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The use of polymeric meshes for pelvic organ prolapse: current concepts, challenges and future perspectives

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Abbreviations: POP, pelvic organ prolapse; POP-Q, Pelvic Organ Prolapse Quantification; POPPY, Pelvic Organ Prolapse Physiotherapy; SUI, stress urinary incontinence; FDA, Food and Drug Administration; PP, polypropylene; PET, polyethylene terephthalate; ePTFE, expanded polytetrafluoroethylene; ECM, extracellular matrix; MHRA, Medicines and Healthcare product Regulatory Agency; NHS, National Health Service; PLA, polylactic acid; PLGA, poly(lactic-co-glycolic acid); PCL, polycaprolactone; PU, polyurethane; PVDF, polyvinylidene fluoride; PLCL, poly (L-lactide-co-caprolactone); PLGA, poly(lactic-co-glycolic acid); PLGT, poly(Llactide)-trimethylene carbonate-gycolide); PEO, polyethylene oxide; bFGF, basic fibroblast growth factor; GTGF, connective tissue growth factor; MSCs, mesenchymal stem cells.

Abstract

Pelvic organ prolapse (POP) is one of the most common chronic disorders in women, impacting the quality of life of millions of them worldwide. More than 100 surgical procedures have been developed over the decades to treat POP. However, the failure of conservative strategies and the number of patients with recurrence risk have increased the need for further adjuvant treatments. Since their introduction, surgical synthetic meshes have dramatically transformed POP repair showing superior anatomic outcomes in comparison to traditional approaches. [Although significant progress has been attained, among the meshes in clinical use, there is no single mesh appropriate for every surgery.](#) Furthermore, due to the risk of complications including acute and chronic infection, mesh shrinkage, and erosion of the tissue, the benefits of the use of meshes have recently been questioned.

The aim of this work is to review the evolution of POP surgery, analysing the current challenges, and detailing the key factors pertinent to the design of new mesh systems. Starting with a description of the pelvic floor anatomy, the paper then presents the traditional treatments used in pelvic organ disorders. Next, the development of synthetic meshes is described with an insight into how their function is dependent on both mesh design variables (*i.e.* material, structure, functional treatment) and surgical applications. These are then linked to common mesh-related complications, and an indication of current research aiming to address these issues.

1. Introduction

Pelvic organ prolapse, which has been defined as “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)” [1], is one of the most common chronic disorders in women, affecting almost half of all women over 50 years of age [2]. The majority of women are asymptomatic. Of the 20% of women who present with clinically relevant symptoms [3], the peak incidence occurs in women aged 60-69 [4]. Symptoms usually involve one or more of the urinary, bowel or vaginal organs. Urinary symptoms range from urgency (the sudden, compelling urge to urinate) and frequency of urination to a weak stream and, ultimately, incontinence. Similarly, bowel symptoms range from a sensation of incomplete emptying to fulminant faecal incontinence. Vaginal symptoms include sexual dysfunction, pain, mucus discharge and bleeding [5].

The anatomy of the female pelvic floor has been exhaustively described in previous literature [6–8]. In brief, the pelvic floor consists of three levels of support. Specifically, the complex architecture of the pelvic floor comprises of a heterogeneous composition of muscles and supporting tissue (fascia), each providing suspension, attachment or fusion (see Figure 1). Level one provides suspension; the cardinal and uterosacral ligaments provide semi-vertical support of the cervix and upper vagina. Level two is comprised of the arcus tendinous fascia and fascia of the pubococcygeus and iliococcygeus muscles; these provide attachment for the pelvic floor muscles and support the middle third of the vagina at the pelvic side wall. The third level is the fusion of the pelvic floor at the urogenital diaphragm and perineal body. The endopelvic fascia provides additional support to the structures of the pelvic floor. The fascia lies inferior to the abdominal peritoneum and can be found as an uninterrupted entity with variations in its density throughout its structure [9,10]. Pelvic organ prolapse occurs due to

reduction in fascia and muscle strength, resulting in descent of the pelvic organs through the vagina as represented in Figure 2 [11].

Although the etiology of POP is multifactorial, multiparity is a major risk factor. Pregnancy and/or vaginal delivery stretch the structural muscles in the pelvis, leading to loss of support. Furthermore, vaginal delivery, especially involving a large baby, a long labour, or the use of forceps or extractive devices may damage nerves, leading to further muscle weakness [12]. Other risk factors include aging and menopause. The decline in oestrogen levels at menopause causes loss of muscle elasticity and weakens pelvic floor support. Increased intra-abdominal pressure due to obesity, pelvic tumours, excess straining or coughing can also contribute to POP disorders [3]. Hysterectomy, nerve disorders, connective tissue disorders, degenerative neurologic conditions and prior pelvic surgery have also been implicated in POP [12].

POP is classified according to the affected anatomical pelvic compartment: anterior, apical or posterior. The anterior compartment includes the bladder, bladder neck, and urethra. The apical compartment includes the uterus (or cul-de-sac after hysterectomy). The posterior compartment includes the rectum and anal canal [10]. An anterior prolapse, also known as a cystocele, is prolapse of the anterior compartment. The bladder descends posteriorly into the genital hiatus toward the vaginal introitus. A posterior prolapse, or rectocele, is prolapse of the rectum anteriorly into the perineal body, compressing the posterior vaginal wall. An enterocele describes an apical prolapse where either the uterus (uterine prolapse) or the distal cervix (vaginal vault prolapse, in cases of previous hysterectomy) descend through the vaginal canal [4].

Several systems exist to grade POP. These systems provide an objective, consistent measure to report the degree of POP, both clinically and for research purposes. The use of a standardized system to describe POP is a key component of treatment decisions. The most commonly used method is the Pelvic Organ Prolapse Quantification (POP-Q) system (see Table 1). This was created by the Standardization Subcommittee of the International Continence Society in an effort to develop an encoding tool useful to both clinicians and researchers. This system relies on specific measurements of defined points in the midline of the vaginal wall [13]. Also, with the POP-Q system grades are assigned according to the amount of prolapse seen whilst the patient undertakes the Valsalva manoeuvre (forced exhalation against a closed glottis) in relation to a fixed reference point, the hymen [14]. Researchers favour this approach because specific measurements at nine sites are recorded in a tic-tac-toe grid. Furthermore, through the use of POP-Q system interobserver agreement and reliability are improved in comparison to the other available systems [13].

2. Management of pelvic organ prolapse: conservative treatments

The initial management of patients with pelvic organ prolapse is non-operative, and includes lifestyle changes, dietary advice and pelvic floor retraining with biofeedback techniques. Conservative measures such as pelvic floor muscle training were discussed in a 2011 review paper by Hagen and Stark and found to be of some benefit [15]; however, the studies were contradictory and, whilst urinary incontinence was improved, there was no effect on the sensation of pressure or dragging. The POPPY (Pelvic Organ Prolapse Physiotherapy) trial randomised 447 participants to receive an individualised programme of pelvic floor muscle training or a prolapse lifestyle advice leaflet and no muscle training. The study showed a reduction in prolapse symptoms with supervised pelvic floor exercises [16]. Although obesity

and heavy lifting initially contribute to prolapse occurrence, reversal of these risk factors does not lead to regression of the POP [17,18], although some symptoms may improve [19].

Conservative methods are employed when surgery is deemed unsuitable for the patient or at the patient's request. Topical hormone delivery systems can help relieve lower urinary tract symptoms and long term replaceable pessaries can re-establish the physical support [20].

Surgery is the mainstay of treatment for pelvic organ prolapse and is indicated once conservative measures have failed to result in adequate symptom reduction. Nevertheless, the optimal operative strategy remains nebulous. To date, more than 100 techniques have been described [20]. There has been a lack of consensus or generally accepted guidelines on the best treatment of these conditions and, until recently, no prospective randomized trials comparing operative strategies [21].

Traditional treatment options for women suffering POP often included hysterectomy plus vaginal wall repair if required. Nowadays, the choice of operation (as detailed in Table 2) depends on the patient's symptoms, degree of prolapse, background (including comorbidities) and request for sexual function.

Whilst hysterectomies are still the mainstay of prolapse surgery, this is often supplemented by McCall culdoplasty, the [Moschcowitz procedure](#) or suturing of the cardinal and uterosacral ligaments to the vaginal [vault](#) [22]. These techniques are thought to prevent vault prolapse post-operatively and provide additional pelvic floor support. If vault prolapse is diagnosed during vaginal hysterectomy then sacrospinous [fixation or uterosacral ligament suspension](#) should be considered [21].

3. The advent of surgical meshes in POP surgery

Many surgical options for the management of POP have been proposed over the years. Even though many advances have been achieved, outcomes after surgery remain far from perfect [23]. Particularly, the high failure rate of traditional techniques (average 30% rate of reoperation) [24], mainly based on the use of native tissue, encouraged clinicians to look for new solutions. Particularly, these aim to *i*) overcome the frequent unsatisfactory outcomes of conservative surgery (i.e. recurrence rate) *ii*) reduce the reoperation rate, and *iii*) enhance the durability of the surgical procedure, providing better anatomical results [25].

