Chapter 4

Synthetic Materials Used in the Surgical Treatment of Pelvic Organ Prolapse: Problems of Currently Used Material and Designing the Ideal Material

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Abstract

Synthetic materials have long been used to provide structural support when surgically repairing pelvic organ prolapse (POP). The most widely used synthetic material is a mesh made of polypropylene (PPL). The use of mesh is intended to improve cure rates and prevent recurrences after POP surgery – however as more mesh materials have been implanted, it has become apparent that serious complications can occur in up to 30% of women, particularly when the mesh is implanted transvaginally. Over the years many different mesh kits have been marketed and used in the treatment of POP however polypropylene mesh was never designed or tested for use in pelvic floor. Instead it was approved for clinical use based on its biocompatibility and success in abdominal hernia repairs. It is now known that PPL meshes are neither compliant with the mechanical forces in the pelvic floor nor do they integrate well into paravaginal tissues. Better materials developed specifically for use in pelvic floor are urgently needed. The aim of this chapter is to define the requirements of an ideal mesh in terms of its material properties and to summarize the ongoing research on developing the next generation pelvic floor repair materials.

Keywords: pelvic organ prolapse, mesh, polypropylene, implant material, biomechanical properties

1. Introduction

Pelvic organ prolapse (POP) is the descent of one or more of the anterior vaginal wall, posterior vaginal wall, the uterus (cervix) or the apex of the vagina (after hysterectomy) which

correlates with patients' symptoms [1]. Prolapse of the anterior vaginal wall (or a cystocele) is the most common type of POP followed by a uterine or vault prolapse and rectal prolapse [2], although they coexist in most patients presenting with symptomatic POP.

Some degree of POP is seen in up to 30–76% of women who have their routine gynaecological examinations [3]. Most of these will be early stage/mild prolapses and cause no symptoms [4]. Although only 3–6% of these cases will have any symptoms, the lifetime risk of a women in the general population undergoing a POP surgery has been reported to be 20% (excluding hysterectomy cases) [3]. As the population ages the prevalence of POP is estimated to increase substantially by 46% between 2010 and 2050 [5].

Reconstructive surgery to improve positioning of the pelvic organs or to restore the supporting structures is often necessary in symptomatic cases and the use of a graft material is often needed to reinforce weakened tissues. The most commonly used material is a surgical mesh made of polypropylene (PPL) which has long been used successfully to treat hernias. Although mesh augmented POP repair procedures have higher anatomical success rates compared to no-mesh, the functional and quality of life outcomes are not as good [6] and severe complications with life changing consequences can occur in up to 10–30% of cases [7]. Complications associated with the use of vaginal mesh are now reported widely in the media together with many litigations against physicians and manufacturers leading to the withdrawal of several mesh products from the USA market [8]. In the UK there are now 800 compensation claims made against the NHS in relation to vaginal mesh related complications [9]. In 2008 and 2011 the Food and Drug Administration (FDA) of United States of America released two public health warnings related to mesh complications [10] which was followed by statements from Medicines and Healthcare products Regulatory Agency (MHRA) in United Kingdom [11] and the European Commission [12]. Consequently transvaginal meshes were re-classified from being class II (a moderate risk device) to class III (a high risk device) making pre-market approval necessary before new devices could be marketed [13]. As a consequence the relative number of mesh augmented transvaginal POP repair procedures decreased sharply from 27 to 2%, among all other types of POP surgeries [14]. The number of mesh sling surgeries for treatment of stress urinary incontinence has also decreased [15].

Factors affecting occurrence of mesh related complications can broadly be classified as factors related to the material itself and factors related to the application of the material [16]. Material properties involve the composition of the polymer used, total bulk of the material used and its biocompatibility, mechanical properties and ultrastructure such as pore size and knit pattern. Factors related to the application of the material are the surgical technique used, the route of implantation [transvaginal vs. transabdominal], surgeon's experience and patient related factors [obesity, smoking status, etc.].

In this chapter we will first explore the evolvement of the surgical mesh as a material used in abdominal hernia repair together with the modifications made to the surgical technique of implantation to improve patient outcomes. We then move on to define the mechanical and biological properties of the female pelvic floor to determine the design requirements of the ideal pelvic floor repair material. Finally we will look at the current approaches to develop novel materials using mainly biomaterials and tissue engineering techniques with reference to some of the work from our own group.

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2. The use of materials in pelvic surgery

In pelvic organ prolapse surgeries, prosthetic materials are either needed to reinforce the surgical repair site in anterior and posterior vaginal wall defect repairs or to suspend the prolapsed uterus or vaginal vault in sacrocolpopexy operations [17]. Surgeries performed for stress urinary incontinence use this material under the urethra as a sling.

