their physical properties include tensile strength and elasticity. As implants are designed to provide permanent reinforcement of the reconstructed fascia, so they should be strong enough to withstand naturally occurring forces. For prolapse surgery, the mechanical requirements for implants to meet have not been defined. Usually, insights from hernia surgery are extrapolated (for what they are worth). The tensile force implants that should withstand naturally occurring forces were modeled mathematically resulting in a calculated minimal strength of 16 N/cm for hernia and 32 N/cm for abdominal wall replacement [24]. In dry conditions, most meshes are much stronger than what is physiologically needed, and recently it was understood that wider woven ("light weight") material could be used without compromising the physical needs. Physiological elasticity requirements, measured at 16 N/cm, are between 20 and 35%; most implants are not that elastic, which may cause symptoms [25]. Clinically intra-abdominal pressures are at their highest 100–150 mmHg. Measurements of intra-abdominal pressure during Shouldice hernia repair under local anesthesia

showed maximum pressures during coughing of around 60 mmHg [26]. Similar to the breaking strength of healthy tissues and that of different suturing techniques, these pressures correspond to a strength *far below* 10 N/cm, so ultimately, even lesser tensile strength might result in good clinical results [27]. Of note is that elasticity and strength can be tested in "dry" lab conditions (before implantation) but measurements in explanted meshes are clinically more relevant.

Host response to implants

Although many of the used materials are referred to as chemically and physically inert, stable and not immunogenic, none of them are truly biologically inert. Most synthetic materials (unlike biomaterials) induce a relatively vigorous foreign body response [28]. The nature of the material, structure, amount, and for synthetics, filament and pore size, determines this process, as well as further tissue in-growth. However, the course of events is initially fairly constant irrespective of the species or material. After implantation, the host immediately reacts to the injury and covers the material with a biofilm. Host proteins are adsorbed at the interface and a complex host-to-implant material interaction sets off [29]. The first step of protein adsorption takes place within seconds and does not require any cellular response. It follows a fixed and hierarchical pattern referred to as the Vroman effect, a phenomenon a bit overlooked in our literature [30]. First, low-molecular-weight proteins, such as albumin, and, later, more complex proteins, like fibrinogen, immunoglobulins, kininogen, and extracellular matrix molecules are adsorbed. When bacteria are present at this stage, they may alter the biofilm to such an extent that clinical problems arise later. Proteins later undergo conformational changes, making them immunogenic. This part of the process is important as it is needed for adequate tissue incorporation of the implant, but it may cause adverse effects on the long term as well [31]. As the biofilm has become immunogenic, it triggers a typical inflammatory response, including leading to activation of the complement system, binding of antibodies, leukocytes, and blood clotting and fibrinolysis activation [32].

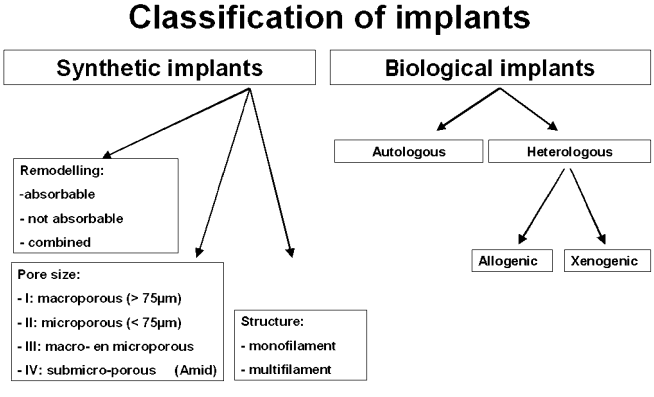

Fig. 1 Schematic representation of classification of implant materials, first on their source, then by other variables