The tremendous improvements of patient conditions, shown after hernia mesh implantation [26], supported by the knowledge and experience gained by the surgeons over the years in their use [27], boosted the introduction of these devices for the management of stress urinary incontinence (SUI) and POP. In the 1970s, for the first time gynaecologists started using surgical meshes intended for hernia repair for pelvic floor reconstructive surgery [24]. However, these meshes were free-form grafts, and the need to cut them into different shapes, and according to the specific procedure, was tedious and unsafe [28]. Hence, to fulfil the perceived desires of the clinical community, medical device manufacturing companies started producing mesh and mesh-based kits in different shapes and sizes [29]. Twenty years ago, the first mesh for the treatment of human incontinence was sanctioned (ProteGen sling). This mesh consisted of a woven polyester sling manufactured by Boston Scientific, and in 2002 the United States' Food and Drug Administration (FDA) approved the first prosthesis for POP treatment [30]. Since then, research on meshes for POP has grown considerably, as demonstrated by the graph in Figure 3, resulting from a search on Scopus using “mesh, pelvic, organ, prolapse” as keywords.

Synthetic surgical meshes, which represent the main focus of this review, were developed as an alternative to biological grafts (autologous fascia has been the most widely employed [31]). This advancement was possible thanks to the benefits of the new implants; mainly these were: the lack of potential infectious disease transmission, the possibility to predict their resulting mechanical properties according to the manufacturing methods, and the benefit to reduce the operative risk associated with harvesting procedures [32]. Synthetic surgical meshes are currently available in many varieties, and usually classified depending on their: material type (non-absorbable, absorbable or composite), filament type (monofilament or multifilament), pore size, textile structure (knitted or woven), weight and mechanical properties.

However, based on the outcomes from medical practice, the use of surgical meshes for the management of both SUI and POP is accompanied by benefits but also risks [23], which in some cases can lead to serious life-threatening conditions, as will be discussed in the following paragraphs [33–36].

4. Synthetic meshes: materials

Over the years, several biomaterials have been proposed for the development of supportive strategies to augment and reinforce pelvic floor region [37]. Likely to the materials intended for abdominal wall repair, the ideal biomaterial should be sterile, durable, not carcinogenic, but also withstand remodelling by body tissues, have minimal risk of infection and rejection, and ultimately be cost-effective [38–40]. Additionally, once implanted the ideal biomaterial should possess adequate mechanical properties, withstand shrinkage, and be pliable and easy to manipulate during surgery [36,41]. However, in comparison to the abdomen, the pelvic floor is a more complex tissue, with an heterogeneous architecture that include muscles,

connective tissue and organs [42], and whose composition changes significantly according to several factors, such as age, pregnancy and menopause [43].

Whilst there is a general consensus of opinion that employed materials should best match the biological environment the optimal surface and mechanical properties for a mesh are still not full known [11, 44–47]. The precedence for material choice in these applications is largely historic and need further consideration.

Commonly used non-absorbable materials for POP surgery have been polypropylene (PP), polyethylene terephthalate (PET) and expanded polytetrafluoroethylene (ePTFE). Among these, polypropylene has remained the most widely adopted. It is an inert and biocompatible material that favours tissue ingrowth, with an acceptable fatigue durability, to last for many years of implantation in the biological environment, and sustainable tensile strength [48].

Particularly in the last decades, there has been an increase of evidence that PP-based meshes are prone to form adhesion with the viscera [49], in some cases induce high inflammatory response [50–52], and they increase their stiffness over time [44], causing the weakening of the surrounding tissue [53]. PET is a thermoplastic polymer belonging to the polyester family.

Regarding its use within the reconstructive surgery, it was processed as multifilament mesh by Ethicon (Somerville, New Jersey, USA) and it has been known as Mersilene®. The adoption of Mersilene® meshes was further promoted by David Nichols in 1973 as the decisive treatment of severe recurrent stress urinary incontinence [54]. However, polyester prostheses were subjected to a controversial reputation during the years. Although they have higher cytocompatibility in comparison to PP meshes [55,56], they are associated with poor clinical outcomes, erosion and chronic infections. Most of the polyester multifilament meshes have interstices of less than 10 µm, which allow small bacteria to infiltrate and proliferate, leading in this way to greater infection and extrusion rates [57–59]. The introduction of

monofilament PP midurethral slings for SUI has led to the adoption of this material in place of Mersilene®. After PP, ePTFE was the second widely used material for reconstructive surgery. It was discovered in 1963, and in 1983 processed as a soft tissue patch (Gore-Tex) and used clinically as hernia repair prosthesis [60]. Contrary to PP, Gore-Tex patches implanted in the abdomen led to a less inflammatory response and visceral adhesion, thanks to its pliable multifilament structure [61]. However, Gore-Tex does not promote incorporation into the surrounding native tissue, and is associated with erosion and high rejection rates which has decreased the use of these meshes [62,63].

Completely absorbable materials were designed in order to develop surgical meshes able to serve as supporting devices while degrading during the healing process [64]. Conversely to permanent meshes, which often resulted as ideal substrates for bacteria growth, leading to the risk of infection post implantation, these new designed meshes have the advantage to minimize the amount of material left in the body and reduce the foreign immune response [35,57]. Furthermore, considering their compositional properties, they can be used in children, without hampering the growth of new tissue, which together with chronic pain and restriction of physical movement were considered the most common drawbacks associated with the use of permanent meshes [64,65]. Among the absorbable materials developed for biomedical application, polylactic acid (Vicryl, Ethicon, Somerville, NJ, USA) and polyglycolic acid (Dexon, Davis and Geck, Danbury, CT, USA), are those most widely applied as meshes for incontinence and pelvic organ prolapse surgery [66].

However, beyond the several advantages mentioned above, one drawback for absorbable meshes is associated with their mechanical behaviour; particularly, they tend to lose tensile strength once absorbed [67]. Thus, absorbable meshes are not indicated when prolonged tensile strength is required. Also, as evaluated in randomised trials, polyglycolic acid and

polyglactin 910 absorbable meshes were found to be associated with high recurrence rates in prolapse surgery [68].

5. Synthetic meshes: structural parameters

According to the filament type, both absorbable and non-absorbable meshes can be classified as multifilament or monofilament, where multifilament fibers are braided or interwoven. Studies have found that multifilament mesh produces more fibrosis and acute inflammation than their monofilament counterparts, believed to arise from the increased surface area of ~1.57 relative to monofilament fibers [69–71]. Also, multifilament meshes are characterised by interstices of less than 10 µm within the filaments. These spaces allow bacteria to enter and proliferate, but prevent the host immune cells to pass through, thus increasing the risk of infection within the mesh. Furthermore, synthetic meshes can be characterized as macroporous or microporous [67,72]. Porosity is defined as a ratio of the void, or empty space, in a mesh [to the area occupied by the mesh](#) (void area in meters/total area in meters). The dimension of mesh pores plays a key role in determining which organisms (macrophages versus bacteria) can pass through the mesh; hence, this is considered the most important factor for improving the host response to mesh [56,73].

[75 µm has been considered a significant value toward the design of a POP mesh, since the presence of pores with such dimension allows ingrowth of fibroblasts, blood vessels, and collagen fibers, which support the formation of fibrous connections with the surrounding tissue. However, meshes having interstices with dimensions below 10 µm provide a suitable housing for bacteria, resulting in higher infection rates. Specifically, the limited dimensions of such pores impede the passage of granulocytes and macrophages, which are too large to infiltrate the prosthesis, eliminate bacteria and thus prevent their proliferation \[74,75\].](#)

Within meshes for hernia repair, the role of pore size has been well characterized, particularly for polypropylene meshes. Larger pores have been shown to improve the mechanical integrity of the resulting mesh-tissue architecture, increasing both strength and collagen deposition in comparison to those resulting from grafts with smaller pore dimensions [55,56]. In fact, the use of this last class of mesh yielded mesh-tissue constructs with limited vascular growth and less mature collagen formation. Pore size also affects the mesh flexural rigidity. Small pores lead to a mesh with high flexural rigidity and a less compliant behaviour. For instance, Prolene and Marlex are both two monofilament synthetic meshes; however, given the larger pore sizes of Prolene in comparison to Marlex, [Prolene is more flexible and pliable](#) [67,76].

Besides the filament type, the geometrical arrangement of filaments is another aspect that [has been linked to a synthetic material's](#) host response. According to the textile structure, POP meshes can be woven, knitted, or unwoven. Woven materials, which include plain, twill and satin, provide superior mechanical strength and shape memory; however, these devices fray when cut and, due to their increased bending stiffness, they are not able to conform to the complex geometries of the pelvic floor [69]. Knitted materials, manufactured by looping individual filament, consist of warp-knit, interlock, and circular knit. They possess flexibility, versatility, and high conformity to the anatomical structures, and most notably, they have a significantly lower number of complications in comparison to woven mesh. The unwoven materials are well absorbed but have the disadvantages of non-conformity and poor visibility [53,77,78].

Along with these, mesh weight is another important parameter that needs to be considered for synthetic materials. In 1997, Amid classified synthetic mesh materials used in abdominal hernia repair according to their filament(s) structure, porosity and thus weight [72]:

Type I: lightweight macroporous monofilament mesh with pores greater than 7 µm in diameter. The large pores make it more flexible and easier to work with, although this allows not only fibroblasts but also bacteria to enter.

Type II: monofilament microporous mesh with pores smaller than 10 µm in diameter with reduced elasticity in comparison to type I. The size of the pores prevents adhesions but allows bacteria infiltration, with the consequent higher risk of infection and the necessity for mesh removal.

Type III: multifilament mesh, predominately macroporous with some microporous components. The large pores and small interstices allow bacteria to infiltrate but not macrophages; infection spread and restricted elasticity can be a problem associated to their use.

