Timeline

Landmarks in vaginal mesh development: polypropylene mesh for treatment of SUI and POP

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Abstract

Vaginal meshes used in the treatment of stress urinary incontinence (SUI) and pelvic organ prolapse (POP) have produced highly variable outcomes causing life-changing complications in some patients while providing others with effective, minimally invasive treatments. The issue surrounding the risk:benefit ratio when using the vaginal meshes is complex in which a combination of several factors, including the inherent incompatibility of the mesh material with some applications in pelvic reconstructive surgeries and the lack of appropriate regulatory approval processes at the time of premarket clearance of these products , have contributed to occurrence of complications caused by vaginal mesh. Surgical mesh used in hernia repair has evolved over many years from metal implants to knitted polymer meshes that were adopted for use in the pelvic floor for treatment of POP and SUI. The evolution of the material and textile properties of the surgical mesh was guided by clinical feedback from hernia repair procedures, which were also being modified to obtain the best outcomes with use of the mesh. Current evidence shows how surgical mesh fails biomechanically when used in pelvic floor and materials with improved performance can be developed using modern material processing and tissue engineering techniques.

[H1] Introduction

Vaginal meshes that are currently used in the surgical treatment of stress urinary incontinence (SUI) and pelvic organ prolapse (POP) can result in life-changing complications in some women who have vaginal mesh implants [1]. These adverse outcomes are now considered a major public health problem; New Zealand becoming the first country in the world to ban the use of transvaginal POP mesh products while still allowing transvaginal SUI meshes (except minislings) in December 2017 [2]. In the UK, two public enquiries performed by the Scottish (in 2015)[3] and English (in 2017) [4] governments, in part, as a result of pressure from patient groups led to suspension of vaginal mesh products, both for SUI and POP, from July 2018 onwards [5]. The newest guidance by the National Institute of Health and Care Excellence (NICE) in the UK recommends that retropubic sling materials can be offered to women with SUI if nonsurgical management has failed [6]. In response, the British Society of Urogynaecologists expressed strong disagreement with the decision to suspend the use of vaginal mesh for SUI, but not POP, stating that this decision would deprive many women of an effective and safe treatment option as demonstrated by level I evidence [7 8]. Mesh manufacturers are currently facing lawsuits in the USA and Europe [9]. The issue with mesh repairs for SUI and POP is complex, as the vaginal mesh is implanted in the female pelvic floor in several different ways with very different outcomes in efficacy and complication outcomes. When used as a tape to treat SUI, many patients are effectively cured with the benefits outweighing the risks [10,11], whereas when used for transvaginal POP repair, complications are more frequent [12] with no obvious improvement in patient outcomes in terms effectiveness and quality of life compared with native tissue repairs [13]. In complex circumstances such as are apparent with the use of mesh,going back to basics and revisiting how the problem began might help clarify the whole picture.

Surgical mesh material was initially designed and used for hernia repair [14]. The clinical need for prosthetic materials to replace the defective abdominal wall fascia was recognized in the 17th century. Theodor Billroth, an eminent general surgeon at the time said “If we could artificially produce tissues of the density and toughness of fascia the secret of the radical cure of hernia would be discovered”[15]. Since then, many materials and several different surgical techniques have been used. The search for an ideal hernia mesh still continues [16]; however, the polypropylene (PPL) meshes are widely accepted as the standard mesh materials [17]. .

Following their success in hernia repair surgeries, PPL meshes started to be used in the female pelvic floor, firstly to treat SUI in 1970s. The initial trials did not lead to widespread clinical use of these meshes for SUI until Ulmsten and Petros popularized the midurethral sling surgeries in early 1990s. . The medical device regulations at the time permitted the widespread clinical use of PPL mesh without requiring evidence from clinical trials to demonstrate their safety and efficacy for these particular new applications in the pelvic floor. The thinking seems to have been that if these mesh implants worked well in one site of the body they would work equally well in another site. This assumption can now be considered naive, as we know today that the anatomical, biological and mechanical

requirements of the female pelvic floor are considerably different from those of the abdominal wall. Briefly, the design requirements for a vaginal mesh to support the pelvic organs and to be inserted through the vagina are different from those needed for an abdominal hernia repair mesh.

In this Perspective, we explore how PPL mesh has evolved as a material used in abdominal hernia repair and how it was translated for use in female pelvic floor. We review the basis for using the mesh for treatment of SUI and POP to elucidate the targets of surgical treatment and how suitable the mesh is to replace the defined target. We describe the material properties of mesh as it relates to occurrence of mesh complications. Finally, we discuss current approaches to developing new materials using a range of nondegradable and degradable materials and tissue engineering techniques.

[H1] The evolution of surgical mesh

[H2] Mesh used for abdominal hernia repair

Ventral hernias occur owing to a defect in the fascia covering abdominal muscles and surgical treatments aim to repair this structural defect. Prosthetic materials are mainly needed to fill in large tissue defects that cannot be closed with primary suture repairs or to reduce the chances of recurrence after primary repairs. The first prosthetic material used in hernia repair in 1902 was made of silver [18] , followed by tantalum in 1940 [19] (Figure 1) Tantalum wire mesh became quite popular at that time owing to its inertness and antimicrobial properties [20]. However, metals are inherently unsuitable for soft tissue repairs such as hernia repairs, as they are stiff and can fragment [21]. After the plastics revolution in the early 20th century materials made of nylon (polyamide) and Dacron (polyester, also known as polyethylene terephthalate) started to be used [22]. Although these plastic meshes offered substantial advantages over metallic meshes owing to their ductility (the ability of a material to undergo plastic deformation without cracking or failure) and strength, their initial design was poor, with small pores and multifilament structure.