The ideal prosthetic material is desired to provide a durable structural support without causing significant complications such as pain, compromise in vaginal capacity or sexual functions. A wide variety of synthetic and biological materials have been used over the years as prosthetics however the perfect material is still to be developed.

Biological materials are mostly in the form of biological grafts from the patient's own tissues from abdomen (rectus fascia) or thigh (fascia lata). These autologous fascia have long been used as a sling in the treatment of stress urinary incontinence [18]. The obvious limitation of using an autologous fascia is increased perioperative morbidity, donor site morbidity and lack of availability of enough material in some patients who require repeated procedures or have large areas of fascia defect. Using natural fascia from allogeneic (e.g. cadaveric) or xenogeneic (e.g. bovine dermis) sources has also been used over the years but these carry a small risk of prion and Human Immunodeficiency Virus transmission. Also the decellularization, sterilization and other processing methods are known to adversely influence the biomechanical properties of the fascia [19]. The clinical efficacy of biological implants are still controversial with some studies showing high anatomical and functional failure rates [20, 21] whereas others report results comparable to mesh repairs in less severe cases of POP [22].

A basic understanding of the material properties of the available grafts and the physiological requirements of the site of implantation is required to select the best material for a specific application.

3. Evolvement of the polypropylene mesh as a material

The concept of using a prosthetic material to reinforce a fascial defect was first developed to treat hernias. Theodore Billroth (1829–1894) stated that "If we could artificially produce tissues of the density and toughness of fascia and tendon the secret of the radical cure of hernia would be discovered" Czerny [23]. The first mesh material was made of metal. In 1902 silver filigrees were used to treat difficult to treat hernias [24]. The silver wires and other metals (tantalum and stainless steel) were used until recently [25] with reasonable success rates to treat large hernia defects however they were eventually abandoned due to their association with excessive abdominal stiffness, sinus tract formation, metal failure (corrosion and fragmentation) and patient discomfort.

Following the plastics revolution in 20th century and the advancements in polymer science many diagnostic and therapeutic medical and surgical instruments made of plastic became available. Plastics had obvious advantages over metals in soft tissue reconstruction with their ductility, lightweight and handleability [26]. Among the plastics used, polypropylene (PPL)

possessed favorable physical properties such as high tensile strength with easy handleability. It could be made into a monofilament, have a high softening temperature (260°F), non wettable and resistant to chemicals. Usher first manufactured and experimentally tested first plastic mesh made of polypropylene [27]. The initial experimental data in dogs with knitted PPL confirmed that it allowed tissue ingrowth in between its fibers, it was strong with excellent tensile properties and it was resistant to infections when compared to other plastics.

The use of synthetic mesh has revolutionized hernia repair surgeries reducing the recurrence rates by 2–3 fold compared to traditional suture repairs [28]. However looking retrospectively it appears that PPL was far from being complication-free when first introduced into abdominal hernia repairs. Over the years, both the surgical implantation site and the material properties of the PPL have been modified to reduce the complication rates of mesh augmented abdominal hernia repair surgeries. A brief revision of the improvements made to the surgical technique and material characteristics over many years can provide a better understanding of the current clinical problem related to vaginal mesh products.

The initial plastic mesh was prepared from a monofilament 8 mils in diameter (200 μm), 42 × 40 per inch thread count by a simple taffeta weave. This mesh was then autoclaved and cut into desired patterns before implantation [33]. On the other hand, the modern surgical mesh constructed from a knitted polypropylene has smaller pores with an area density of 90–95 g/m^2. These heavy-weight, first generation meshes are now known to cause a vigorous foreign body reaction and resulting dense scar tissue leading to a loss of the compliance of the abdominal wall [34].

Over the next few years heavy weight meshes were replaced by medium to light weight meshes that reduced the bulk of the foreign material leading to less inflammation, foreign body reaction, fibrosis and the associated pain sensation [34]. Also the pore sizes were made larger (macroporous). A study demonstrated that the bulk density of PPL (Prolene®) mesh could be reduced down to 25% of its original weight without significantly compromising its efficacy with reduced major and minor complications [35]. Also clinical studies comparing

1902 [24]	First prosthetic mesh (silver filigrees) to be routinely used to treat difficult to treat hernias.
1940 [29]	Tantalum gauze fabric introduced
1948 [30]	Formation of a darn using a Nylon suture for inguinal hernia repair.
1963	Francis Usher (1908–1980) introduced first woven, plastic mesh made of polypropylene for hernia repair.
1995 [31]	Ulmsten and Petros described the Integral theory of stress urinary continence and performed the first intravaginal mesh-sling surgery
1996*	PPL (Marlex®) received FDA clearance for SUI.
1998*	First lightweight PPL mesh introduced.
2002*	First mesh product for POP (Gyneacare®).
2004*	First 'mesh kit' (Apogee®, Perigee®) cleared by FDA for POP.