From then on, a more typical course of an acute inflammatory, followed by chronic inflammatory reaction will follow, transiting ultimately into a foreign body reaction, i.e., formation of granulation tissue with fibroblasts, macrophages and eventually foreign body giant cells, with the occurrence of neovascularization as well as fibrosis. The inflammatory cell type predominantly present at the interface will vary according to the phase of the host response. Initially, neutrophils predominate, but they are gradually replaced by monocytes, which differentiate extravascular to macrophages. Macrophages are the crucial cell type in the ultimate clinical response of either biotolerance or rejection of the foreign body. In reality, they already play a role from the moment the complement cascades and blood clotting process is activated; they interact with lymphocytes, and produce mediators that induce protein synthesis and cell proliferation (such as endothelial cells and fibroblasts) [33]. They are also constantly found in explanted materials. They can morphologically mimic other cell types, like epitheloid macrophages, or fuse in typical foreign body giant cells, just like the Langhans cells in tuberculosis. Because of the activated status and production of mediators, other cell types migrate to the implant site and participate in a chronic wound-healing process that can go on for years [34].

As capillaries and inflammatory cells get less in number, fibroblasts become increasingly predominant and deposit collagen and other matrix proteins, and a more fibrous tissue becomes evident. There is progressively more zonation in the interface area, with most cells in direct contact with the foreign material. At this moment in time, the implant is also mechanically stabilized, at least if there is no remnant micromotion. The collagen deposited at the mesh interface unfortunately is of lesser quality than after suture repair, irrespective of the type of material used [35]. The remodeling process also takes place in an individual who already had a defective collagen metabolism to start off with.

While the inflammatory phases are necessary for the desired fibrosis part of the process, it may be the source of some adverse effects, such as implant-shrinkage, erosion, or adhesion formation [36, 37]. The amount of foreign body reaction increases with the surface of the foreign material being exposed to the host. Reduction in material can be achieved through different variables. It would follow that multifilament meshes inherently induce more reaction, but there seems to be an absolute lower limit for filament size. When filament size is <4/0, a constant granulomatous reaction was demonstrated, irrespective of the polymer or number of filaments [38]. Pore size is also an important factor for fibroblast infiltration, flexibility, and mechanical integration. Pore sizes >75 μm allow for rapid in-growth of fibroblasts and vascular elements necessary to anchor the implant within the native tissue [39, 40]. Peak in-growth is reached at pore size around 400–500 μm. Larger pores limit the fibrosis process to the perifilament region, and the pores get filled with fat [38]. A solid product as well as one with smaller (<50 μm) pores will be encapsulated or induce an increased foreign body

reaction, bridging from one filament to the other—filling the entire pore [41]. Based on all the above, there is now a consensus in the surgical literature that improved results will be achieved by using a *low weight, large pore, monofilament* mesh, with an elasticity between 20 and 35% [42].

Animal studies in fascial repairs with implants

To study the improvement of fascial repairs using meshes, surgical animal models are used. Again, rats often serve as an incisional hernia model or, more generically, as a model for fascial defect repair, with or without the use of implant materials [43, 44]. These are laid in or over the defect, with or without direct contact to the peritoneal cavity (Fig. 2). Direct contact with the viscera may be interesting in the study of adhesion formation. Such animal models are very important in preclinical "mechanical" evaluation of implants, as well as evaluation of their biocompatibility.

Adult rabbits weigh between 3 and 5 kg in larger breeds, so their size allows for the creation of several defects and for these to be covered by different materials within the same animal [45]. Even laparoscopy is possible. Rabbits have a larger bowel size than rats, but have a different collagen metabolism, a factor that must be taken into account when analyzing the wound-healing process. Vaginal surgery can be done in these animals as well [46]. Sheep are much larger, and adult weight, according to the breed, varies between 50 and 100 kg. As ruminants, they probably have an increased abdominal pressure, which makes them interesting for abdominal wall reconstruction. Vaginal surgery is possible, and recently the model was proposed by de Tayrac [65] for the study of the occurrence of erosions.