It was only after Usher, a hernia surgeon, optimized both the material and textile properties of plastic mesh (Marlex) that acceptance became widespread[14]. He used a high-density polyethylene and a new manufacturing method to extrude it as a monofilament [14]. He optimized the textile properties such as porosity, stretchability and tensile strength of the new mesh to enable fibroplasia while keeping the necessary tensile strength. In 1962, an improved version of Marlex mesh made of PPL was introduced. PPL had improved material and textile properties (such as high tensile strength and good flexibility) and increased heat resistance compared with polyethylene, enabling effective sterilization without compromising the material properties [23]. PPL became the standard material for modern surgical mesh over the next couple of decades [17]. The initial PPL design remained largely unchanged over the next 50 years, but modifications to the textile properties of the mesh were continuously made to improve clinical outcomes. A relationship between the physical properties (pore size, fibre diameter) of the material and material related complications had become a well- defined phenomenon by 1997 which is crystalized by the Amid classification of the surgical meshes [24]. Basically, light-weight meshes reduced inflammation, foreign body reaction, fibrosis [25,26], chronic pain and abdominal stiffness in clinical studies [27]. Also light-weight meshes with large pores had increased flexibility compared to heavy- weight meshes and were similarly elastic to the abdominal wall [28]. As a result, the initial heavy-weight meshes with small pores (≤10 μm) (such as Marlex) were replaced with lighter-weight

meshes with larger pores. Nevertheless, the heavy-weight mesh can still be necessary for selected hernia repairs in which maximum mechanical stability is desired [29].

Thus, mesh for surgical repair has evolved from a metal wire through plastic fabrics to the current PPL mesh that has a range of bulk densities and pore sizes (Fig 1). This evolution and refinement of mesh composition was conducted on the basis of clinical feedback over a considerable period of time and the process is probably ongoing.

[H2] Surgical technique for abdominal mesh use

In parallel to the modifications made to the textile properties of mesh, surgeons also modified the way they use the new plastic prosthesis when treating hernia. Many different surgical approaches and operative techniques have been described in the literature concerning hernia repair [30]. Development of some of these techniques seems to have been driven by the availability of the plastic mesh and efforts to make use of its material properties. For example, mesh plug surgeries for inguinal hernia repair were introduced making use of the flexibility and fibrosis-inducing properties of plastic meshes [20] The concept of creating an inflammatory reaction at the site of the hernia to stimulate fibrous tissue formation was previously known, but this reaction could only be achieved using caustic substances or wooden plugs before plastic mesh was introduced [31]. Another example of how surgeons developed surgical technique to use plastic mesh is incisional hernia repair. The first technique used for repair of midline incisional hernia using plastic mesh was the inlay technique in which the mesh is inserted in between the edges of the fascia defect to fill the gap (Figure 2). The inlay positioning was, unfortunately, associated with high recurrence rates. In a pooled analysis, inlay mesh placement had a recurrence rate of 30.2% compared to 16.5% and 7.0% for onlay and sublay placements, respectively [32]. The next development or surgery for this repair was the onlay technique, in which mesh is placed on top of the repaired fascia defect in a tension-free manner (Fig. 2) . Onlay repairs involve extensive subcutaneous tissue dissection and a large area of the mesh implant stayed very close to skin, increasing the chances of wound complications such as infection and seroma formation [33]. To reduce complications a sublay (retrorectus) technique was then developed, in which the mesh is put underneath thick muscle tissue (retrorectus, Fig. 2); specifically, the mesh is placed under the rectus muscle and over the posterior sheath of the rectus muscle (above the linea semilunaris). Below the semilunar line, the mesh is placed underneath the rectus muscle and just over the preperitoneal fat. It appears that the sublay technique is now considered the gold-standard technique for incisional hernia repair, particularly in wound beds that are difficult to treat (for example, poorly vascularized or wounds that have been repeatedly operated on) [32,34]. Thus, the position of the mesh in relation to the tissue layers to be repaired seems to be a factor that is relevant to mesh-related complications in hernia repair surgeries [35]. Taking altogether, it appears that some surgical techniques in hernia repair surgeries have been driven by the availability of new materials that than went through a process of further refinement over years until the technique was optimized in the particular clinical context.

Just as new materials necessitated new surgical approaches, developments in surgical technologies also required modifications in material properties for hernia surgery. Widespread use of laparoscopy led to the development of an underlay repair technique, that can be performed in the introcorporeal environment by placing the mesh on the inside surface of the abdominal wall in direct contact with intra-abdominal organs (Fig. 2). The mesh in these cases needed to have additional antiadhesive properties to prevent adhesion of intra-abdominal organs, achieved by using materials with this characteristic (such as Teflon-based materials) to fabricate or coat the mesh [28]. The success rates of laparoscopic mesh repair surgeries appear to be similar to open hernia repairs with lower incidence of wound complications and higher incidence of bowel obstruction in laparoscopic technique [36,37].

In conclusion, the use of synthetic mesh has revolutionized hernia repair surgeries [38]. Retrospectively, the material and the surgical technique seem to have developed concurrently over >50 years to obtain good surgical outcomes for hernia repairs.

[H2] Meshes in pelvic floor surgery

The first prosthetic material used in pelvic floor surgery, in a 1947 case series, was a tantalum plate implanted transvaginally to treat SUI [39]. The underlying theory was to induce fibrosis and form a fixed plane at the posterior part of the proximal urethra [39]. The same material was then implanted transvaginally to treat cystoceles in an effort to reduce recurrence after surgery [40]. Exposure of the tantalum mesh was reported in 4 out of 10 patients within 6–18 months indicating that tantalum is not suitable for use in the pelvic floor[39].