Type IV: mesh with submicroscopic pore size (<1 µm). Often used for adhesion prevention in abdominal surgery, less in pelvic reconstructive surgery.

6. Synthetic meshes: biomechanical properties

Since their inception, there has been recognition that the requirements for the mechanical properties of POP meshes differ significantly to the hernia meshes from which they were derived. Furthermore, these mechanical properties are fundamental to the success or failure of an implanted prosthesis. These aspects were explored in reviews of early POP meshes, which identified that ‘the perfect product does not exist at present’ and that there is an associated need for meshes exhibiting greater durability and elasticity [69]. Research has since helped improve our definition of mechanical factors relevant to mesh success, which include elastic modulus, failure load and stress transmission at the tissue-implant interface [66, 67]. Mazza and Ehret [79] describe the pursuit of ‘*mechanical biocompatibility*’ by analysing the mechanical behaviour of implanted materials and associated soft tissues at different length scales. They demonstrate that multi-scale deformation behaviour is important when trying to match or tailor mesh properties to those of surrounding tissue.

It is clear that the mechanical properties of POP mesh should be linked to those of the soft tissues and organs which it seeks to support. Studies have found that the biomechanical properties of vaginal tissue varies significantly pre and post menopause (see Table 3) [80], there is significant differentiation in mechanical properties between organs of the pelvic floor (bladder, vagina, rectum) and that tissues exhibit Mullins-effect ‘stress softening’ with significant hysteresis effects [71]. For a more complete understanding of the environment in which POP meshes operate it is necessary to consider **the pelvic floor as a biomechanical structure in its entirety. This should include** the complex interaction between constituent organs, soft tissues and support structures [77]. This can be represented through **animal models, although** this involves significant approximations and limits the ability to represent different pathologies related to POP [48, 71]. An increasingly popular alternative is provided

through computational finite element [modelling \[38\]](#), which provides a potentially powerful tool to investigate dynamic loading and patient specific anatomy in POP [81] and to examine the response of different types of mesh implant [82].

In conjunction to understanding the anatomy, studies have sought to characterise the mechanics of mesh implants and link these to pelvic floor biomechanics. The mechanical response of meshes is closely related to both material and structural composition (e.g. mono vs multi-filament and weave type), factors which are also tightly coupled with biocompatibility (e.g. pore size effects tissue integration) which could potentially complicate optimisation [38]. Testing of meshes in isolation reveals that they typically possess a complex set of mechanical characteristics including anisotropic viscoelastic behaviour, plastic deformation under typical load regimes [83] and flexural rigidity which varies with mesh orientation [45]. Nevertheless, there is no clear consensus on [what constitutes](#) an appropriate range of tests and biomechanical descriptors for comparing POP meshes [49, 72] but it is evident that the mechanical response changes significantly after implantation. [This is notable](#) in a reduction of stiffness and ultimate tensile strength and a permanent increase in length [84]. Additionally, loading and implantation can change structural parameters (e.g. pore size) which compromise biocompatibility of the implant [85].

It is clear that the ‘mechanical characteristics’ of POP mesh are critical in determining implant success. Design requirements emerging from recent research include a need for anisotropic meshes with properties tailored and matched to the contacting soft tissues at its surface, features which could be realised using techniques such as electrospinning [46]. Mechanical characteristics are also highly relevant to surgical application, and further work is required to improve our understanding of how meshes will respond when implanted to ensure they avoid

failure (e.g. mechanical biocompatibility) and remain effective in supporting the pelvic floor long-term [82].

7. Synthetic meshes: surface treatments

As well as the exploration of novel mesh materials, coatings and surface treatments have been explored in an attempt to increase biocompatibility and reduce soft tissue trauma. The surface properties of the interfacing mesh are, without a doubt, one of the most important aspects of a device. To date, a variety of metal based and hydrophilic coatings technologies have been used to optimise the soft tissue- mesh interface from an adhesion, infection and trauma point of view. The use of bio-polymers such as alginate, collagen and dextran have been widely reported in literature and surface functionalisation methods. Synthetic polymers, such as poly-lactic-acid, poly-lactic-glycolic-acid and poly-vinyl-alcohol have also been mooted as potential materials to enhance and optimise the device/tissue interface. In a move towards more biosynthetic meshes, approaches such as collagen coating of polypropylene have been explored. Collagen-based biomaterials have been available for several decades and are becoming increasingly popular due to their perceived biocompatibility and low immunogenicity [68,86]. However, results and outcomes for collagen based implants vary substantially when translated from and between animal models to the actual clinical applications [87,88]. Cervigni et al. [89] evaluated the efficacy of collagen-coated polypropylene mesh in the correction of anterior vaginal prolapse. A commercially available porous collagen mesh was evaluated and was found to give high recurrence and exposure rates at one-year follow-up. This study is in contrast to that of Lo et al. [90] where 'A substantially good clinical outcome' was noted for patients receiving a similar mesh system. Another approach, presented by Faulk et al. [91], functionalised polypropylene mesh

materials with an extracellular matrix (ECM) material. ECM was isolated from porcine skin and converted to a hydrogel, enabling coating of the polypropylene mesh surfaces. Using a mouse model, they were able to mitigate foreign body response and associated fibrous connective tissue deposition that are common complications with these materials.

Barski et al. [92] investigated the use of autologous whole blood plasma as a means of modifying mesh surfaces for enhance bio-compatibility. Here the sling was immersed in plasma **30 min prior** to the procedure enabling absorption of the plasma onto the mesh surfaces. Results demonstrated that the functional outcomes and quality of life improved significantly in all groups. Other studies have quantified this approach further using animal models where improved cell adhesion was observed when compared to non-plasma treated surfaces [93,94].

8. Clinical outcomes and insight into the existing challenges

Over recent years' attention has increased on complications that can occur with the use of mesh to treat POP and SUI. The use of mesh for POP surgery has been the source of much scrutiny, including two public health notifications from the US Food and Drug Administration (FDA), and substantial litigation [23].

In 2008 and 2011, the FDA expressed its concern about the high rate of mesh-related complications in POP surgery [95]. Specifically, the FDA reclassified these devices from class II, which generally includes moderate-risk devices, to class III, which generally includes high-risk devices [96]. Furthermore, the FDA issued an order for all manufacturers to submit a premarket approval application to support the safety and effectiveness of surgical mesh for the transvaginal repair of POP.

Additionally, Departments of Health in both England and Scotland have undertaken work in this area, as have the Medicines and Healthcare products Regulatory Agency (MHRA) and the European Commission. A review by the National Health Service (NHS) England reported that collection of data on complications after POP surgery with and without mesh had been ‘insufficient’ to date [97]. Lately, the first large-scale robust observational study of outcomes after surgical management of both incontinence and POP has been reported by the Lancet [98]. The study involved women aged 20 years or older, undergoing a first, single incontinence procedure or prolapse procedure between 1997 and 2016. According to the findings, mesh procedures for the treatment of incontinence are recommended, although longer term outcomes would be beneficial. In relation to POP procedures, the use of mesh is not suggested for primary prolapse repair. Conversely, similar effectiveness and complication rates have been found for vaginal and abdominal mesh procedures for vault prolapse, in comparison to non-mesh vaginal repair [98]. Hence, the study results do not favour as elective any vault repair procedure for POP.

Whilst a number of meshes have been withdrawn from the market, following on the FDA multiple warnings, there are still several commercially-available and currently in use. These are reported and described in terms of key properties, advantages and disadvantages in Table 4.

The complications associated with mesh after pelvic organ prolapse surgery can be categorised into erosion, infection and retraction (see Table 5), and may co-exist. Mesh-related complications can cause pain and sexual dysfunction. They have a significant impact on patients' quality of life and the cost of their healthcare. Understanding the causes may

help elucidate new mesh designs and operative approaches to minimise these distressing complications.

Mesh erosion: a generic term which includes mesh exposure (visualisation of the mesh, usually through the vaginal epithelium), extrusion (the passage of the mesh out of a tissue) and perforation. Incidence of mesh erosion varies in the literature, but a large meta-analysis estimated the mean incidence of graft erosion at 10.3% [99]. Presenting symptoms depend on the organs involved. Vaginal mesh exposure or extrusion can sometimes be managed with oestrogen cream, but frequently requires either partial or complete removal of the mesh. Intravesical or intraurethral mesh erosion necessitates removal of the mesh from the bladder or urethra and may require partial cystectomy, if the mesh has eroded into the bladder wall [100]. Erosion into bowel is rare and requires specialist management [101].

The type and size of the mesh used may have an effect on the rate of complications, and no mesh is immune to erosions [102]. Erosions may be due to a foreign-body reaction or the result of bacterial colonisation. Type I (monofilament, macroporous polypropylene) mesh is the preferred graft choice as it allows host tissue to infiltrate the implant, resulting in good support and low infection rate [102]. Laparoscopic or robotic approaches are associated with a lower rate of erosions [103], as is raising a full-thickness vaginal flap [102].

Mesh infection: the incidence of mesh infection ranges from 0-8% in the literature [35]. Presenting symptoms include pain, fever, discharge and dyspareunia. Late signs are fistulae, discharging sinuses and osteomyelitis. Mesh infection requires total removal of the mesh and intravenous antibiotics [102]. A number of techniques can be used to minimise the risk of infection. Peri-operative antibiotics and thorough asepsis are recommended. It is thought that Type 1 mesh reduces the risk of infection by allowing the infiltration of host immune cells alongside bacterial cells, unlike microporous mesh which only permits the latter [102].