*Reviewed in Dällenbach [32].

Table 1. Milestones in the development of surgical mesh materials and their use in pelvic floor disorders.

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heavy and light-weight mesh materials implanted for inguinal hernia repairs demonstrated less pain and less sensation of a foreign material with lighter meshes [36]. Thus the polypropylene mesh evolved over the years from a heavy weight, small pore sized mesh to a light-weight, and large pore sized mesh material.

Efforts to make further improvements to the current surgical mesh are still ongoing. One strategy to modify the geometry/knitting pattern of PPL to make it mechanically more compliant with the pelvic floor [37]. Another strategy is enhancing the biocompatibility of PPL by coating it with more biocompatible materials to obtain a more favorable tissue response. An extracellular matrix coated PPL when implanted in rats demonstrated an inflammatory response that is more reflective of a tissue remodeling type rather than a fibrotic one [38]. There has also been research on degradable and hybrid degradable/nondegradable mesh materials. The main idea behind a degradable mesh was that it would be absorbed after a period of time by which time the patients' own tissues would have recovered and this would avoid the long term complications of permanent mesh like infection and fistula formation. Nevertheless polypropylene is still the most widely used polymer in mesh products used clinically at the time of writing.

4. Modifications to the surgical technique to improve outcomes of mesh-augmented hernia repairs

In parallel to improvements made to the material, modifications to the surgical technique were also made to reduce side effects and recurrences. Advances in both inguinal and abdominal hernia repair techniques can be observed mainly led by Usher and Rives [39]. Usher has also made contributions to developing the technique of hernia repair, mainly he introduced the concept of buttressing a sutured repair instead of bridging the gap with a mesh. On other words the mesh would not only just fit in the hole but be 2–3 cm larger to underlap with the underlying tissues.

We will only review the improvements made to the surgical approach to incisional hernia repair in the abdominal wall, where we feel it is relevant to the pelvic floor repair. The abdominal hernia repair technique evolved from an 'inlay technique' where the mesh is placed in-between the edges of the fascia defect to an 'onlay technique' where the mesh was placed on top of the repaired fascia defect in a tension-free manner. To further reduce the complications of mesh augmented repairs, a 'sublay (retrorectus) technique' was introduced where the mesh was placed underneath a well vascularized, thick muscle tissue (the rectus abdominis muscle) in-between two fascial layers (**Figure 1**). Proximity to a well vascularized wound bed is arguably a key factor in the success of this technique [40]. Additionally in the sublay technique, as opposed to inlay and onlay, mesh had less contact with subcutaneous tissues that prevented transmission of the infection from subcutaneous tissues to the mesh as it lies quite deep in the abdominal wall [41]. Abdominal hernias are heterogeneous with regards to why they occur and how extensive they are. No single technique is suitable or feasible for all types of hernias and different methods of repair may be indicated for specific defects and locations. Nevertheless the sublay technique appears to be superior to other techniques particularly in difficult to treat wound beds (for example poorly vascularized or repeatedly operated wounds) [42, 43].