The first nonmetallic prosthetic material used for pelvic floor surgery, in 1968, was a gauze hammock made of polyethylene (Mersilene) that was used as a sling to treat SUI [41]. This hammock was placed at the bladder neck in a tensionless manner and the edges were fixed to the rectus fascia. A success rate of >80% was reported in 71 patients at up to 5 years follow-up monitoring [41]. Although no long-term follow up data was ever presented, tissue damage with dense scarring was reported in the early postoperative period [41]. Two years later, polyethylene was replaced with PPL (Marlex) mesh [42], which was considered inert and resistant to infection. This mesh was used to treat SUI in a modified gauze hammock operation in 20 patients in which mesh is placed at the bladder neck and attached to the Cooper ligament. A 5% erosion rate was reported with most of 281 patients followed for 5 years [43]. This erosion rate could be the reason why these operations have not gained widespread acceptance. The chronology of events shows that materials were adopted for use in the pelvic floor after they were first used in hernia surgeries (Figure 1).

Widespread use of the surgical mesh in the pelvic floor started after 1995 when Ulmsten and Petros first described intravaginal slingoplasty [44]. In these operations, a mesh sling made of

PPL was applied with its own introducer (tunnelling device) as day-case procedures, , forming the basis of the modern midurethral tape procedures (Figure 3c) [45]. The first intravaginal synthetic sling material received clearance from the FDA in 1996 was ProteGen, which is a polyester mesh coated in bovine collagen [46]. Notably, this product was recalled 3 years after it was cleared owing to severe complications such as erosion, infection and pain [47]. Despite this experience, ProteGen was used as a predicate device and the TVT of Ethicon made of PPL was approved by the FDA in 1999 [48] which then generated the forward chain together with many others [46]. The transvaginal mesh devices for POP repair were also approved on the basis of their equivalence to ProteGen as the predicate device[46].

The first prosthetic materials used in pelvic floor reconstruction were reproductions of hernia meshes, such as Gyneacare®. Subsequently, mesh kit devices such as Perigee and Apogee were manufactured and the first mesh kit device was approved by the FDA in 2004 . Efforts were then made to adjust the textile properties, such as weave pattern and geometry, of the mesh specifically for urogyneacological applications. Studies on mesh geometry and its relationship with pore stability under mechanical distension led to the introduction of new mesh materials that were designed specifically for applications in the pelvic floor, such as DynaMesh [49]; however, to the extent of the effect on reducing mesh-related complications is unclear.

[H1] PPL mesh as a material

PPL ($[C3H6]_n$) is a thermoplastic polymer (meaning it can be processed and reprocessed when heated) that is synthesized from propylene monomers by addition polymerization [50]. After the raw material of PPL is synthesized, it is melted and extruded into a continuous monofilament (rather than alternative processes, such as electrospinning; Fig 4.). Different polymer processing technologies can lead to considerable differences in the final product and tissue response to it (Table 2) .The monofilament can then be woven or knitted [51]. Knitted meshes are preferable to woven meshes for use in the pelvic floor as they are more porous and flexible; furthermore, woven meshes are associated with an increased complication rate as the filaments of the woven mesh can slide together resulting in interfibre spaces that allow bacteria in but not immune cells [52]. After knitting, the mesh is cleaned of the residual chemicals, cut into shape and sterilized by autoclaving or high-pressure steam.

As well as the raw material, additives are included in the polymer mixture to help the raw material become suitable for industrial processing. Additives can also be used for property enhancement and to neutralize the effects of other additives. For example, the PPL needs to be thermally stabilized by additives to survive melt processing, antioxidants can be added to enhance material properties and catalyst deactivators neutralize any remaining catalyst residues [53]. Although additives are used much less in medical-grade materials than in industrial plastics, not to compromise biologic compatibility of medical grade plastics, when

they can constitute up to 30% of their total polymer weight [54]. Thus, the substance of finished mesh product constitutes the raw material and the additives.

The device manufacturers rely on suppliers of raw materials and components to obtain polymer resins. They are required to implement supplier qualification procedures that include audits, incoming raw material and component specifications and quality metrics [55]. These qualification processes have been the subject of an FDA statement [56] in which a change in supplier together with variability between the polymer resins from both suppliers were found; however, the difference did not raise any new safety and effectiveness concerns with no evidence of adverse clinical reports.

Surgical meshes made of other raw materials, such as polyester, polytetrafluoroethylene (PTFE) and polyvinylidenfluoride (PVDF) have also been used clinically [20]. Different polymers can be used for different purposes with distinct biological effects. For example, PTFE has antiadhesive properties making it preferable for intraperitoneal applications [57]. However for the treatment of SUI, PTFE (Goretex®) was not considered an ideal material [45] as the initial reports showed mesh removal rates of up to 21% in 31 months after surgery [58]. PPL was suggested to have two main advantages over polyester and PTFE meshes: PPL is better accepted by tissues owing to inherent material properties and has strong adhesive properties that prevented sliding, removing the need for any fixation points during application, unlike PTFE for example. [44,59] PPL is the most commonly used material in all hernia surgeries.