Mesh retraction: a certain degree of mesh contraction is normal and anticipated [104]. Many surgeons use large implants to account for the anticipated shrinkage over time [105]. Excessive mesh retraction can present with dyspareunia and incontinence due to non-compliance of the vaginal wall, in addition to recurrence of the original pelvic organ prolapse [106][65]. If analgesia and oestrogen gels are insufficient, surgery is required to relieve the tension on the pelvic organs. Total removal of the mesh is rarely required, but steps can be taken to reduce the risk. Lightweight meshes with decreased polypropylene density are thought to induce less of a foreign-body response, improving tissue compliance and causing less contraction of the mesh [64].

Chronic pain: The prevalence of chronic pain (lasting more than 6 months) after vaginal mesh surgery has been estimated up to 30% [107]. Pain is often associated with other complications such as mesh exposure or infection [108]. The management of chronic pain is dependent on its underlying cause. Muscle spasm can be treated with muscle relaxants and anti-inflammatories [109]. Nerve pain can be managed with local anaesthetic injections to the nerve [110]. In patients where all other treatments have failed, mesh release or removal may be required [107]. This then poses the challenge of how to manage secondary prolapse once the mesh is removed; this is a complex topic beyond the scope of this work.

Given the importance of pore size and porosity in the host response, it can be argued that maintaining these properties of a mesh is crucial for biocompatibility and positive patient outcomes. Unfortunately, the majority of current synthetic meshes have unstable geometries when loaded, resulting in the collapse of pores, nonplanar deformation (buckling and wrinkling) and narrowing at the midportion of the mesh (Poisson's effect). Thus, a future goal of synthetic mesh is the development of a mesh that maintains a stable geometry with loading, does not experience pore collapse or narrowing, regardless of the direction in which

the load is applied. There are numerous ways in which this can be accomplished including reinforcing the mesh such that the pores remain stable (i.e. open) early after implantation or changing the geometry of the pores such that they remain open in response to loading.

Finally, developing meshes from a biomaterial that does not permanently deform when loaded but rather returns to its original shape, is a desirable feature of future meshes.

Regardless of the approach taken, it is believed that preventing the reduction in pore size and loss of porosity in response to loading will allow for adequate tissue in-growth and integration. This offers significant promise to reduce the risk of mesh-related complications.

9. Future perspective

9.1. Research on pelvic tissue regeneration

Despite advanced knowledge that has been gained during the last decades regarding POP surgical procedures, and also mesh material properties and manufacturing methods, it is evident that the ideal POP mesh has not been developed yet. Moreover, following numerous warnings released by the FDA, there remain concerns associated with the use of POP surgical meshes which has caused a notable decrease in the use of POP meshes worldwide [111–113].

These problems present real opportunities for the application of new research from the biomaterials and tissue engineering field [114]. Recent literature highlights that researchers are exploring the capabilities of nanofiber-based scaffolds to develop meshes able to *i*) enhance tissue remodelling (promoting fibroblast ingrowth, extracellular matrix production and angiogenesis), *ii*) provide tensile support and *iii*) remain elastic to allow natural movement of vaginal tissue [68,114–116].

Among the several methods currently investigated to prepare polymer-based nanofiber systems, electrospinning is the process most widely applied, being simple, cost-effective and

versatile [117]. The possibility to tailor material chemistry, surface functionality and biomechanical properties, together with the opportunity to load active agents, make electrospun scaffolds an appealing tissue engineering-based approach [118–120]. Briefly, with this method, a syringe pump drives a polymeric solvent-based solution through an electrified orifice with an applied voltage (between 5 and 30 kV). By stretching the solubilized polymer, the electrostatic force induces firstly the formation of a polymeric jet, and ultimately (after the evaporation of the solvent) the deposition of nano- and micro-sized fibers onto a collection system. The choice of the most appropriate collection system (i.e. plate, disc, drum collector) depends on the desired design of the fibers (random, aligned and hybrid) and their final application [118,121].

The underlying rationale of using nanofiber scaffolds is based on the biomimetic principle that electrospun fibers can emulate the sophisticated architecture of the native extracellular matrix. Moreover, fiber-based matrix in comparison to commercial surgical meshes have higher porosity, with pore size in a wider range, and fiber diameters down to the nanoscale [119]. These characteristics provide environmental and physical cues to cell attachment, growth, and proliferation making them a suitable POP strategy [122–124].

Furthermore, more than currently used knitted meshes, electrospun scaffolds allow the possibility to combine polymeric materials of either natural and synthetic origin within the same implant. This positively contributes to the development of meshes able to induce a constructive remodelling process, by achieving a wider range of degradation profiles as well as mechanical properties, and thus matching better the host tissue needs and regenerative potential [125]. Additionally, the pliability and adjustable stiffness of electrospun meshes help in preventing the formation of fibrous and scar-type tissue that, beyond bearing a high risk of

contraction, represents one of the greatest challenges of conventional knitted POP implants [126].

9.2. Electrospun nanomaterials-based meshes

Currently, the most commonly investigated electrospun synthetic and natural polymers for pelvic floor tissue are polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), polyurethane (PU), gelatin and fibrinogen, used alone or as a combination [68,116]. Table 6 provides a summary of recently published works regarding nanofiber-based meshes intended for pelvic organ prolapse.

Roman et al. evaluated the *in vivo* host response of two newly developed electrospun meshes, PLA and PU, in comparison to commercial PP and PVDF surgical meshes. After 90 days of implantation into an animal model, the PLA and PU meshes showed a superior integration than commercially available meshes, with no sign of inflammation (see Figure 4). Particularly, the PLA mesh exhibited better biomechanical properties, with higher degree of cell infiltration and neovascularization, in comparison to PU meshes [115]. Furthermore, for the first time, the short term efficacy of a co-electrospun PLCL/Fibrinogen in comparison to a PP mesh was evaluated in human pelvic floor. It was found that the use of either PLCL/Fibrinogen or PP mesh improved patient's POP symptoms. However, the electrospun mesh had no occurrence of erosion, foreign body sensation or dyspareunia and demonstrated improved patient outcomes in terms of anterior vaginal prolapse when compared to commercial PP mesh [127]. Furthermore, besides their lightweight characteristics, electrospun meshes can provide a better interaction with the host cells and limit the shear stresses at the interface implant/tissue *in vivo* [47]. The potential of both synthetic and semi-synthetic nanofiber systems to prevent stress-shielding and shear stress at the implant/tissue interface has been

recently explored. Specifically, three different material compositions were tested: nylon, PCL/Gelatin and PLGA/PCL. All the electrospun meshes exhibited mechanical properties close to the soft pelvic tissues, **and were less stiff** than commercially available transvaginal synthetic meshes. Also, following *in vitro* tests using fibroblasts derived from both healthy patients and women with pelvic prolapse, all the materials revealed a positive response in terms of cell adhesion, proliferation and matrix production, showing promise for a new generation of implants for pelvic floor repair [128].

In addition to the possibility of **using an** electrospinning process to manufacture 3D scaffolds with tailorable fiber design (in terms of both diameter and distribution) as well as mechanical properties, other studies have considered the opportunity to use electrospun meshes **as a vehicle** to deliver bioactive factors [129,130]. Over the years, a number of drugs including antibiotics, anticancer drugs, as well as vitamins and proteins have been investigated as loading agents for the development of smart electrospun tissue engineering meshes, **particularly for skin wound healing and bone tissue engineering applications** [131–136].

Within the pelvic floor regeneration field, this possibility has been only partially explored and the number of research studies published is still limited. In 2016, the use of PLA meshes as a substrate for the incorporation and subsequent release of two derivatives (L-ascorbic acid and ascorbate-2-phosphate) of ascorbic acid has been explored. Ascorbic acid is known for being a potent stimulant of collagen synthesis [137,138]. In their study, **Mangir et al. [139]** found out that scaffolds containing both the derivatives showed a more hydrophilic behaviour and better mechanical properties in comparison to bare PLA scaffolds, which were used as control. Moreover, after *in vitro* tests, they concluded that fibroblast grown on the scaffolds treated with both ascorbic acid derivatives produced more collagen **with respect** to the control PLA scaffolds. Lately, the effect of 17-β-estradiol releasing electrospun PU scaffolds

has also been investigated [140]. Estradiol is the most abundant form of circulating estrogens during the premenopausal years and considered the main female hormone, which is responsible for modulating endothelial cell migration, fibroblast proliferation, ECM production and neoangiogenesis [141,142]. Similarly to PLA/Ascorbic acid scaffolds, the presence of the releasing agent improves the mechanical properties of the implant, in terms of both strength and elasticity. In addition, the newly developed meshes showed superior biocompatibility (compared to PU scaffolds with no 17- β -estradiol), which enhanced the proangiogenic potential of human adipose mesenchymal stem cells and improved tissue integration [140]. Moreover, the incorporation of different growth factors has been investigated in recent studies. Glindtvad et al. explored the effect of bFGF within a PCL/PEO mesh. Implants with and without growth factor were tested *in vivo* up to 24 weeks, using a rat abdominal wall model. Although both the mesh types performed well *in vivo*, the addition of bFGF did not represent an advantage both in the short and in the long term for the regeneration of new tissue [124]. Very recently, in an effort to improve the outcomes of the previous study, the same research group redesigned the PCL-based implant by incorporating GTGF and rat MSCs [143]. The new developed mesh showed better biomechanical and biochemical properties in comparison to the previous one. Hence, the possibility of combining tissue engineering and stem cells could be a new promising approach for the repair of POP. Following on the most recent findings, electropun-based implants represent a very promising solution to the still open challenges in POP repair procedures. However, there are some aspects that require further consideration and understanding. Particularly, biomechanical studies on explanted electrospun matrices are still limited; hence, more evidences about the changes in biomechanical properties of electrospun biomaterials after *in vivo* implantation and in the long term are required. Moreover, as mentioned above, the

anatomical structure of pelvic floor is more complex and heterogeneous in comparison to human abdominal wall. Therefore, it is essential that the new proposed solutions will be tested in the clinically relevant position rather than another anatomical site, as very recent studies performed [115,127,143]. This in order to avoid the adverse events often associated with new released implants. Ultimately, as suggested by Vashaghian et al., clinical application should start with small patient studies with detailed follow-up to evaluate mesh safety and efficacy [126].