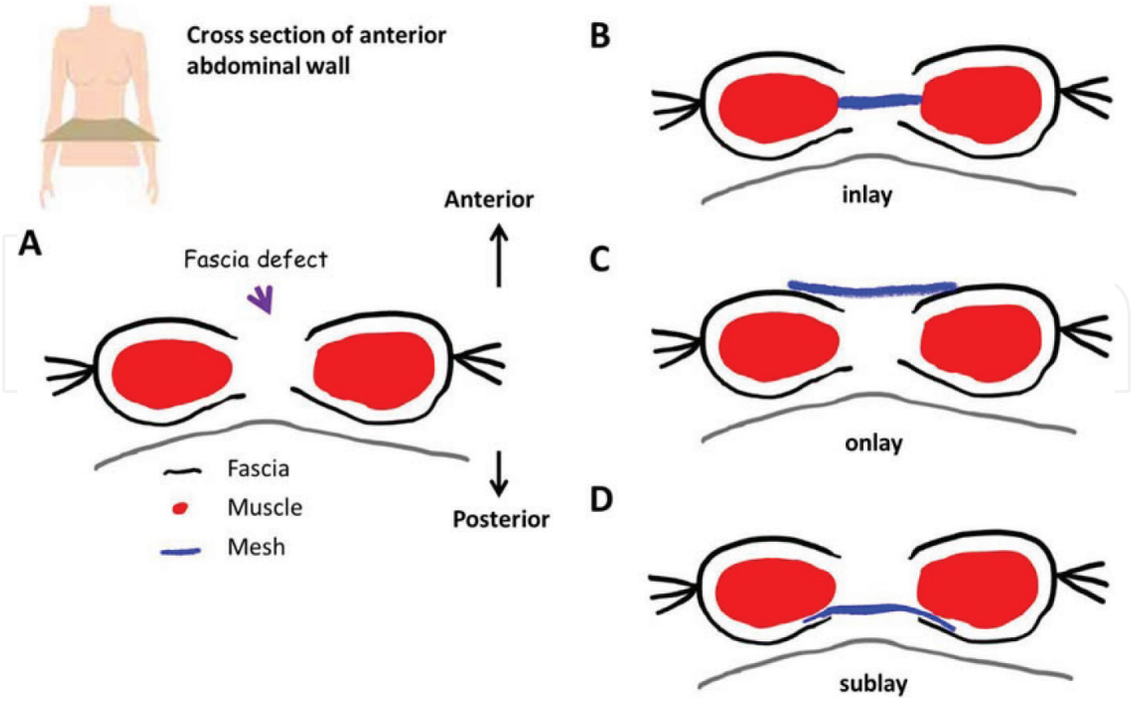

Figure 1. Graphical demonstration of surgical implantation sites of mesh material in relation to muscle and fascia in abdominal hernia repairs. (A) A cross section of anterior abdominal wall with a fascia defect causing hernia can be seen with muscle (red), fascia (black) and mesh (blue) labeled in different colors. (B) Inlay mesh implantation to fit in the gap created by the fascia and muscle defect. This method was largely abandoned due to high recurrence rates. (C) Onlay placement of mesh material to overlie and reinforce the fascia and muscle defect. (D) In the sublay technique mesh material is placed on a well vascularized wound bed underneath the muscle and it is also covered by two fascial layers. This technique is considered the current gold standard with less complication and high success rates.

5. The failure of PPL in the pelvic floor

The first use of polypropylene in the pelvic floor was based on the integral theory [44]. The integral theory of female stress urinary incontinence stated that the pubourethral ligament in women creates a physiologic 'backboard' by fixing the mid-urethra to the pubic bone and that the laxity of this ligament results in the loss of the backboard inhibiting the urethral coaptation during times of increased intra-abdominal pressure that results in urinary incontinence. The synthetic midurethral slings (MUS) based on the integral theory came as a minimally invasive treatment modality with very high success rates. The initial description of the methodology used plastic tapes with the patient under local anesthesia [31]. The high initial success rates of the minimally invasive, relatively easy to perform MUS operations soon led to the use of the PPL mesh for transvaginal repair of pelvic organ prolapse.

The POP occurs as a result of loss of support at three levels in the pelvis. Level I cardinal-uterosacral ligaments providing apical support, level II arcus tendineus fascia pelvis supporting middle part of vagina laterally and level III urogenital diaphragm and perineal body supporting lower part of the vagina [45]. The contribution of each of these structures to occurrence of prolapse as we see it in the clinic, is not well defined. A recent work, for example, suggests that lack of vaginal apical support was a significant contributor to the occurrence of anterior compartment

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prolapse and that correcting the apical descent when treating cystoceles would reduce re-operation rates [46]. Thus the exact pathophysiology of POP, its correlations with clinical presentations and the theoretical basis of surgical techniques performed to treat POP are not well described. Nevertheless most of POP repair procedures are performed via a vaginal route (transvaginally) [47] either by placing the mesh directly on to the native tissue repair or suturing it to a strong ligament such as the sacrospinous ligament or arcus tendinous fascia pelvis [17]. Regardless of at what level the defect is and what the mesh restores, the transvaginal POP repair is more reflective of an onlay technique (mesh onlay repair) which did not work very well in the abdomen arguably due to being prone to be colonized by skin microbial flora as it lies very close to the skin [48]. Additionally, the mesh is not placed on a well vascularized wound bed in mesh onlay vaginal repairs. This can have particular importance in the postmenopausal women undergoing these operations as they already have poorly oestrogenised tissues.