Understandably, most clinicians are not familiar with the experimental design of studies on implants. Basically, one or more standardized full-thickness defects are created in the abdominal wall of the selected species (Fig. 3). Defects are primarily repaired, using an implant overlay and

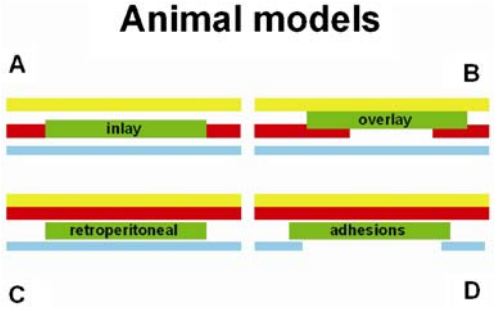

Fig. 2 Different implantation sites for meshes in experimental models. First the skin is incised (*yellow or top bar*) and a defect is created involving the muscle and fascia of the abdominal wall (*red or middle bar*). An implant (*green or lower bar*) can be positioned as an "inlay" (**a**) or "overlay (**b**), and even retroperitoneal (**c**). Theoretically, the fascial defect is not relevant when only adhesion formation is the purpose of the study (**d**). *Top* of the section is the skin and subcutis, *bottom* is the peritoneum (*blue*)

sutures, and/or a suture repair group. Animals are allowed to survive days to months, and in rabbits even for years. Sacrifice takes place at given times, depending on the purpose of the study. At that moment, the implant, the interface and neighboring host tissue, together referred to as *explant*, are harvested, divided, and conserved in the appropriate way for further evaluation. We have used mainly the rat to document all phases of the remodeling process. This includes the early phases of the acute and chronic inflammatory reaction, when standard morphometric techniques are used to identify and count the inflammatory cells (polymorphonuclear, mononuclear/macrophages, leukocyte-type, and fibroblast neovascularization) at the host-implant interface. Occasionally, immunohistochemistry or flow cytometry will be used [47]. Fibrosis is semi-quantitatively assessed by Movat or Sirius Red stain. More quantitative and qualitative methods are available but logistically more complex and expensive. Immunohistochemistry for different subtypes of collagen can be done, but it needs to be species-specific. Molecular techniques can be used to quantitate cytokines or other proteins of interest. Biomechanics are tested by tensiometry of explants; for long-term (2 years or longer) experiments, rabbits may be more suitable. Immunologic reactions can be studied in euthymic mice or mouse strains without functional T or/and B lymphocytes (nude or SCID mice) [48]. Rats and mice are very resistant to infections, rendering them suboptimal models for the study of perioperative wound infections.

Synthetic materials

Synthetic implants can be made from knitted single-fiber filaments (monofilament materials) or they can be braided with monofilament yarns, further woven as multifilament fibers in different ways and pore sizes (Figs. 1 and 4). Knitted fabrics have a more open structure than woven [49]. Such materials are usually further classified according to their pore size (Amid classification; Table 1) [50], the nature of their composing fibers (mono- or multifilament), and their resistance to degradation (absorbable, non-absorbable, or composite or mixed materials).

The nature and extent of the inflammatory reaction these materials generate is regulated by the chemical and physical structure of the implant, the amount of material, and surface of the contact-area with the host [51]. Flexibility and strength are other physical properties. The flexibility of an implant is determined by the individual stiffness of its yarns, the knitting procedure, the pore size, or, in general, the amount of material per unit of surface. In that respect, the density of the product is an interesting variable. Implants with large pores are more flexible than implants with smaller pores. Implants that are more interlooped have smaller pores and a higher degree of stiffness; multifilament meshes are more flexible or supple [41, 49].