10. Conclusion

While the benefits of mesh implants can be life changing, so can the consequences of the adverse events linked with these interventions, which often aggravate the very condition they were intended to address (e.g. incontinence) or create new complications such as long-term pain. While any surgical procedure brings associated risks, the incidence of these in mesh implants is unacceptably high, which has led to regulatory action, product recall and widespread negative media coverage across the globe. In short, it is evident that current mesh technology is not fit for purpose.

However, use of mesh implants for pelvic floor support is still widely practised, and with a paucity of alternative options it is crucial that research is translated to improve mesh technology. It is evident that the typical failure modes seen with current mesh (erosion, infection and retraction) stem from implants which neglect the complexities of pelvic floor physiology, biomechanics and biochemistry. Ideally, meshes should replicate the physical compliance of the pelvic floor and surrounding organs while supporting the dynamic loading and movement associated with normal function. This is highly challenging, particularly

considering that the physical properties of current clinically available mesh structures typically alter over time as result of tissue integration.

Here we have reviewed how aspects of material, structure, porosity, biomechanics and surface treatment are intrinsic to mesh function and highly interrelated. For example, research addressing the challenge of providing compliant meshes which mimic soft tissue biomechanics must consider material and structure while ensuring that porosity and biocompatibility is not adversely affected during loading or tissue integration. Research into surface treatments shows real opportunities to improve mesh acceptance by promoting integration while minimising foreign body response and infection. However, **the surface treatment effect** is transient and it remains crucial that long-term mesh performance is appropriate and not overlooked.

Although there is unlikely to be a single ‘silver bullet’ solution to achieving a next-generation mesh for POP, research has highlighted that nanofiber meshes represents an exciting opportunity. The nano-scale nature of these materials affords improved biocompatibility and tissue integration while permitting the design of mechanically compliant structures which retain their properties after tissue integration. Furthermore, the structures high surface area provides the ability for long-term drug delivery through surface coatings. These features represent the prospect of achieving a step-change in mesh performance, notably the minimisation of failure modes associated with current technology. **However, challenges remain in the adoption of this research into commercially available products.** Much of the emerging mesh technology is at an early stage of development and has yet to be tested in humans. The ‘pathway to translation’ for this research will require extensive clinical studies and work to obtain regulatory approval [144].

For new POP meshes this process will be more demanding given the recent reclassification of meshes by the FDA and public controversies concerning adverse events. This will require continued interdisciplinary research, combined with close industry engagement, to exploit the extant knowledge in this rapidly developing field. However, it is clear that addressing these challenges is crucial and offers the promise to bring life-changing advances in the quality of life to an underserved population.

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References

1. Haylen BT, Maher CF, Barber MD et al. An International Urogynecological Association (IUGA) / International Continence Society (ICS) Joint Report on the Terminology for Female Pelvic Organ Prolapse (POP). *Neurourology and Urodynamics* 2016; **35**: 137–68.
2. Giannini A, Russo E, Cano A et al. Current management of pelvic organ prolapse in aging women: EMAS clinical guide. *Maturitas* 2018; **110**: 118–23.
3. Olsen A, Smith V, Bergstrom J, Colling J, Clark A. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. *Obstetrics & Gynecology* 1997; **89**: 501–6.
4. Wu JM, Vaughan CP, Goode PS et al. Prevalence and trends of symptomatic pelvic floor disorders in U.S. women. *Obstetrics and Gynecology* 2014; **123**: 141–8.
5. Voulimeneas I, Antonopoulos C, Alifierakis E, Ioannides P. Perineal rectosigmoidectomy for gangrenous rectal prolapse. *World Journal of Gastroenterology* 2010; **16**: 2689.
6. Fritsch H, Lienemann A, Brenner E, Ludwikowski B. Clinical anatomy of the pelvic floor. *Adv Anat Embryol Cell Biol* 2004; **175**: 1–64.
7. Bidmead, Cardozo. Pelvic floor changes in the older woman. *British Journal of Urology* 1998; **82**: 18–25.
8. Raizada V, Mittal RK. Pelvic floor anatomy and applied physiology. *Gastroenterology clinics of North America* 2008; **37**: 493–vii.
9. DeLancey J. Anatomic aspects of vaginal eversion after hysterectomy. *American Journal of Obstetrics and Gynecology* 1992; **266**: 1717–28.
10. Herschorn S. Female Pelvic Floor Anatomy: The Pelvic Floor, Supporting Structures, and Pelvic Organs. *Reviews in Urology* 2004; **6**: S2–10.
11. Cardozo L. The use of synthetic mesh in female pelvic reconstructive surgery. *BJU International* 2006; **98**: 77–77.
12. Kim CM, Jeon MJ, Chung DJ, Kim SK, Kim JW, Bai SW. Risk factors for pelvic organ prolapse. *International Journal of Gynecology & Obstetrics* 2007; **98**: 248–51.
13. Persu C, Chapple C, Cauni V, Gutue S, Geavlete P. Pelvic Organ Prolapse Quantification System (POP-Q) – a new era in pelvic prolapse staging. *Journal of Medicine and Life* 2011; **4**: 75–81.
14. Ohmann E, Brucker B. Management of Pelvic Organ Prolapse in the Elderly. *Current Geriatrics Reports* 2015; **4**: 16–23.
15. Hagen S, Stark D. Conservative prevention and management of pelvic organ prolapse in women. In: Hagen S, ed. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd, 2011.
16. Hagen S, Stark D, Glazener C et al. Individualised pelvic floor muscle training in women with pelvic organ prolapse (POPPY): a multicentre randomised controlled trial. *Lancet*, 2014; doi 10.1016/S0140-6736(13)61977-7.
17. SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks). The safety of surgical meshes used in urogynecological surgery. 2015.
18. Kudish BI, Iglesia CB, Sokol RJ et al. Effect of weight change on natural history of pelvic

- organ prolapse. *Obstetrics and gynecology* 2009; **113**: 81–8.
19. Myers DL, Sung VW, Richter HE, Creasman J, Subak LL. Prolapse symptoms in overweight and obese women before and after weight loss. *Female pelvic medicine & reconstructive surgery* 2012; **18**: 55–9.
20. Krause M, Wheeler T, Snyder T, Richter H. Local Effects of Vaginally Administered Estrogen Therapy: A Review. *Journal of Pelvic Medicine & Surgery* 2009; **15**: 105–14.
21. El Naqa A, Guerrero K, Abdel Fattah M. Post-Hysterectomy Vaginal Vault Prolapse. *RCOG/BSUG Green-top Guideline* 2015; **46**.
22. Jefferis H, Jackson SR, Price N. Management of uterine prolapse: is hysterectomy necessary? *The Obstetrician & Gynaecologist* 2016; **18**: 17–23.
23. Barber MD. Mesh use in surgery for pelvic organ prolapse. *BMJ* 2015; **350**: h2910.
24. Ulmsten U, Henriksson L, Johnson P, Varhos G. An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct* 1996; **7**: 81-5-6.
25. Cervigni M, Natale F. A comprehensive view on the actual trend in pelvic organ prolapse repair. *Abdom Imaging* 2013; **38**: 884–93.
26. Burger JW, Luijendijk RW, Hop WC, Halm JA, Verdaasdonk EG, Jeekel J. Long-term follow-up of a randomized controlled trial of suture versus mesh repair of incisional hernia. *Ann Surg* 2004; **240**: 578-83-5.
27. Cassar K, Munro A. Surgical treatment of incisional hernia. *Br J Surg* 2002; **89**: 534–45.
28. Arora S, Kapoor R, Yadav P, Mittal V, Sureka SK, Kapoor D. Trans-vaginal anterior vaginal wall prolapse repair using a customized tension-free bell-shaped prolene mesh: A single-center experience with long-term functional analysis. *Indian journal of urology: IJU: journal of the Urological Society of India* 2015; **31**: 339–43.
29. Unger CA. An Update on the Use of Mesh in Pelvic Reconstructive Surgery. *Current Obstetrics and Gynecology Reports* 2016; **5**: 131–8.
30. PROLAPSE PO. Surgical mesh for treatment of women with pelvic organ prolapse and stress urinary incontinence. 2011.
31. Jeon MJ, Bai SW. Use of Grafts in Pelvic Reconstructive Surgery. *Yonsei Medical Journal* 2007; **48**: 147–56.
32. Funk MJ, Edenfield AL, Pate V, Visco AG, Weidner AC, Wu JM. Trends in use of surgical mesh for pelvic organ prolapse. *American journal of obstetrics and gynecology* 2013; **208**: 79.e1-79.e7.
33. van Iersel JJ, Paulides TJ, Verheijen PM, Lumley JW, Broeders IA, Consten EC. Current status of laparoscopic and robotic ventral mesh rectopexy for external and internal rectal prolapse. *World J Gastroenterol* 2016; **22**: 4977–87.
34. Keys T, Campeau L, Badlani G. Synthetic mesh in the surgical repair of pelvic organ prolapse: current status and future directions. *Urology* 2012; **80**: 237–43.
35. Falagas M, Velakoulis S, Iavazzo C, Athanasiou S. Mesh-related infections after pelvic organ prolapse repair surgery. *Eur J Obstet Gynecol Reprod Biol* 2007; **134**: 147–56.