In addition to the limitations related to the surgical technique of implantation, the PPL mesh also has some inherent characteristics that make it unsuitable for use in pelvic floor. Recent animal studies in sheep confirmed a site specific response to implanted PPL mesh, where a 5 × 5 cm piece of PPL mesh led to contraction and erosion in 3 out of 10 sheep in 12 months when implanted vaginally in contrast to no erosions in abdominal implantations [49]. The animal studies also showed that the host response to the PPL initiated by macrophages in the mesh-tissue interface was mainly an M1 (proinflammatory) response, instead of an M2 (remodeling) response, characterized by secretion of matrix metalloproteinases and pro-inflammatory cytokines leading to a vigorous foreign body reaction [50]. An M2 response is favorable for tissue integration while an M1 dominated response is now thought to explain the pain associated with mesh and mesh exposure. Clinical data obtained from women who underwent mesh excision due to severe pain or mesh exposure also confirmed that there was an M1 predominant macrophage response observed in the histological sections of the mesh-vagina explants [51]. Essentially a high M1 response indicates persistent inflammation. Thus there is a site-specific response to PPL mesh and the failure of PPL in the pelvic floor is partially due to the unfavorable mesh-tissue interaction leading to poor tissue integration.

In conclusion the use of mesh evolved over many years from an initial metal wire mesh to the monofilament, macroporous PPL mesh used in contemporary practice. Together with the improvements made in the surgical implantation technique mesh augmented surgical repairs now have very reasonable success rates in abdominal hernia surgeries. Although some of these improvements made to the material have been translated to the pelvic floor, we know that the same material when implanted vaginally to treat POP has resulted in unacceptably high complication rates.

This can be partially explained by factors related to the current surgical technique. The standard surgical technique, particularly those of transvaginal POP repairs, may need further improvements which will clearly require a better understanding of the pathophysiology of POP in women. Another important aspect is related to the pre and postoperative factors. It is now recognized that mesh augmented pelvic floor repair procedures, although conducted as minimally invasive day case procedures, involve placement of a permanent implant into the patients' body making post implantation surveillance necessary [12, 16]. Also factors related to patient selection, especially when the patients have co-morbidities such as diabetes and obesity, are known to influence

postoperative outcomes. Surgeons' experience is another potentially important factor in the mesh implant procedures. Several recent consensus reports on how to control vaginal mesh related complications are now emphasizing that only surgeons/centers with subspecialist experience on implantation and postoperative management of patients with stress urinary incontinence and pelvic organ prolapse should undertake these procedures. Also the implementation of national mesh registries, thus not relying solely on the manufacturers to report mesh related adverse event and mandatory post-implantation surveillance systems are recommended.

6. Designing synthetic materials to be used in pelvic floor reconstruction

The PPL vaginal meshes in current clinical use were never designed or tested specifically for use in pelvic floor. Instead they were cleared in regulatory terms based on their biocompatibility and the similarity of their textile properties to the existing abdominal hernia products via a 510(k) loophole. In other words, PPL mesh was used in pelvic floor based on an assumption that if it worked well in the abdomen to reinforce hernia repairs it would work equally well to support vaginal prolapse repairs. It is now being recognized that this approach was inherently flawed as the microbial flora, pH, vascular supply and physiological mechanical requirements of the pelvic floor are different from that of the abdomen.

Novel synthetic materials that are mechanically compatible with the requirements of the pelvic floor and that can effectively integrate into host tissues after implantation can be designed by using biomaterials and tissue engineering techniques. This requires an in depth understanding of the mechanical and biochemical properties of the pelvic floor. This section will review the available evidence on the biomechanics of the pelvic floor with a view to defining the design requirements for pelvic floor tissue engineering.

6.1. Basic definitions in biomechanics

The pelvic floor is the hammock-like structure made up of skeletal and smooth muscles surrounded by connective tissues and attached to pelvic bones. Its' main function is to counteract the forces generated by gravity and intra-abdominal pressure. When studying bioengineering of the pelvic floor we need to consider its biological constitution in relation to the mechanical forces acting on it. Namely, any material used to support the pelvic floor needs to have defined characteristics of material deformation and load bearing as well as how it contributes to tissue remodeling once it is implanted in to the body. It is important that clinicians/surgeons have a basic understanding of biomechanical principles so that they can define the biomechanics of the tissue to be replaced and select the best material to meet the specific needs.

Briefly, when a force is applied to a material it cause a change in size or shape of the material (deformation). This is most commonly expressed in a stress-strain curve from a uniaxial tensile test (**Figure 2**). This test gives an idea about the maximum forces needed to break the material (ultimate tensile strength) and the point where plastic deformation starts (yield strength). These parameters need to be considered together with the requirements of the site of implantation when designing an implant material.