Polypropylene (Fig. 4) is the most widely used material to fabricate cheap, inert, and easily tailorable implants. It preserves its chemical and mechanical integrity for years

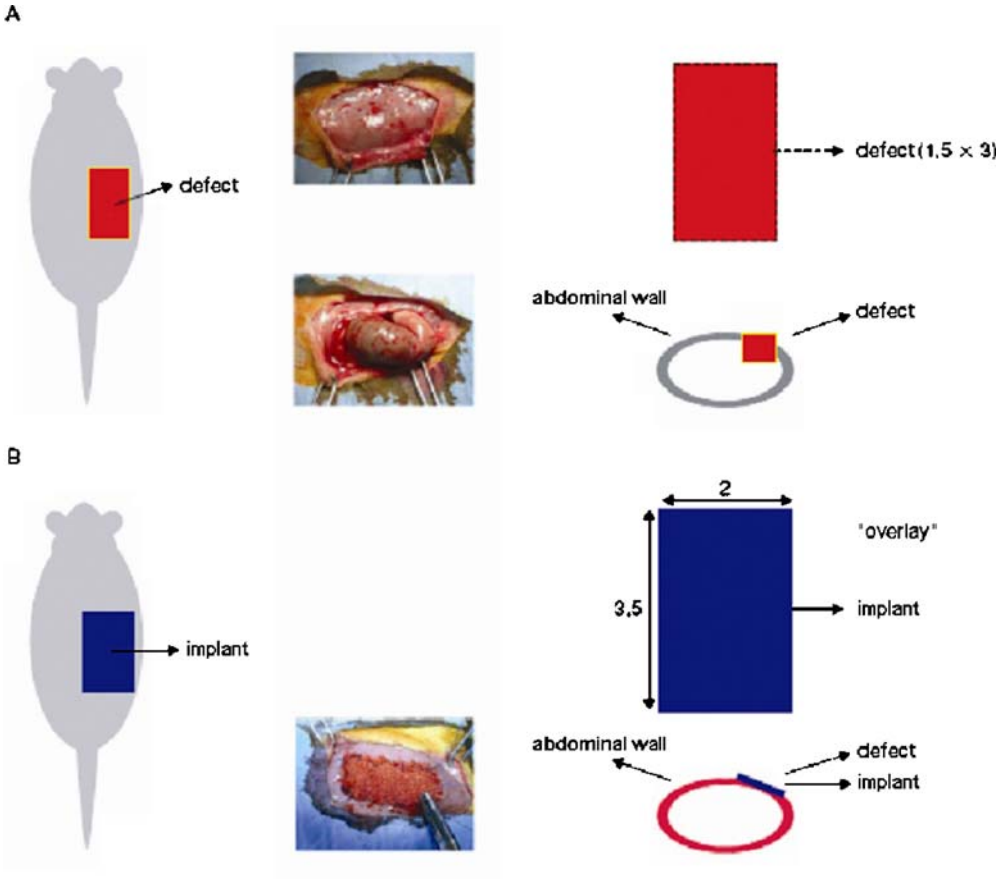

Fig. 3 Typical design of a rat experiment. **a** A standardized defect is induced using a grid, involving the entire thickness of the abdominal wall. **b** A mesh is laid over the defect, with its border exceeding the initial incision, and the mesh is sutured to the fascia. Experiments are done sterile and under general anesthesia

and exhibits high burst and tensile strength in dry laboratory conditions and when incorporated in the native tissue [52]. The majority are monofilament, woven over the years with increasingly large pore sizes, resulting in more elasticity without compromising the physical strength and less local side effects. When applied within the peritoneal cavity, adhesions may develop, which bears relevance to procedures such as sacropexy or abdominal wall hernia repair. Polypropylene is used to weave different type of fabrics, sometimes under the same name. This might be confusing. For instance, Surgipro (Tyco Healthcare, Mechelen, Belgium) is a trademark of a range of polypropylene products, including a typical monofilament as well as two multifilament mesh types (Table 1; Fig. 5). Multifilament implants have *interstices* between threads, which are much smaller than the actual pores, and increase the contact surface with the host. Again, this results in better integration but also a stronger inflammatory reaction. Pore sizes or interstices of less than 10 μm *theoretically* allow passage of bacteria (usually 2 μm or less) but not leucocytes (9–15 μm) and macrophages (16–20 μm). Both cell populations are important in the fibrosis process and in eventual clearance of infection.