[H2] Outcomes of mesh for SUI and POP

When used as a tape to treat SUI , mesh has a long-term subjective cure rate of up to 93% [10]. Serious mesh-related complications still occur in at least 4% of patients who had a mesh implant for SUI. [11]. When used for POP repair, mesh can be implanted either transvaginally or transabdominally. The success of transabdominal repairs can be >90% [60], but the rates can change considerably depending on the definition of success [61]. Mesh erosion still occurs in up to 6% of women who had abdominal sacrocolpopexy by 2 years after abdominal sacrocolpopexy [62] and 10% at the 7-year follow-up point [63] . However, when the same mesh is implanted via the vagina the results are very different. Transvaginal mesh implantations result in a decrease in awareness of prolapse, reduced recurrence of prolapse on physical examination and reduced rates of repeat surgery compared with native tissue repairs in the short term (1-3 years). However, these outcomes came at the expense of increased rates of repeat surgery for mesh complications or recurrent incontinence and/or prolapse in another vaginal compartment [64]. The safety of using mesh for transvaginal POP repair procedures is now widely questioned as a mesh erosion rate of 8% in the 1–3 year follow-up period has been reported [64] and a rate of up to 42% was observed in a study that monitored patients for 7 years [12]. Growing public concern about mesh complications contributed to the initiation of investigation of the use of mesh for POP and SUI in two public inquiries in the UK

in 2017[3,4]. The Scottish Independent Review on the use, safety and efficacy of transvaginal mesh implants looked at the frequencies of midurethral sling surgeries, transvaginal mesh and transabdominal mesh insertions for POP and SUI and compared them with nonmesh alternatives retrospectively between 1997 and 2016 [3]. For SUI repair, this review demonstrated that hospital admission rates for late complications and for further SUI surgeries within 5 years of the surgery with mesh slings was not different from colposuspension (the most commonly performed anti-incontinence operation not using the mesh). Fewer immediate postoperative complications occurred with mesh slings surgery than colposuspension . However, for transvaginal POP repair the use of mesh did not reduce the need for further surgery [3] and readmission rates within 5 years were higher with all transvaginal mesh implantations than with native tissue repairs. Similarly, the review of hospital episode statistics by NHS England did not show any difference in outpatient hospital admissions after vaginal mesh surgeries compared to native tissue repairs [3]. However, it is worth noting that in this review surgery for prolapse was not sub- grouped into POP repair via transvaginal versus transabdominal approaches. Such a subgroup analysis may have led to different figures as we know transvaginal mesh surgeries are associated with more complications than transabdominal route. A recent consensus document recommends that transvaginal mesh for POP should be reserved for selected patients and performed only in specialized centres [65]. The number of mesh-augmented transvaginal POP repair procedures sharply declined from 27% of all POP repairs to 2% after the FDA warning on the use transvaginal mesh products in 2011 [66]. A similar trend was observed in the use of transvaginal mesh for SUI: the review of hospital episode statistics by NHS England showed a 48% reduction in mesh tape procedures performed in England between 2008 and 2017, with a sharper decline after 2013 [4]. Also, the data show a decrease in the number of midurethral sling (MUS) surgeries performed in academic centres and an increase in pubovaginal sling procedures [67]. Taken altogether there appears to be a considerable reduction in use of vaginal mesh implants for treatment of SUI and POP while the number of native tissue repairs increase.

[H2] Issues with medical device regulations

Medical devices comprise a wide range of tools from gloves to sophisticated prosthetic devices. Accordingly, these devices are approved by regulatory bodies via a variety of different routes. Medical devices are classified by the FDA in the USA, and similarly by other regulatory bodies such as the Medicines and Healthcare products Regulatory Agency (MHRA) and European Medicines Agency (EMA), into three classes based on the level of control required to assure of their safety and efficacy [68]. About two-thirds of devices (such as tongue depressors and gloves) are low risk (class I). Low-risk devices are subject to the least control and are exempt from premarket submission [69]. The other approximately one-third of medical devices are moderate risk (class II, such as catheters and surgical sutures). Most class II devices are approved via a process called the 510k, in which proof that the device is substantially equivalent to previous legally marketed devices is enough for clearance [70]. Only

1% of medical devices are classified as high risk (class lll, such as pacemakers and artificial urinary sphincters) and premarket approval is necessary for these devices. Premarket approval involves determination of safety and efficacy on the basis of results of clinical trials [69].

The vaginal meshes used in the treatment SUI and POP were cleared via the 510k route as being equivalent to hernia meshes and made available for widespread use, in the absence of clinical evidence of their safety and efficacy when used in pelvic floor surgery [46]. A total of 61 mesh products were cleared via the 510k route with claimed equivalence to Ethicon' s Mersilene hernia mesh (approved in 1985) and the ProteGen sling (approved in 1996) [46]. As no clinical trials were required before marketingmanufacturers did not monitor long-term adverse effects and the opportunity to refine and improve materials was largely neglected for at least a decade. Real-life data now show that the use of PPL mesh in urogyneacological surgery for SUI and POP can have life-changing consequences such as chronic pain, infection and organ perforation [71,72] for some women. Eventually in 2016, the FDA reclassified transvaginal mesh devices from being class II (moderate-risk device) to class III (high-risk device) requiring clinical data on efficacy and safety of these devices before clearance [73]. As a result, some manufacturers removed the products from the market [74]. As a result of lessons learnt from the vaginal mesh experience, new European regulations on medical devices entered into force on May 2017 that aim to establish a robust, transparent, predictable and sustainable regulatory framework for medical devices which ensures public safety while supporting innovation [75,76]. . New definitions to refer medical devices have been introduced (such as active device, implantable device and single use device) and regulations for placing them on the market, tracing the supply chains and postmarket surveillance are now implicated force.