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6.2. Defining the mechanical characteristics of the native human pelvic floor

Our knowledge on the mechanical properties of the female pelvic floor mainly comes from mechanical testing of samples from the pelvic floor from human and animal samples. The availability of human samples for mechanical testing is often limited due to challenges and ethical concerns related to obtaining large tissue samples. Whole pelvic floor samples of animals that contain all the muscles and the connective tissues of the pelvic floor (e.g. 'vaginal supportive tissue complex') have been obtained from rats demonstrating that the ultimate failure in the testing protocol was due to a failure of paravaginal attachments [52]. Samples that only contain the connective tissues (e.g. fascia) have also been tested [53]. Disruption in the fascial structures is thought to be the main mechanism by which pelvic organ prolapse occurs [52].

Another factor limiting our ability to have robust definitions of mechanical properties of pelvic floor structures is the lack of standardized mechanical testing protocols for biological tissue samples. To obtain reproducible results when mechanically testing biological samples their unique organization, composition and *in vivo* functions need to be adopted to the mechanical testing protocols. Currently mechanical testing of samples from animal or human pelvic floor can mainly be tested by uniaxial and biaxial tensile testing. In uniaxial testing, the tissue to be tested is placed between two clamps (clamp-to-clamp testing) and a load is applied to the sample in one direction while observing for elongation/strain. Uniaxial testing is most commonly performed in these studies and it gives more reproducible results.

From a biomechanical point of view, the pelvic floor is a complex structure composed of active (e.g. muscles) and passive soft tissue (e.g. fascia) components attached to the pelvic bones all

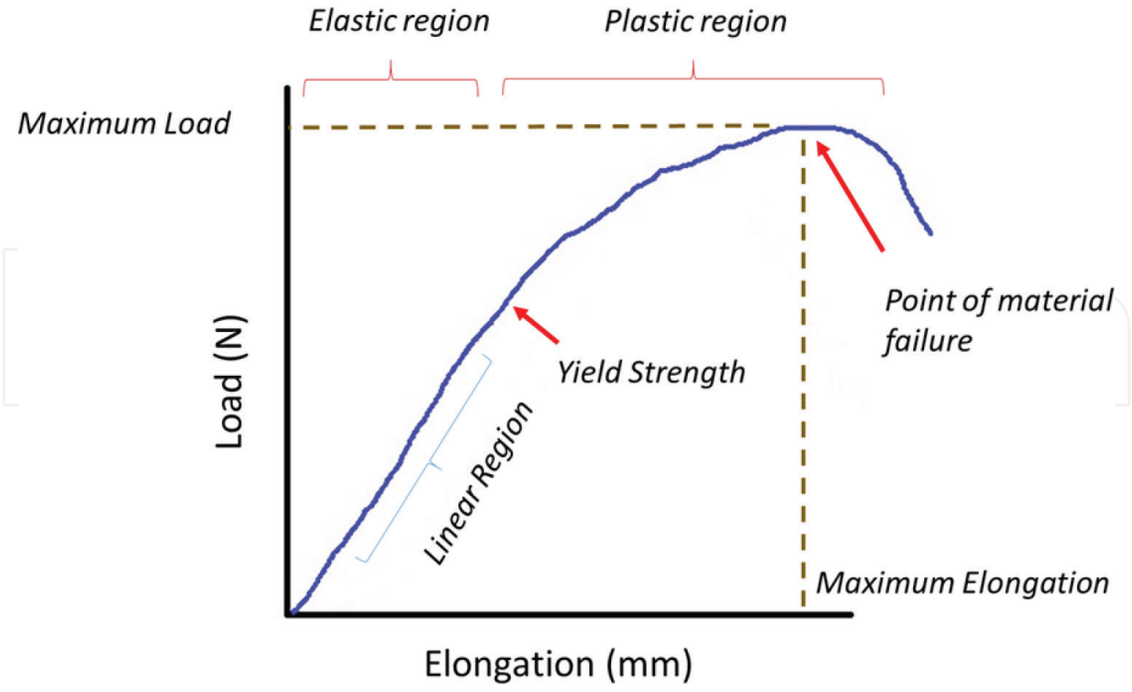

Figure 2. Defining the basic mechanical properties of a material by uniaxial mechanical testing. The 'maximum load' is the maximum amount of stress that a material can bear before it fails. The 'maximum elongation' is the maximum strain a material can achieve before it fails. The 'yield strength' is where irreversible deformation to the material starts.

contributing to the mechanical strength [54]. Computational models have the potential to mathematically combine all the complex anatomical, mechanical and biochemical data pertinent to pelvic floor to create computational models predicting the biomechanical behavior of the female pelvic floor in health and disease. Anatomical models demonstrating detailed 3D anatomy of the pelvic floor can now be reliably produced thanks to magnetic resonance imaging [55]. The remaining considerable challenge seems to be integrating the functionality of the muscles and other soft tissues into these models. The hope they offer is that once an accurate biomechanical model is created, population based data can be applied to these models before they are used clinically to predict individual patient/disease outcomes.