Interestingly, these three different products are marketed without clear directions towards their exact clinical applications. The multifilament materials are typically used for hernia repair, where increased malleability, resistance to wrinkling, and softness are important to prevent undesired local side effects [53]. In urogynaecology, Surgipro SPM is used to manufacture the Intra Vaginal Sling (IVS) tape. SPMW is used by some surgeons to augment vaginal prolapse repairs (von Theobald, personal communication). We recently compared these different Surgipro products and suture repair experimentally in the rat fascial defect model [54]. Multifilament materials

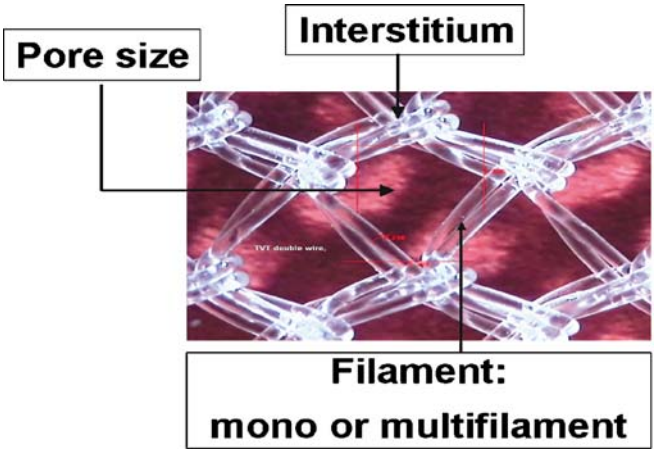

Fig. 4 Terminology used to classify synthetic implants. Magnified view of a part of a polypropylene tape as used for TVT procedure (Gynaecare, Johnson and Johnson) with identification of filament, interstitium, and pore

Table 1 Classification of synthetic implant materials

	Component	Trade name	Fibre type
Type I: Totally macroporous	Polypropylene	Prolene, Gynemesh, Gynemesh PS (Ethicon)	Monofilament
		Marlex, Pelvitex[a] (Bard)	Monofilament
		Surgipro[b] SPMM (Tyco)	Monofilament
	Polypropylene/Polyglactin 910	Vypro (Ethicon)	Mono-multifilament
	Polyglactin 910	Vicryl (Ethicon)	Multifilament
Type II: Totally microporous	Expanded polytetrafluoroethylene	Gore-Tex (Gore)	Multifilament
Type III: Micro or macro-micro	Polyethylene	Mersilene (Ethicon)	Multifilament
	Polytetrafluoroethylene	Teflon (Gore)	Multifilament
	Braided polypropylene	Surgipro[b] SPM (Tyco)	Multifilament
	Braided polypropylene–open weave	Surgipro[b] SPMW (Tyco)	Multifilament
	Perforated Expanded Polytetrafluoroethylene	Mycro-mesh (Gore)	Multifilament
Type IV: Submicronic pore size	Polypropylene sheet	Cellgard	Monofilament

Macroporous is defined as pore size >75 μm, microporous ≤75 μm
[a]Recently collagen coated macroporous polypropylene materials like Pelvitex (Bard) came on the market; their place, if any, needs to be defined
[b]Several kinds of Surgipro (Tyco) materials are marketed under the same name and have different constructs

induced a shorter lasting acute inflammatory response, transiting in a more pronounced chronic inflammatory reaction, as compared to monofilament implants. Foreign body giant cells were localized mostly around individual filaments. Macrophages could, in contrast to what is usually assumed, be found in interstices as small as 7.5 by 12.5 μm. No difference in collagen deposition and neovascularisation was observed between the three constructs. Multifilament materials were equally resistant to tensiometry, except at the last (90 days) time point, when tighter woven multifilament SPM explants were significantly weaker than polypropylene sutured or SPMM controls. Overall shrinkage was 10% over 3 months, and comparable for all groups.