[H1] The mechanics of mesh for SUI and POP

[H2] Use of mesh for SUI

In the past 100 years, surgical treatment of SUI has developed for three main purposes: restoration of normal retropubic position of the urethra (retropubic suspensions), strengthening of the external sphincter (transvaginal plications) and sling operations [77]. Sling operations were the precursor for synthetic midurethral sling surgeries. The fascia sling surgeries that are still performed were popularized by McGuire [78] who defined a subgroup of patients using urodynamic studies who would benefit most from an autologous sling procedure (patients with type 3 SUI (intrinsic sphincter deficiency))[79]. The introduction of urodynamic studies enabled assessment of the functionality of the lower urinary tract by 1970s, leading to an increased understanding of urinary incontinence and exploration of its potential to improve patient selection for a particular surgical intervention [77].

In the 1990s, the integral theory was introduced, forming the basis of the modern tension-free vaginal tape procedures [80]. According to this theory, urethral closure occurs by forward contraction of pubococcygeus muscles and backward contraction of levator muscles in the presence of an adequate tension in the pubourethral ligament when intra-abdominal pressure increases [80]. A synthetic mesh placed in the position of the pubourethral ligament in a tension-free manner would induce fibrosis and form a collagenous neoligament to replace the pubourethral ligament forming a backboard against which the urethra can be compressed [81]. Furthermore,, the midurethra was shown to be the most critical location to place the mesh, instead of the bladder neck, owing to the laxity of the pubourethral ligament at this level, which has been observed in urodynamic (urethral pressure profile) studies [44]. Importantly, the midurethra was validated as a target by measuring the improvements in urethral closure pressures preoperatively and postoperatively [44]. Thus, the pubourethral ligament was accepted as the target tissue replaced by mesh in synthetic midurethral sling surgeries. The pubourethral ligament descends like a hammock from the inferior part of the pubic bone towards the urethra and vagina (Figure 3c). Biomechanically, the pubourethral ligament consists of collagen, elastin, smooth muscle, nerves and blood vessels actively and passively suspending the urethra [82]. Although mechanical testing of the pubourethral ligament was never performed, the proximal part was defined as a fibrous, pearly white tissue that is resistant to stretching [83] which histologically consists of dense, parallel bundles of collagen fibres directed longitudinally [84]. This structural organization can be hypothesized to translate into a function that is stronger in one direction rather than a predominantly elastic one. Thus, the mesh implanted to replace pubourethral ligament would work mostly under unidirectional forces not needing substantial elasticity (Figure 3c).

[H2] The use of mesh for POP

Current surgical treatments for POP are based on identification and repair of anatomical defects that broadly occur at three levels in the pelvis: level I, the cardinal (Figure 3a) - uterosacral ligaments (that provide apical support); level II arcus tendinous fascia pelvis (that supports the middle part of vagina laterally); and level III, the urogenital diaphragm and perineal body (that supports lower part of the vagina) [85]. This anatomical description provides the basis of pelvic floor support structures that guides the reconstructive surgeon. After the level of the defect is identified it can be repaired by either an abdominal or a vaginal approach (Figure 3b-d).

Considering the biomechanical environment of the female pelvic floor when treating POP is also important; however, this factor is relatively poorly understood compared to its anatomy. Biomechanically, the pelvic floor is known to be composed of active and passive soft tissue components attached to the pelvic bones. Passive components, mainly the fascia, are unable to generate force but can resist when force is applied to them. The active components are the muscles, such as levator ani and the sphincters, which can contract and independently generate force [86]. How these structures each contribute to the generation of the biomechanical environment of the pelvic floor is not completely understood, particularly

as they relate to the occurrence and treatment of SUI and POP [87]. Nevertheless, some deductions can be made with regards to the biomechanical forces acting on the mesh when implanted for surgical treatment of SUI and POP.

Abdominal sacrocolpopexy operations using surgical mesh have been performed since the 1960s (Figure 3b) [88]. In these operations, the mesh material is used to attach the apex of the vagina (and the uterus in patients who did not undergo a hysterectomy) to the sacrum replacing a defective cardinal- uterosacral ligament complex [88]. This ligament complex is composed of thick and strong collagenous fibres extending vertically and posteriorly towards the sacrum (figure 3a) meaning that it is not necessarily flexible but strong in the vertical direction [89]. The mesh in these operations is secured in a relatively fixed position in the retroperitoneum and would be expected to be loaded mainly by a unidimensional vertical force.

The forces that act on the mesh are not well defined in transvaginal mesh-augmented POP repair procedures. Understanding these forces is complex as the visceral pelvic fascia consists of both passive and active soft tissue components, such as muscle fibre s that can generate force and fascia that cannot generate force but provide structural support [90]. Additionally, transvaginal repairs are essentially mesh onlay repairs (Figure 3d), particularly anterior and posterior colporraphy procedures, which makes them prone to colonization by vaginal microbial flora as they lie very close to the skin [91]. This phenomenon is well-known in abdominal hernia repairs, in which the chances of mesh colonization and infection is increased with onlay mesh hernia repairs (in which the mesh is implanted on top of the fascia defect in very close proximity to skin). [35] (figure 2c). Furthermore, with transvaginal mesh implants, meshes are probably not placed on a well-vascularized wound bed in most patients as many of these patients are postmenopausal and already have poorly oestrogenised, less vascularized tissues [92]. Thus, in abdominal sacrocolpopexies the mesh mostly replaces a passive soft tissue component and the mechanical properties of the mesh can probably better match with the requirements at the site of implantation. In contrast, the in vivo loading conditions for the mesh are largely unpredictable in transvaginal POP repair procedures, where the mesh probably is loaded under multidimensional forces and many meshes cope poorly with these mechanical demands [93].

Considering all these together, it could be suggested that both the factors related to surgical technique and the mechanical mismatch between the mesh and the pelvic floor tissues could have contributed to the complication rates observed with these surgeries (Table 1). The main problem with the surgical technique when performing vaginal mesh implantations appears to be the insertion of the mesh through a vaginal skin incision where the mesh lies in a tissue plane where it is too close to the vaginal skin. The biomechanical problem is that of a combination of a mismatch between the mechanical properties of the mesh material and the biomechanical requirements of the female pelvic floor, the latter is poorly defined.