6.3. Biological requirements of pelvic floor

Early materials implanted into the human body were designed to have appropriate physical properties to match tissues at the site of implantation and to be made of materials which would have minimal toxicity. These materials were biologically 'inert' which ensured a minimal immune response to the foreign material. Although the consideration of the predicted immune response to an implanted material is still conceptually valid, there is a shift of paradigm about the inertness of a biomaterial. The next generation of biomaterials were purposefully designed to be bioactive to achieve a desired reaction post-implantation (e.g. antibiotic or extracellular matrix coated materials). Additionally the degradation times of the materials started to be finely tuned with advancements in resorbable biomaterials. The main advantage of using a degradable material would be that the foreign material would eventually be degraded after guiding the host to achieve a desired tissue regeneration (e.g. absorbable sutures commonly used in surgery).

The polypropylene material commonly used is traditionally considered 'inert'. Although PPL completely degrades over many years, its' inertness is now questioned after repeated demonstrations of surface degradation on the PPL fibers [56, 57]. The most common complication of surgical implantation of the mesh is spontaneous pain, occurring in 32.5% patients (pain during sexual intercourse 14.7%) [58]. The mechanisms leading to this pain are complex, probably involving infection, nerve and muscle injury and mesh contraction [59]. It has been demonstrated in mesh samples explanted from patients that PPL can actually degrade *in vivo* as early as 18 months after implantation [56]. This PPL polymer can breakdown in response to high temperature, UV light and oxidation [57].

Another important point to consider is the tissue specific immune response to the implanted biomaterial. The host immune system, mainly affected by tissue macrophages, initiate a cascade of events as soon as the material is implanted in the body. These reactions mainly take place at the material-tissue interface meaning that the surface structure and chemistry can potentially influence the initial macrophage response to the implanted material. Modifications of the surface properties of materials have been investigated as a potential strategy to shift the macrophage polarization towards a constructive remodeling type (M2) of reaction instead of a pro-inflammatory (M1) type. A well described pathway leading to biomaterial failure in the long term is development of a foreign body reaction leading to encapsulation of the material isolating it from the surrounding tissues. A foreign body reaction is a result of chronic M1 predominated inflammatory reaction. It has been demonstrated that synthetic materials when designed with a highly porous structure elicit less chronic inflammation leading to encapsulation [60, 61].

It is now widely accepted that the failure of PPL in pelvic floor is due to its mechanical incompatibility and the unfavorable mesh-tissue interaction leading to poor tissue integration. Essentially the PPL mesh is too strong and not elastic enough to be used in the pelvic floor [62, 63]. Additionally, animal studies have confirmed that the host response to the PPL initiated by macrophages in the mesh-tissue interface is mainly an M1 (proinflammatory) response, instead of an M2 (remodeling) response, characterized by secretion of matrix metalloproteinases and pro-inflammatory cytokines leading to a vigorous and persistent foreign body reaction [50]. Thus PPL is biologically and mechanically not the best material for pelvic floor repair. A recent European consensus report acknowledged the need for more research into more acceptable materials for use in the pelvic floor [12].

In conclusion when designing a material for use in the pelvic floor, the design characteristics should be optimized to consider its biodegradation and immunological response to it. When defining degradability of a material *in vivo* degradation characteristics and degradation products need to be defined. In case of non-degradable materials the chemical and mechanical changes to the material over many years need to be considered. Irrespective of this the host response to the material needs to be investigated in terms of both the acute and the longer term immunological response to the material. Finally its resistance to infection needs to be considered-this is often a combination of the material and its method of implantation.

7. Tissue engineering approaches to design novel materials to be used in pelvic floor repair

Tissue engineering and regenerative medicine can meet the clinical need in this area by either constructing biodegradable scaffolds that the host cells and tissues can use to remodel or directly by constructing a cell-tissue construct for implantation.

Compared to tissue engineering of other organs, such as bone and blood vessels, the area of pelvic floor tissue engineering is newly developing necessitating a better understanding of pelvic floor anatomy, physiology and mechanics. The first tissue engineered approach to construct an autologous fascia equivalent for POP repair was reported in 2010. In this study human vaginal fibroblasts were seeded on a PLGA knitted mesh before implantation into nude mice for 12 weeks and a well-organized new fascia with a high collagen I/III ratio was demonstrated [64]. A stronger tissue engineered material was also constructed from knitted silk mesh seeded with adipose derived MSCs in 2013 [65]. In 2013 comparative studies evaluated novel synthetic materials such as polyetheretherketone and polyamide as alternative materials to the PPL [66]. A gelatin-coated polyamide knit mesh seeded with endometrial MSCs that was designed for POP repair was also shown to reduce inflammatory cell infiltration and increase neovascularization in a rat model in 2013 [67].