Other polymers have been used as well, such as polyester. This leads to more foreign body reaction as well as more wound-healing complications, at least in hernia patients [55].

Biologic implants

Biologic materials conceptually would be an alternative for synthetics as to alter the foreign body reaction, hence avoiding local complications. Biologic implant materials can be divided into *autologous* implants, where the patient serves as its own donor, *heterologous* implants, where the material usually comes from the same species but another individual (usually cadaveric material), and *xenogenic* implants, i.e., material derived from other species. At present, most xenogenic materials are from porcine source, as bovine material became less acceptable.

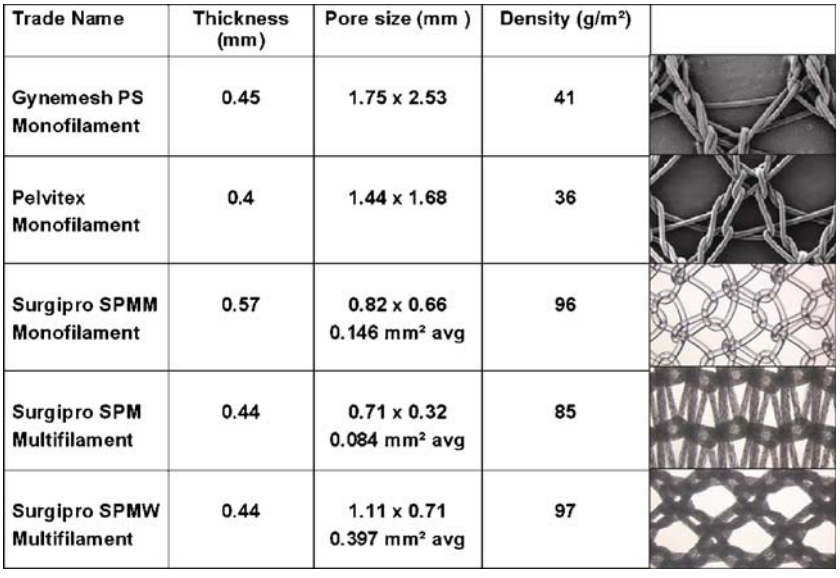

Fig. 5 A selection of different polypropylene implants on the market, showing monofilament (upper three) vs multifilament texture (lower two) and variability of knitting and pore size in between. Variables of interest are pore size and density of material. Materials may not have been photographed at the same magnification (lower three at ×38)

Table 2 Classification of biologic implant materials marketed for urogynecologic indications

	Component	Trade name (non-limiting list)
Autologous grafts	Rectus fascia	–
	Fascia lata	
	Vaginal mucosa	
Allografts	Fascia lata	–
	Dura mater	Lyodura
Xenografts	Porcine non-cross-linked small intestine submucosal collagen	Surgisis (Cook)
	Porcine non cross-linked dermal collagen	InteXen (AMS)
	Porcine dermal cross-linked collagen	Pelvicol, Pelvisoft, Pelvilace (Bard)
	Fetal bovine skin derived collagen scaffold	Xenform (Boston Scientific)
	Bovine non-cross-linked pericardium	Veritas (Synovis)

Autologous grafts usually induce very limited foreign body reaction, are well-incorporated into native tissue and they can, in theory, be used in an infected environment. Disadvantages, however, are the surgical morbidity at the prelevation site and the unpredictable durability of the repair, because after absorption they are replaced by host connective tissue that is inherently weak.

Allografts can overcome the problem of surgical morbidity associated with the prelevation of autografts, but not the unpredictable resorption and integration process. Fitzgerald reported autolysis in 20% of the implanted fascia lata grafts [56]. Histological analysis of the grafts showed areas of linear organization of the collagen fibers similar to native fascia altered with areas of poor linear organization and total tissue breakdown. Donor fascia lata is obtained from post mortem tissue banks. Although fastidious steps are taken in the preparation, concerns about the potential risk of viral particles, but more particularly prion transmission remain. The risk of HIV transmission is estimated to be one in eight million [57].