[H1] Mechanisms of mesh-related complications

Complications caused by vaginal mesh occur as a result of a combination of several factors, including problems related to the mesh material itself, incomplete understanding of disease processes leading to SUI and POP, limitations of the surgical techniques used in the treatment of SUI and POP, failure of regulatory processes for approval and of surveillance of implantable medical devices for this application, factors related to the surgeon and factors related to the patient (Boxes 1 and 2) [65].

[H2] Factors related to the mesh material

The development of the surgical mesh from metal implants to the modern polymer-based meshes shows that the material properties are the main determinants of the surgical outcomes with mesh repairs.

[H3] Biocompatibility

Biocompatibility is "the ability of a material to perform with an appropriate host response in a specific application" [94]. In other words, the material should be able to exert its desired function without an unacceptable degree of harm to the host. A host response is expected to any synthetic implant and a mutually acceptable coexistence of materials and tissues is required. Materials and tissues can interact in many different ways and research on the mechanisms of these interactions and their associations with clinical outcomes is still ongoing.

For PPL mesh, the host response has been mainly studied in the context of hernia surgery. PPL mesh has been repeatedly shown to trigger a macrophage polarization towards an undesirable increased M1:M2 ratio early in the inflammation process [95]. A classical M1 macrophage response is characterized by a proinflammatory state, whereas an M2 response is a constructive remodelling response [96]. The M1:M2 ratio is increased with high-weight meshes with small pores than with light-weight meshes with larger pores [97]. Thus, the amount of mesh (the mesh burden) in contact with tissue could be a determinant of its biocompatibility [98].

Experimental studies to characterize the inflammatory response to PPL when implanted transvaginally started in 2007 in sheep [99]. These experiments clearly showed that graft-related complications (exposure and contraction) occurred considerably more when the mesh was implanted in the vagina than in the abdominal wall, with mesh exposure occurring in 3 of 10 implanted meshes [100]. Thus, the host response to PPL mesh is site specific. In a study of women who underwent mesh excision after midurethral sling and prolapse mesh implantation, the excised mesh–vagina complexes were examined to define the type of the inflammatory response [101]. Women with mesh complications had a proinflammatory (M1)

macrophage response years after the implantation. Additionally, in explants of women who had mesh exposure, expression of proteolytic enzymes such as matrix metalloproteinase 9 was increased compared with explants of women who had pain [101].

The most important factor that affects the biocompatibility of the mesh is its porosity and pore size [24]. Light-weight meshes with large pores seem to have the best outcomes, especially when used in surgical treatment of POP [102]. However, as meshes became lighter with increased pore sizes their flexibility also increased. Increased flexibility resulted in a change in the overall mesh geometry, causing loss of pores after mechanical loading of the mesh at the site of implantation [103]. Thus, the concepts of pore stability and effective porosity were introduced [104]. These factors have become particularly important for POP meshes as these meshes are more likely to undergo tensile forces *in vivo* than hernia meshes. Most of the commonly used prolapse meshes have a considerably reduced porosity after uniaxial loading [105,106], meaning that the porosity of the meshes are effectively lost after implantation There have also been studies on improving the mesh design by using auxetic geometries, unlike most materials that would become narrower with longitudinal stretch auxetic materials expand laterally when they are stretched in a longitudinal direction, for prolapse meshes that can avoid pore collapse after implantation *in vivo* [107]. The auxetic design allows maintenance of the porosity of the mesh when it is loaded leading to a better host response. This could be a strategy to improve the biocompatibility of the meshes; however, the ability of these materials to reduce graft related complications, such as mesh exposure, contraction and pain, has not yet been demonstrated.

Changes to the chemical structure of mesh *in vivo* is another factor that affects biocompatibility. Traditionally, PPL mesh was considered not to undergo any physical changes after being implanted into human body; however, current evidence suggests that the surface of the mesh can crack [108]. Out of 164 meshes explanted to treat complications, 162 demonstrated polymer degradation and superficial inflammatory cells trapped within these cracks [108]. The biochemical environment of the human body is an aggressive medium for mesh materials with a set temperature (37° C), oxygen level (approximatelt 20%), pH (7.4 in blood) and salt concentration (0.9% NaCl) [109]. This environment can cause PPL degradation by oxidation [110]. Furthermore, degradation can be considerably facilitated by the presence of static or cyclic mechanical forces [111]. Theoretically, a focal site of surface cracking, abrasion or wear can induce generation of macroradicals (a macromolecule that can act as a free radical), such as peroxide macroradicals originating from chain rupture leading to increased brittleness and deterioration in strength. In conclusion, PPL mesh is resistant to hydrolytic (bulk) degradation (which is breaking of chemical bonds in the hydrophilic groups at the polymer backbone to form oligomers and monomers) [112], but growing evidence suggests that it can undergo considerable chemical and mechanical changes in the human body.

[H3] Mechanical failure

Plastics have unique mechanical properties that are time dependent, often nonlinear and these affect their performance in the long term [113]. When a controlled force (stress) is applied to a plastic, it causes a change in its size (strain), which is initially proportionate to the force applied (linear elasticity) [114]. This proportionality is lost at some point during loading and the stress–strain curve becomes nonlinear and the material starts to deform irreversibly, whereas it remains elastic when the curve is linear [114] (Figure 5).