36. Wu M-P. The Use of Prostheses in Pelvic Reconstructive Surgery: Joy or Toy? *Taiwanese Journal of Obstetrics and Gynecology* 2008; **47**: 151–6.
37. Brown RA, Ellis CN. The Role of Synthetic and Biologic Materials in the Treatment of Pelvic Organ Prolapse. *Clinics in Colon and Rectal Surgery* 2014; **27**: 182–90.
38. Todros S, Pavan PG, Natali AN. Biomechanical properties of synthetic surgical meshes for pelvic prolapse repair. *J Mech Behav Biomed Mater* 2015; **55**: 271–85.
39. Gigliobianco G, Regueros SR, Osman NI et al. Biomaterials for pelvic floor reconstructive surgery: how can we do better? *Biomed Res Int* 2015; **2015**: 968087.
40. Winters JC, Fitzgerald MP, Barber MD. The use of synthetic mesh in female pelvic reconstructive surgery. *BJU International* 2006; **98**: 70–6.
41. Sangster P, Morley R. Biomaterials in urinary incontinence and treatment of their complications. *Indian Journal of Urology : IJU : Journal of the Urological Society of India* 2010; **26**: 221–9.
42. Herschorn S. Female Pelvic Floor Anatomy: The Pelvic Floor, Supporting Structures, and Pelvic Organs. *Reviews in Urology* 2004; **6**: S2–10.
43. Machin SE, Mukhopadhyay S. Pelvic organ prolapse: review of the aetiology, presentation, diagnosis and management. *Menopause Int* 2011; **17**: 132–6.
44. Mangera A, Bullock AJ, Chapple CR, MacNeil S. Are biomechanical properties predictive of the success of prostheses used in stress urinary incontinence and pelvic organ prolapse? A systematic review. *Neurourology and Urodynamics* 2012; **31**: 13–21.
45. Simon DD, Andrews SM, Robinson-Zeigler R, Valdes T, Woods TO. Surface orientation effects on bending properties of surgical mesh are independent of tensile properties. *Journal of Biomedical Materials Research Part B: Applied Biomaterials* 2018; **106**: 854–62.
46. Roman S, Mangir N, Bissoli J, Chapple CR, MacNeil S. Biodegradable scaffolds designed to mimic fascia-like properties for the treatment of pelvic organ prolapse and stress urinary incontinence. *Journal of Biomaterials Applications* 2016; **30**: 1578–88.
47. Mangera A, Bullock AJ, Roman S, Chapple CR, MacNeil S. Comparison of candidate scaffolds for tissue engineering for stress urinary incontinence and pelvic organ prolapse repair. *BJU International* 2012; **112**: 674–85.
48. Gomelsky A, Dmochowski RR. Biocompatibility Assessment of Synthetic Sling Materials for Female Stress Urinary Incontinence. *The Journal of Urology* 2007; **178**: 1171–81.
49. Matthews BD, Pratt BL, Pollinger HS et al. Assessment of adhesion formation to intra-abdominal polypropylene mesh and polytetrafluoroethylene mesh. *Journal of Surgical Research* 2003; **114**: 126–32.
50. Woodruff AJ, Cole EE, Dmochowski RR, Scarpero HM, Beckman EN, Winters JC. Histologic Comparison of Pubovaginal Sling Graft Materials: A Comparative Study. *Urology* 2008; **72**: 85–9.
51. Konstantinovic ML, Lagae P, Zheng F, Verbeken EK, De Ridder D, Deprest JA. Comparison of host response to polypropylene and non-cross-linked porcine small intestine serosal-derived collagen implants in a rat model. *BJOG: An International Journal of Obstetrics and Gynaecology* 2005; **112**: 1554–60.

52. Pascual G, Rodríguez M, Sotomayor S, Pérez-Köhler B, Bellón JM. Inflammatory reaction and neotissue maturation in the early host tissue incorporation of polypropylene prostheses. *Hernia* 2012; **16**: 697–707.
53. Feola A, Barone W, Moalli P, Abramowitch S. Characterizing the ex vivo textile and structural properties of synthetic prolapse mesh products. *International Urogynecology Journal* 2013; **24**: 559–64.
54. Nichols DH. The Mersilene mesh gauze-hammock for severe urinary stress incontinence. *Obstet Gynecol* 1973; **41**: 88–93.
55. Klinge U, Klosterhalfen B, Muller M, Schumpelick V. Foreign body reaction to meshes used for the repair of abdominal wall hernias. *Eur J Surg* 1999; **165**: 665–73.
56. Klosterhalfen B, Junge K, Klinge U. The lightweight and large porous mesh concept for hernia repair. *Expert Rev Med Devices* 2005; **2**: 103–17.
57. Lee JK, Agnew G, Dwyer PL. Mesh-related chronic infections in silicone-coated polyester suburethral slings. *Int Urogynecol J* 2011; **22**: 29–35.
58. Govier FE, Kobashi KC, Kuznetsov DD et al. Complications of transvaginal silicone-coated polyester synthetic mesh sling. *Urology* 2005; **66**: 741–5.
59. Dällenbach P, De Oliveira SS, Marras S, Boulvain M. Incidence and risk factors for mesh erosion after laparoscopic repair of pelvic organ prolapse by lateral suspension with mesh. *International Urogynecology Journal* 2016; **27**: 1347–55.
60. DeBord JR. The historical development of prosthetics in hernia surgery. *Surg Clin North Am* 1998; **78**: 973–1006, vi.
61. Read RC. Milestones in the history of hernia surgery: prosthetic repair. *Hernia* 2004; **8**: 8–14.
62. Debodinance P, De Bievre P, Parmentier D, Dubrulle R, Querleu D, Crepin G. [The “hazards” of using a Gore-Tex sling in the treatment of stress urinary incontinence]. *J Gynecol Obstet Biol Reprod (Paris)* 1994; **23**: 665–70.
63. Young RM, Gustafson R, Dinsmore RC. Sepramesh vs. Dualmesh for abdominal wall hernia repairs in a rabbit model. *Current Surgery* 61: 77–9.
64. Kalaba S, Gerhard E, Winder JS, Pauli EM, Haluck RS, Yang J. Design strategies and applications of biomaterials and devices for Hernia repair. *Bioactive Materials* 2016; **1**: 2–17.
65. Rogowski A, Bienkowski P, Tosiak A, Jerzak M, Mierzejewski P, Baranowski W. Mesh retraction correlates with vaginal pain and overactive bladder symptoms after anterior vaginal mesh repair. *International Urogynecology Journal* 2013; **24**: 2087–92.
66. Devaseelan P, Fogarty P. The role of synthetic mesh in the treatment of pelvic organ prolapse. *The Obstetrician & Gynaecologist* 11: 169–76.
67. Baylón K, Rodríguez-Camarillo P, Elías-Zúñiga A, Díaz-Elizondo AJ, Gilkerson R, Lozano K. Past, Present and Future of Surgical Meshes: A Review. *Membranes*, 2017.
68. Dias FGF, Dias PHGF, Prudente A, Riccetto C. New strategies to improve results of mesh surgeries for vaginal prolapses repair – an update. *International Brazilian Journal of Urology : official journal of the Brazilian Society of Urology* 2015; **41**: 623–34.