Xenografts are acellular collagen-based scaffolds harvested in certain animals raised for that purpose. Production is strictly controlled by Food and Drug Administration (FDA) guidelines, which include knowledge of the animal herd, vaccination status, feed source, abattoir approval and bovine spongiform encephalopathy clearance. The most commonly used xenografts are porcine derived; bovine material is on the market as well (Table 2). Collagen based implants can either be cross-linked or not. Cross-linking protects the implant against degradation by collagenases, so that they remain intact very long, if not ever. Surgisis is manufactured from porcine small intestinal submucosa in such a way that all cells responsible for an eventual immune response are removed, but the complex extracellular matrix and natural growth factors are left intact. It contains collagen types I, III, and V and growth factors TGF-beta and FGF-2. It exists at present in two-, four-, and eight-layer implants. Small intestinal submucosa (SIS) is degraded in 4 to 12 weeks by a "constructive" remodeling process that replaces the graft gradually by host connective tissue [58, 59]. Tensiometric strength initially decreases down to 45% 10 days after implantation, but by 1 month it is identical to that of the native material [60]. Two years after implantation it exceeds the strength of native tissue. We compared SIS with Marlex (Bard), an elder, rather dense type I polypropylene mesh. The strength of Marlex gradually increased over the experiment, but it induced a more pronounced inflammatory and foreign body reaction. Fibrosis occurs faster with more intense collagen deposition. A number of rats implanted with SIS developed seromas, with fluid accumulation between layers, and even some low-grade local infections. SIS

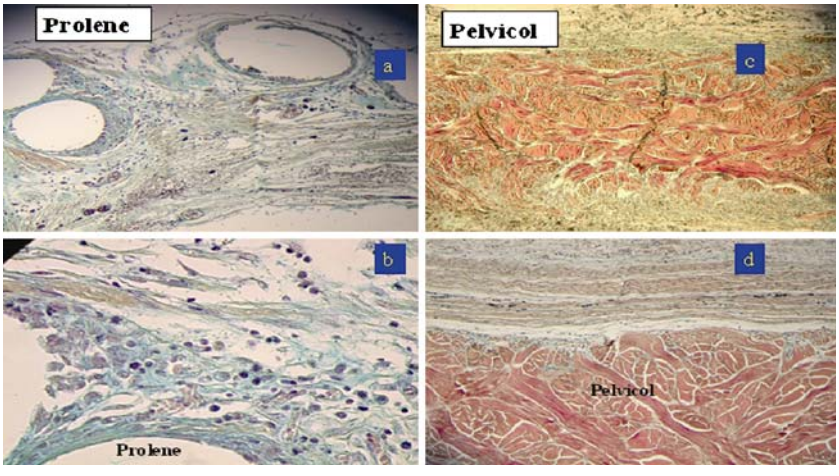

Fig. 6 Cross-section through implant areas in rats, either Prolene (*left*) or Pelvicol (*right*). The material can be easily recognized at smaller magnification (**a**, **c**). At larger magnification, the intensity of a more pronounced inflammatory reaction becomes more clear in Prolene (**b**) than Pelvicol (**d**). From Zheng et al. (2004) [47]