The mechanical properties of the PPL mesh are a function of the raw material and its textile characteristics [93]. These properties have mainly been defined under uniaxial tensile testing [115]. This test gives the maximum strength and strainability of the material before it fails. Loads above the failure point can also considerably change the material and textile properties of the mesh when repeated overtime [116]. An *in vitro* study evaluating the dynamic creep behaviour of four commercially available PPL meshes with different pore size, bulk density and geometries under physiological conditions showed that all meshes underwent strain hardening and plastic deformation after cyclic uniaxial loading [117]. Strain hardening is strengthening of the material during loading when they are stretched above their yield point. Data from another study showed that 3 days of fatigue testing in culture conditions was enough to demonstrate strain hardening and subsequent failure of some meshes [93]. Strain hardening is a well-defined phenomenon for thermoplastics [116] that are used in engineering and, from an engineering perspective, cyclic and fatigue tests would be expected to be performed to evaluate the deformation of the mesh. Although fatigue tests have been widely used for other biomedical implants (such as heart valves and stents) they have not been used, to the best of our knowledge, to evaluate vaginal meshes as they were considered low-risk medical implants.

Biomedical implants are normally designed to match the biomechanical environment of the implantation site. Biomechanics is an interdisciplinary area of research that involves the study of how the forces acting on structural elements of the human body create the motion that leads to normal development and functioning or to tissue damage under overloaded conditions [118]. The biomechanics of the female pelvic floor is a developing area of interest and limited knowledge of it is one of the factors that precludes definition of treatment targets and, therefore, the design requirements for prosthetic materials [119]. Current knowledge of the mechanical characteristics of the female pelvic floor is based on mechanical testing of whole pelvic floor samples from small animals (such as vaginal supportive tissue complex described in rats for experimental purposes) [120,121] or biopsies from humans [122]. These studies showed that the mechanical characteristics of healthy vaginal tissue in women has an ultimate tensile strength of 0.79±0.05 MPa, a maximum elongation of 1.68±0.11 mm and an elastic modulus of 6.65±1.48 MPa . Computational models of the female pelvic floor have the potential to reliably define normal biomechanical behaviour and can predict the biomechanical mechanisms leading to damage to pelvic floor structures (for example, birth trauma) and pelvic floor disorders [86]. Ideally measurements

made on specific groups of patients *in vivo* would be used to characterize the mechanical properties of the pelvic floor. Up to now anatomical models demonstrating detailed 3D anatomy of the pelvic floor have reliably been produced thanks to magnetic resonance imaging [123]. Additionally wearable devices that are temporarily implanted into woman vagina have been developed to obtain real time measurements of the pressures acting on the vaginal tissues [124]. The remaining challenge seems to be integrating the functionality of the muscles and other soft tissues into these models. What is really needed is computer based models where anatomical, mechanical and biochemical data pertinent to pelvic floor muscles and soft tissues can be combined mathematically. Once an accurate biomechanical model is created, population based data can be applied onto these model before they are used clinically to predict individual patient/ disease outcomes.

The mechanical properties of the mesh product can also have an effect on its biocompatibility; however this influence is much less studied than other biomedical implants such as hip prostheses. When an implant material is too strong and too stiff for the host tissues, a phenomenon called stress shielding can occur in the adjacent tissues leading to defective extracellular matrix production [125]. This concept is well-defined for bone implants and has also been studied in pelvic floor. A study in rhesus macaques showed that meshes with increased stiffness caused thinning of the smooth muscle layer, decreased vaginal contractility, decreased collagen and elastin content and increased total collagenase activity in the vaginal tissues adjacent to implanted mesh [125,126]. Thus, the vaginal mesh is too strong for the site of implantation and this can lead to deterioration in the strength of tissues around the mesh.

Deformation of the mesh under cyclic distension in the pelvic floor could possibly have contributed to the occurrence of mesh-related complications, but demonstrating this direct association *in vivo* would be difficult.

[H2] Surgical technique

In vaginal mesh implantations, the mesh stays in very close proximity to the vaginal mucosa as no natural tissue planes are present in this region (such as subcutaneous or muscle tissue layers) unlike in the abdominal implantations in which the mesh material is implanted in between clearly identifiable fat, muscle and fascia tissue planes [127] (Fig 2c-d).

Several observations suggest that mesh-related complications can result from limitations of surgical techniques used for mesh implantation, particularly for POP treatment. First, vaginal mesh complications are known to increase when a larger area of the mesh is used [65,100], for instance more complications occur with prolapse meshes compared to mesh slings. Second, some clinical studies demonstrate that avoiding a vaginal incision suture line being in direct contact with the mesh material could decrease mesh exposure [128,129]. Additionally, avoiding a vaginal incision when implanting a natural scaffold derived from natural extracellular matrix on the vaginal wall of rhesus macaques, in these cases the material was implanted transabdominally rather than through a vaginal incision,was also shown to eliminate the

negative effects on overall structure and function of the vagina with increased vaginal stiffness, collagen content and an increased collagen I/ III ratio at 3 months [130]. Finally, vaginal mesh extrusion described as vaginal mesh being visualized through the separated vaginal epithelium most commonly occurs in the midline where the surgical incision is made [131]. Taken together, these observations imply that mesh erosion can be an abnormal wound healing response of the incised vaginal mucosa in which a poorly vascularized wound bed combined with the surgical intervention and the presence of large amount of mesh material leads to poor wound healing.