69. Cosson M, Debodinance P, Boukerrou M et al. Mechanical properties of synthetic implants used in the repair of prolapse and urinary incontinence in women: which is the ideal material? *International Urogynecology Journal* 2003; **14**: 169–78.
70. De Maria C, Santoro V, Vozzi G. Biomechanical, Topological and Chemical Features That Influence the Implant Success of an Urogynecological Mesh: A Review. *BioMed Research International* 2016; **2016**: e1267521.
71. Rubod C, Brieu M, Cosson M et al. Biomechanical Properties of Human Pelvic Organs. *Urology* 2012; **79**: 968.e17-968.e22.
72. Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. *Hernia* 1997; **1**: 15–21.
73. Otto J, Kaldenhoff E, Kirschner-Hermanns R, Mühl T, Klinge U. Elongation of textile pelvic floor implants under load is related to complete loss of effective porosity, thereby favoring incorporation in scar plates. *Journal of Biomedical Materials Research Part A* 2013; **102**: 1079–84.
74. Alexander JW, Kaplan JZ, Altemeier WA. Role of suture materials in the development of wound infection. *Annals of surgery* 1967; **165**: 192–9.
75. Brun JL, Bordenave L, Lefebvre F et al. Physical and biological characteristics of the main biomaterials used in pelvic surgery. *Bio-medical materials and engineering* 1992; **2**: 203–25.
76. Weyhe D, Cobb W, Lecuire J et al. Large pore size and controlled mesh elongation are relevant predictors for mesh integration quality and low shrinkage – Systematic analysis of key parameters of meshes in a novel minipig hernia model. *International Journal of Surgery* 2015; **22**: 46–53.
77. Abramowitch SD, Feola A, Jallah Z, Moalli PA. Tissue mechanics, animal models, and pelvic organ prolapse: A review. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2009; **144, Suppl**: S146–58.
78. Maurer M, Röhrnbauer B, Feola A, Deprest J, Mazza E. Prosthetic Meshes for Repair of Hernia and Pelvic Organ Prolapse: Comparison of Biomechanical Properties. *Materials* 2015; **8**: 2794–808.
79. Mazza E, Ehret AE. Mechanical biocompatibility of highly deformable biomedical materials. *Journal of the Mechanical Behavior of Biomedical Materials* 2015; **48**: 100–24.
80. Lei L, Song Y, Chen R. Biomechanical properties of prolapsed vaginal tissue in pre- and postmenopausal women. *International Urogynecology Journal* 2007; **18**: 603–7.
81. Chen Z-W, Joli P, Feng Z-Q, Rahim M, Pirró N, Bellemare M-E. Female patient-specific finite element modeling of pelvic organ prolapse (POP). *Journal of Biomechanics* 2015; **48**: 238–45.
82. Bhattacharai A, Jabbari M, Anding R, Staat M. Surgical treatment of vaginal vault prolapse using different prosthetic mesh implants: a finite element analysis. *tm - Technisches Messen* 2018; **85**: 331–342.
83. Li X, Kruger JA, Jor JWY et al. Characterizing the ex vivo mechanical properties of synthetic polypropylene surgical mesh. *Journal of the Mechanical Behavior of Biomedical Materials* 2014; **37**: 48–55.
84. Ulrich D, Edwards SL, Alexander DLJ et al. Changes in pelvic organ prolapse mesh

mechanical properties following implantation in rats. *American Journal of Obstetrics and Gynecology* 2016; **214**: 260.e1-260.e8.

85. Barone WR, Moalli PA, Abramowitch SD. Textile properties of synthetic prolapse mesh in response to uniaxial loading. *American Journal of Obstetrics and Gynecology* 2016; **215**: 326.e1-326.e9.
86. Sternschuss G, Ostergard D, Patel H. Post-implantation alterations of polypropylene in the human. *The Journal of Urology* 2012; **188**: 27–32.
87. Meimandi-Parizi A, Oryan A, Moshiri A, Silver IA. Novel application of a tissue-engineered collagen-based three-dimensional bio-implant in a large tendon defect model: A broad-based study with high value in translational medicine. *Tissue and Cell* 2013; **45**: 282–94.
88. Dlaska CE, Andersson G, Brittberg M, Suedkamp NP, Raschke MJ, Schuetz MA. Clinical Translation in Tissue Engineering—The Surgeon’s View. *Current Molecular Biology Reports* 2015; **1**: 61–70.
89. Cervigni M, Natale F, La Penna C, Saltari M, Padoa A, Agostini M. Collagen-coated polypropylene mesh in vaginal prolapse surgery: an observational study. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2011; **156**: 223–7.
90. Lo T-S, Tan YL, Khanuengkitkong S, Dass AK, Cortes EFM, Wu P-Y. Assessment of Collagen-Coated Anterior Mesh Through Morphology and Clinical Outcomes in Pelvic Reconstructive Surgery for Pelvic Organ Prolapse. *Journal of Minimally Invasive Gynecology* 2014; **21**: 753–61.
91. Faulk DM, Londono R, Wolf MT et al. ECM hydrogel coating mitigates the chronic inflammatory response to polypropylene mesh. *Biomaterials* 2014; **35**: 8585–95.
92. Barski D, Gerullis H, Georgas E et al. Coating of Mesh Grafts for Prolapse and Urinary Incontinence Repair with Autologous Plasma: Exploration Stage of a Surgical Innovation. *BioMed Research International* 2014.
93. Holger G, Cristoph E, Albert R et al. Improved biocompatibility of meshes used for hernia, incontinence and organ prolapse repair by plasma coating - results of in vitro and in vivo studies. *Journal of Urology* 2011; **185**: e317–e317.
94. Bagner J, Gerullis H, Karig R, Ramon A, Otto T. In vitro test system for the evaluation of the biocompatibility of alloplastic materials and its improvement by autologous coating. *Urology* 2010; **76**.
95. Consten E, Van Lersel J, Verheijen P, Broeders I, Wolthuis A, D’Hoore A. Long-term Outcome After Laparoscopic Ventral Mesh Rectopexy. *Annals of Surgery* 2015; **262**: 742–8.
96. US-Food-and-Drug-Administration. *FDA Strengthens Requirements for Surgical Mesh for the Transvaginal Repair of Pelvic Organ Prolapse to Address Safety Risks.*, 2016.
97. NHS England. *Mesh Oversight Group Report.*, 2017.
98. Morling JR, McAllister DA, Agur W et al. Adverse events after first, single, mesh and non-mesh surgical procedures for stress urinary incontinence and pelvic organ prolapse in Scotland, 1997–2016: a population-based cohort study. *The Lancet* 2017; **389**: 629–40.
99. Abed H, Rahn D, Lowenstein L, Balk E, Clemons J, Rogers R. Incidence and management of graft erosion, wound granulation, and dyspareunia following vaginal prolapse repair with

- graft materials: A systematic review. *Int Urogynecol J*. 2011; **22**: 789–98.
100. Nitti VW. Complications of midurethral slings and their management. *Canadian Urological Association Journal* 2012; **6**: S120–2.
101. Kemp MM, Slim K, Rabischong B, Bourdel N, Canis M, Botchorishvili R. Transrectal Mesh Erosion Requiring Bowel Resection. *Journal of Minimally Invasive Gynecology* 2017; **24**: 717–21.
102. Shah H, Badlani G. Mesh complications in female pelvic floor reconstructive surgery and their management: A systematic review. *Indian Journal of Urology* 2012; **28**: 129–53.
103. Maher C, Feiner B, Decuyper E, Nichlos C, Hickey K, O'Rourke P. Laparoscopic sacral colpopexy versus total vaginal mesh for vaginal vault prolapse: A randomized trial. *Am J Obstet Gynecol* 2011; **204**: e1–7.
104. Tunn R, Picot A, Marschke J, Gauruder-Burmester A. Sonomorphological evaluation of polypropylene mesh implants after vaginal mesh repair in women with cystocele or rectocele. *Ultrasound in Obstetrics & Gynecology* 2007; **29**: 449–52.
105. Gauruder-Burmester A, Koutouzidou P, Rohne J, Gronewold M, Tunn R. Follow-up after polypropylene mesh repair of anterior and posterior compartments in patients with recurrent prolapse. *International Urogynecology Journal* 2007; **18**: 1059–64.
106. Velemir L, Amblard J, Fatton B, Savary D, Jacquetin B. Transvaginal mesh repair of anterior and posterior vaginal wall prolapse: a clinical and ultrasonographic study. *Ultrasound in Obstetrics & Gynecology* 2010; **35**: 474–80.
107. Gyang AN, Feranec JB, Patel RC, Lamvu GM. Managing chronic pelvic pain following reconstructive pelvic surgery with transvaginal mesh. *International Urogynecology Journal* 2014; **25**: 313–8.
108. Giannitsas K, Costantini E. How to Deal with Pain Following a Vaginal Mesh Insertion. *European Urology Focus* 2016; **2**: 268–71.
109. Abbott JA, Jarvis SK, Lyons SD, Thomson A, Vancaille TG. Botulinum toxin type A for chronic pain and pelvic floor spasm in women: a randomized controlled trial. *Obstetrics & Gynecology* 2006; **108**: 915–23.
110. Hibner M, Desai N, Robertson LJ, Nour M. Pudendal neuralgia. *Journal of Minimally Invasive Gynecology* 2010; **17**: 148–53.
111. Sedrakyan A, Chughtai B, Mao J. Regulatory Warnings and Use of Surgical Mesh in Pelvic Organ Prolapse. *JAMA Internal Medicine* 2016; **176**: 275–7.
112. Clemons JL, Weinstein M, Guess MK et al. Impact of the 2011 FDA transvaginal mesh safety update on AUGS members' use of synthetic mesh and biologic grafts in pelvic reconstructive surgery. *Female Pelvic Medicine & Reconstructive Surgery* 2013; **19**: 191–8.
113. Campbell P, Jha S, Cutner A. Vaginal mesh in prolapse surgery. *The Obstetrician & Gynaecologist* 2018; **20**: 49–56.
114. Chapple CR, Osman NI, Mangera A et al. Application of Tissue Engineering to Pelvic Organ Prolapse and Stress Urinary Incontinence. *Low Urin Tract Symptoms* 2015; **7**: 63–70.
115. Roman S, Urbánková I, Callewaert G et al. Evaluating Alternative Materials for the Treatment of Stress Urinary Incontinence and Pelvic Organ Prolapse: A Comparison of the In