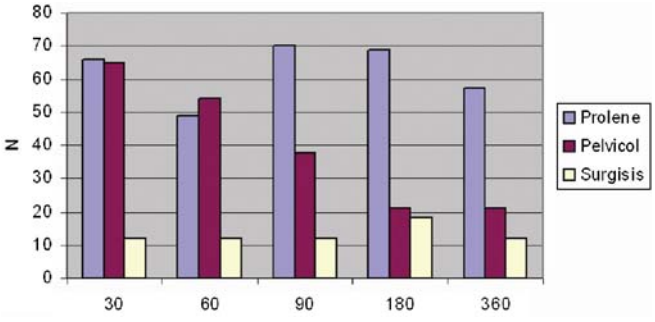

Fig. 7 Long-term evaluation of tensiometric strength in the rabbit model. Pelvicol and SIS are biomaterials, compared to a monofilament polypropylene product. *X*-axis are days post implantation; *Y*-axis is breaking force in N. From: Claerhout et al. (2003) [45]

induced less adhesions, an initial slower deposition of less mature collagen, but ultimately became more organized by the end of the study period. Tensile strength was initially lower than for Marlex; however, it reached comparable levels after 3 months [61].

Pelvicol is a porcine dermal collagen implant consisting of a sterile off-white tough but flexible flat sheet of fibrous, acellular collagen and its constituent elastin fibers cross-linked with hexamethylene-di-isocyanate (HMDI). In a rat model, we documented a lesser inflammatory response as compared with Prolene (Johnson & Johnson): there were lesser granulocytes and macrophages, and cells expressed less surface activation markers ICAM-1 and CD11b. Pelvicol induced a slower, but more orderly collagen deposition paralleling the surface of the implant. However, the product is encapsulated rather than a formal in-growth process occurs (Fig. 6). Encapsulation may challenge mechanical strength and has other side effects, such as seroma formation. Tensile strength was initially lower in Pelvicol, slowly increasing to comparable levels by day 90 [47]. An improved strength early on could be obtained by modifying the product with pores of 2.0 mm in diameter. This allows for better tissue ingrowth and more neovascularization [62]. In rabbit experiments, we demonstrated that 1 year after implantation half of the Pelvicol implants were still intact. However, half of them showed progressive signs of degradation, its cause and clinical relevance remaining undetermined. On tensiometry, tensile strength of Pelvicol was initially as strong as Prolene explants but started to decrease 3 months after implantation. In that study also four-layered SIS was used. Tensiometric strength of SIS explants progressively decreased, and some animals displayed bulging through the defect [45] (Fig. 7).

The nature and course of the inflammatory process is different for synthetic and bio-grafts as studied in immunologic models [48, 63, 64]. Synthetics make leukocytes produce a cytokine profile dominated by TNF-α, IFN-γ, and IL-1, which are usually referred to as "T helper 1 type" (Th1) cytokines. They are "pro-inflammatory" in nature: they activate macrophages and are typical for rejection processes. SIS and also Pelvicol, as we demonstrated, will induce a "T helper 2 type" (Th2) cytokine profile, wherein IL-10 and TGF-β are predominant. These do not activate macrophages and affect humoral immunity through production of non-complement-fixing antibody isotypes. After organ transplantation, activation of the Th2 pathway coincides with graft acceptance. Seemingly xenogenic implants are more biocompatible, which may reduce local complications. This remains to be clinically demonstrated. Actually, the mechanisms causing local complications in urogynaecology are still poorly understood. Prospective data collection on patient presenting with pain, infections, wound dehiscence, erosions or fistula (for as much as the latter can be discriminated), as well as recurrence rates, are very important objectives in any clinical study on the use of meshes for prolapse repair.

Conclusion

A growing number of aging women are presenting as candidates for surgical repair of genital prolapse. The scientific background of tissue changes and wound healing, both in hernia as well as prolapse patients; as well as the fate of implant materials used to reinforce repairs, is, therefore, a clinical need. The perfect implant material certainly is not available yet, but in general surgery there is now a consensus, funded on experimental data, that low-weight, large pore, monofilament materials are preferable. However, local complications may still occur and seem related to an increased foreign body reaction. Xenogenic implants were introduced in an effort to reduce these local complications, hopefully without compromising surgical results. Animal experiments show that the inflammatory response to these materials definitely is different. In tensiometric experiments, some products show comparable strength, but the longevity of these products, as well as functional results, remain to be demonstrated.

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