Our own group in Sheffield has also been developing biomaterials and tissue engineered substitutes to be used in pelvic floor repair over the last 6 years. To produce the materials we have selected the technique of electrospinning. Electrospinning is a widely used technique in tissue engineering that allows fabrication of scaffolds with micro/nano sized fibers with different compositions

and configurations. With respect to choice of materials for POP we have suggested a biodegradable material, poly-L-lactic acid (PLA). This is a polymer of lactic acid which is among the most commonly used polymers in biomedical applications [68]. For a biomaterial to treat stress urinary incontinence (SUI) we have selected a nondegradable polymer of polyurethane Z3-as this is not the subject of this chapter this will not be discussed further in this review.

PLA is highly biocompatible and as a degradable polymer it is commonly used as a drug delivery material [69]. In one of our first studies with a biodegradable PLA scaffold produced using the electrospinning technique we showed that the material was extensively infiltrated by host cells together with new collagen deposition and new blood vessel formation after 7 days of implantation into the rat abdomen [70]. We than tried to mimic the organization of the natural extracellular matrix by spinning transversely, obliquely and irregularly aligned PLA electrospun fibers. Here we sought to achieve the viscoelastic mechanical properties of native fascia. We confirmed that MSC cells would grow on these fibers and produce new extracellular matrix. This allowed us to report in 2016 that electrospun scaffolds with several layers of different polymers to achieve the desired biomechanical properties of native fascia [71] maintained good mechanical integrity, compared to PPL meshes, over 90 days following implantation using a rabbit model [50]. The host response to these multi-layered PLA scaffolds was characterized as a predominantly M2 (remodeling) type 30 and 90 days after implantation onto the abdomen of the rabbit.

Another crucial requirement to achieve a rapid integration into host issues is related to vascular supply in and around the biomaterial. This can be particularly concerning in cases where the wound bed is already poorly vascularized, such as pelvic floor tissues of postmenopausal women with SUI and POP [72]. The growth of new blood vessels into a tissue engineered substitute is crucial to improve its' tissue integration and to obtain a successful long term clinical outcome. It has been estimated that a distance of less than 200 μM from the supplying capillary is the critical distance for diffusion of oxygen and nutrients to any new tissue introduced into the body. Because of this, the survival of any three-dimensional tissue graft relies on rapid development of new blood vessels to supply not only the center but also the margins of the graft [73].

Accordingly we have explored the introduction of clinically acceptable agents (specifically ascorbic acid and estradiol) that would stimulate neovascularisation and new extra cellular matrix production by the patient's endogenous cells. To this end we have demonstrated effective pharmacological functionalization of electrospun PLA scaffolds by incorporating ascorbic acid into them to stimulate ECM production without compromising mechanical properties [74]. We have also recently described an estradiol releasing, biocompatible mesh of electrospun PLA which doubled the number of blood vessels in and around the mesh when tested *in vivo* [75].

8. Conclusion

Polypropylene based vaginal meshes were never designed or tested specifically for use in the pelvic floor. The complications associated with the use of these vaginal mesh implants are largely due to a poor choice of material. A basic understanding of the material properties in relation to the physiological requirements of the site of implantation is essential for those developing and evaluating materials to assist surgeons seeking to repair the weakened pelvic floor.

A major limitation here is the relative infancy of the field of urogynecology and our current inability to characterize the biomechanical features of the pelvic floor. Despite this there are now a small number of academic groups (and a very few number of commercial manufacturers) worldwide engaged in understanding the biomechanical challenges of the pelvic floor, the host response to implanted materials and how to develop biomaterials which will be designed specifically for use in the pelvic floor to be introduced on their own or with patient derived cells.

Although it is too soon for any of these approaches to have translated into clinical trials there are now alternative materials which have been rigorously evaluated *in vitro* for mechanical properties and these are starting to be evaluated in appropriate models (the sheep in Europe and monkeys in the US) which can discriminate between materials which will fail mechanically or provoke sustained inflammation and those which do not. There is now reason for optimism that better materials can and will be developed which can translate into more effective surgical support for patients without causing the unacceptably high level of severe side-effects which patients are currently suffering with PPL mesh.

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