- Vivo Response to Meshes Implanted in Rabbits. *The Journal of Urology* 2016; **196**: 261–9.
116. Bissoli J, Bruschini H. Scaffolds for Pelvic Floor Prolapse: Logical Pathways. *International Journal of Biomaterials* 2018; **2018**.
117. Lim CT. Nanofiber technology: current status and emerging developments. *Progress in Polymer Science* 2017; **70**: 1–17.
118. Lannutti J, Reneker D, Ma T, Tomasko D, Farson D. Electrospinning for tissue engineering scaffolds. *Materials Science and Engineering: C* 2007; **27**: 504–9.
119. Liu H, Ding X, Zhou G, Li P, Wei X, Fan Y. Electrospinning of Nanofibers for Tissue Engineering Applications. *Journal of Nanomaterials*, 2013.
120. Puppi D, Zhang X, Yang L, Chiellini F, Sun X, Chiellini E. Nano/microfibrous polymeric constructs loaded with bioactive agents and designed for tissue engineering applications: A review. *Journal of Biomedical Materials Research Part B: Applied Biomaterials* 2014; **102**: 1562–79.
121. Bhardwaj N, Kundu SC. Electrospinning: A fascinating fiber fabrication technique. *Biotechnology Advances* 2010; **28**: 325–47.
122. Wang X, Chen Y, Fan Z, Hua K. Comparing different tissue-engineered repair materials for the treatment of pelvic organ prolapse and urinary incontinence: which material is better? *International Urogynecology Journal* 2018; **29**: 131–8.
123. Watanabe K, Kim B-S, Kim I-S. Development of Polypropylene Nanofiber Production System. *Polymer Reviews* 2011; **51**: 288–308.
124. Glindtvad C, Chen M, Vinge Nygaard J et al. Electrospun biodegradable microfibers induce new collagen formation in a rat abdominal wall defect model: A possible treatment for pelvic floor repair? *Journal of Biomedical Materials Research. Part B, Applied Biomaterials* 2018; **106**: 680–8.
125. Hympánová L, Rynkevicius R, Román S et al. Assessment of Electrospun and Ultra-lightweight Polypropylene Meshes in the Sheep Model for Vaginal Surgery. *European Urology Focus* 2018; doi <https://doi.org/10.1016/j.euf.2018.07.024>.
126. Vashaghian M, Zaai SJ, Smit TH, Roovers J-P. Biomimetic implants for pelvic floor repair. *Neurourology and Urodynamics* 2018; **37**: 566–80.
127. Wu X, Wang Y, Zhu C et al. Preclinical animal study and human clinical trial data of co-electrospun poly(L-lactide-co-caprolactone) and fibrinogen mesh for anterior pelvic floor reconstruction. *International Journal of Nanomedicine* 2016; **11**: 389–97.
128. Vashaghian M, Ruiz-Zapata AM, Kerkhof MH et al. Toward a new generation of pelvic floor implants with electrospun nanofibrous matrices: A feasibility study. *Neurourology and Urodynamics* 2017; **36**: 565–73.
129. Hu X, Liu S, Zhou G, Huang Y, Xie Z, Jing X. Electrospinning of polymeric nanofibers for drug delivery applications. *Journal of Controlled Release* 2014; **185**: 12–21.
130. Sill TJ, von Recum HA. Electrospinning: Applications in drug delivery and tissue engineering. *Biomaterials* 2008; **29**: 1989–2006.
131. Huang L-Y, Branford-White C, Shen X-X, Yu D-G, Zhu L-M. Time-engineered biphasic drug release by electrospun nanofiber meshes. *International Journal of Pharmaceutics* 2012;

436: 88–96.

132. Zahedi P, Karami Z, Rezaeian I et al. Preparation and performance evaluation of tetracycline hydrochloride loaded wound dressing mats based on electrospun nanofibrous poly(lactic acid)/poly(ϵ -caprolactone) blends. *Journal of Applied Polymer Science* 2012; **124**: 4174–83.
133. Lu T, Jing X, Song X, Wang X. Doxorubicin-loaded ultrafine PEG-PLA fiber mats against hepatocarcinoma. *Journal of Applied Polymer Science* 2012; **123**: 209–17.
134. Zhang YZ, Wang X, Feng Y, Li J, Lim CT, Ramakrishna S. Coaxial electrospinning of (fluorescein isothiocyanate-conjugated bovine serum albumin)-encapsulated poly(epsilon-caprolactone) nanofibers for sustained release. *Biomacromolecules* 2006; **7**: 1049–57.
135. Sattary M, Khorasani MT, Rafienia M, Rozve HS. Incorporation of nanohydroxyapatite and vitamin D3 into electrospun PCL/Gelatin scaffolds: The influence on the physical and chemical properties and cell behavior for bone tissue engineering. *Polymers for Advanced Technologies* 2018; **29**: 451–62.
136. Li H, Wang M, Williams GR et al. Electrospun gelatin nanofibers loaded with vitamins A and E as antibacterial wound dressing materials. *RSC Advances* 2016; **6**: 50267–77.
137. Hougum KP, Brenner DA, Chojkier M. Ascorbic acid stimulation of collagen biosynthesis independent of hydroxylation. *The American Journal of Clinical Nutrition* 1991; **54**: 1141S–1143S.
138. Kishimoto Y, Saito N, Kurita K, Shimokado K, Maruyama N, Ishigami A. Ascorbic acid enhances the expression of type 1 and type 4 collagen and SVCT2 in cultured human skin fibroblasts. *Biochemical and Biophysical Research Communications* 2013; **430**: 579–84.
139. Mangir N, Bullock AJ, Roman S, Osman N, Chapple C, MacNeil S. Production of ascorbic acid releasing biomaterials for pelvic floor repair. *Acta Biomaterialia* 2016; **29**: 188–97.
140. Shafaat S, Mangir N, Regureos SR, Chapple CR, MacNeil S. Demonstration of improved tissue integration and angiogenesis with an elastic, estradiol releasing polyurethane material designed for use in pelvic floor repair. *Neurourology and Urodynamics* 2018; **37**: 716–25.
141. Thornton MJ. Estrogens and aging skin. *Dermato-endocrinology* 2013; **5**: 264–70.
142. Bello YM, Phillips TJ. Recent Advances in Wound Healing. *JAMA* 2000; **283**: 716–8.
143. Hansen SG, Taskin MB, Chen M, Wogensen L, Vinge Nygaard J, Axelsen SM. Electrospun nanofiber mesh with fibroblast growth factor and stem cells for pelvic floor repair. *Journal of Biomedical Materials Research Part B: Applied Biomaterials* 2019; **0**.
144. Culmer P, Alazmani A, Bryant M et al. Continence technologies whitepaper: Informing new engineering science research. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine* 2018; **233**: 138–53.
145. Alas A, Chandrasekaran N, Devakumar H, Martin L, Hurtado E, Davila GW. Advanced uterovaginal prolapse: is vaginal hysterectomy with McCall culdoplasty as effective as in lesser degrees of prolapse? *International Urogynecology Journal* 2018; **29**: 139–44.
146. Cruikshank SH, Kovac SR. Randomized comparison of three surgical methods used at the time of vaginal hysterectomy to prevent posterior enterocele. *American Journal of Obstetrics and Gynecology* 1999; **180**: 859–65.

147. Goh JT W. Biomechanical properties of prolapsed vaginal tissue in pre- and postmenopausal women. *International Urogynecology Journal and Pelvic Floor Dysfunction* 2002; **13**: 76–79; discussion 79.
148. Caquant F, Collinet P, Debodinance P et al. Safety of Trans Vaginal Mesh procedure: Retrospective study of 684 patients. *Journal of Obstetrics and Gynaecology Research* 2008; **34**: 449–56.
149. Benhaim Y, Tayrac R de, Deffieux X et al. Traitement du prolapsus génital avec mise en place d'une prothèse de polypropylène par voie vaginale. *Journal de Gynécologie Obstétrique et Biologie de la Reproduction* 2006; **1094**: 1 YP-306.
150. Sayasneh A, Johnson H. Risk factors for mesh erosion complicating vaginal reconstructive surgery. *Journal of Obstetrics and Gynaecology* 2010; **30**: 721–4.
151. De Vita D, Araco F, Gravante G, Sesti F, Piccione E. Vaginal reconstructive surgery for severe pelvic organ prolapses: A “uterine-sparing” technique using polypropylene prostheses. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2008; **139**: 245–51.
152. de Tayrac R, Deffieux X, Gervaise A, Chauveaud-Lambling A, Fernandez H. Long-term anatomical and functional assessment of trans-vaginal cystocele repair using a tension-free polypropylene mesh. *International Urogynecology Journal* 2006; **17**: 483–8.
153. Brown BN, Mani D, Nolfi AL, Liang R, Abramowitch SD, Moalli PA. Characterization of the host inflammatory response following implantation of prolapse mesh in rhesus macaque. *American Journal of Obstetrics and Gynecology* 2015; **213**: 668.e1-668.e10.
154. Scheidbach H, Tamme C, Tannapfel A, Lippert H, Köckerling F. In vivo studies comparing the biocompatibility of various polypropylene meshes and their handling properties during endoscopic total extraperitoneal (TEP) patchplasty: an experimental study in pigs. *Surgical Endoscopy And Other Interventional Techniques* 2004; **18**: 211–20.
155. Bako A, Dhar R. Review of synthetic mesh-related complications in pelvic floor reconstructive surgery. *International Urogynecology Journal* 2008; **20**: 103.
156. Fang Z, Fu W, Dong Z et al. Preparation and biocompatibility of electrospun poly(l-lactide-co-ε-caprolactone)/fibrinogen blended nanofibrous scaffolds. *Applied Surface Science* 2011; **257**: 4133–8.
157. Vashaghian M, Zandieh-Doulabi B, Roovers J-P, Smit TH. Electrospun Matrices for Pelvic Floor Repair: Effect of Fiber Diameter on Mechanical Properties and Cell Behavior. *Tissue Engineering Part A* 2016; **22**: 1305–16.