[H1] Designing improved materials

Owing to the aforementioned factors, efforts are being made to improve mesh materials for use in pelvic floor reconstruction. The first approach to designing improved materials to support the pelvic floor is to develop the existing PPL meshes. The new generation of light-weight, macroporous meshes with high porosities are associated with reduced fibrosis, pain and mesh erosion [132]. The knit pattern and geometry of the mesh can also be modified to obtain the desired mechanical properties and a more stable effective porosity that function well under bilateral dynamic distension [133]. To enhance the biocompatibility of PPL, a bioactive coating of biocompatible substances (such as natural extracellular matrix [95] or titanium [134]) can be applied. The usefulness of bioactive coating in improving the biocompatibility of the meshes although has been assessed in pre-clinical studies still needs to be evaluated further in clinical studies.

Advances in materials science and tissue engineering are now being applied to designing novel materials specifically for use in the pelvic floor. The first tissue-engineering approach to construct an autologous fascia equivalent for POP repair was reported in 2010 [135]. In this study, human vaginal fibroblasts were seeded on a PLGA (poly(lactic-co-glycolic acid) knitted mesh before implantation into nude mice for 12 weeks and formation of a well-organized new fascia-like tissue was demonstrated [135]. PLGA-based materials may fail to provide durable structural support, a stronger tissue-engineered material was also constructed from knitted silk mesh seeded with adipose-derived mesenchymal stem cells (MSCs) in 2013 [136]. This material was not tested for their efficacy in relevant animal models. Including cellular components or naturally derived matrix proteins in mesh materials have been evaluated as a strategy to improve the biocompatibility of the materials. In 2013, novel synthetic materials such as polyether ether ketone and polyamide as alternative materials to PPL were evaluated in comparative studies [137]. A polyamide knitted mesh coated in gelatine and seeded with endometrial MSCs that was designed for POP repair was shown to reduce inflammatory cell infiltration and increase neovascularization in a rat model in 2013 [138].

Materials can also be fabricated using alternative methods. For example, electrospinning produces microsized or nanosized fibres with different compositions and configurations that can mimic the organization of natural extracellular matrix. Electrospinning can create

transversely, obliquely and irregularly aligned fibres consisting of poly-L-lactic acid (PLA) in a trilayer structure with biomechanical properties similar to native fascia [139]. Host immune response to these layered PLA scaffolds was characterized as a predominantly M2 (remodelling) type of immune response 30 and 90 days after implantation onto the abdomen of a cohort of rabbits [140]. Considering a range of degradable and nondegradable materials, such as PLA and a polymer of polyurethane, respectively, is important as different applications in the pelvic floor might require different material characteristics. For example, a relatively strong and degradable mesh material would be required for treatment of uterine or vault prolapse, whereas degradable materials that are not necessarily as strong would be better suited for low-grade prolapse in anterior or posterior vaginal compartments. PLA is known to have good biocompatibility and is commonly used in drug delivery applications [141]. Another promising material is polyurethane which has increased elasticity that can withstand cyclic mechanical distension *in vitro* [142]. Electrospun polyurethanes and electrospun ureidopyrimidinone-polycarbonate scaffolds, led to a better host response with an M2 type predominant (remodelling response) inflammatory response than ultralightweight PPL meshes after implantation into sheep vagina for 6 months [143]. Electrospun materials and ultralightweight PPL were similar with regards to graft-related complications, passive mechanical properties and their effects on vaginal contractility [143]. These suggest that materials with increased elasticity can be promising candidate materials for use in pelvic floor reconstruction.

Another desirable property of these biomaterials is, arguably, their ability to stimulate new blood vessel formation at the site of implantation. This stimulation could result in an improved wound healing, which is particularly important in circumstances in which the wound bed is already poorly vascularized, such as the pelvic floor tissues of postmenopausal women with SUI and POP [92]. Polymers can be combined with bioactive factors such as ascorbic acid [144] and estradiol [145,146] to stimulate neovascularisation and new extra cellular matrix production without having an adverse effect on mechanical properties of these materials[144-140]. These materials are yet to be tested in appropriate animal models, such as the sheep vagina in which the failure of some existing materials can be demonstrated [100].

From a regulatory perspective, novel products to be used in pelvic reconstructive surgeries should be subject to regulations for advanced therapy medicinal products if they involve a gene and/or cell therapy component or it is a tissue engineered product. These products should also be subject to regulations for medical devices if the biomaterial is composed only of a material (not involving a cellular products). Nevertheless, the regulations for any implantable medical devices are increasingly being criticized and clinical trials should be mandatory before any new devices are approved, especially for those used in pelvic floor surgery. Establishing registries for monitoring adverse outcomes is also required.

[H1] Conclusions

Surgical mesh has evolved over many years from an initial metal wire mesh to the monofilament, macroporous PPL mesh used in contemporary practice. The developments made to the material were a result of clinical feedback, mostly in the context of hernia repair, over a considerable period of time. Surgical techniques of implantation were also modified to make use of the newly available material to obtain best surgical outcomes for patients. As a result, mesh-augmented surgical repairs now have reasonable success rates in abdominal hernia surgeries, in which they resulted a considerable reduction in hernia recurrence after repair surgeries. However, hindsight shows that the assumption that materials that work well in hernia repair would work equally well when used in the pelvic floor was naive. At the time of making this assumption, knowledge of the forces that the materials experience in the pelvic floor was poor and the available regulatory processes did not require either efficacy data from in vivo studies or clinical data before these devices were approved for clinical use in women. As a result, the vaginal mesh has both mechanically and biologically failed when used in pelvic floor. The scientific and surgical communities now have clear evidence that an implant material needs to be designed and tested for a particular clinical applications using relevant animal models, which will then inform the legal decision makers on the necessity of clinical trials before approval and postmarket surveillance.

Mesh materials to be implanted in the vagina have now been upgraded to a category III regulatory risk. In the future, any new materials to be evaluated will need to undergo much more rigorous evaluation in appropriate animal models and also clinical safety studies.

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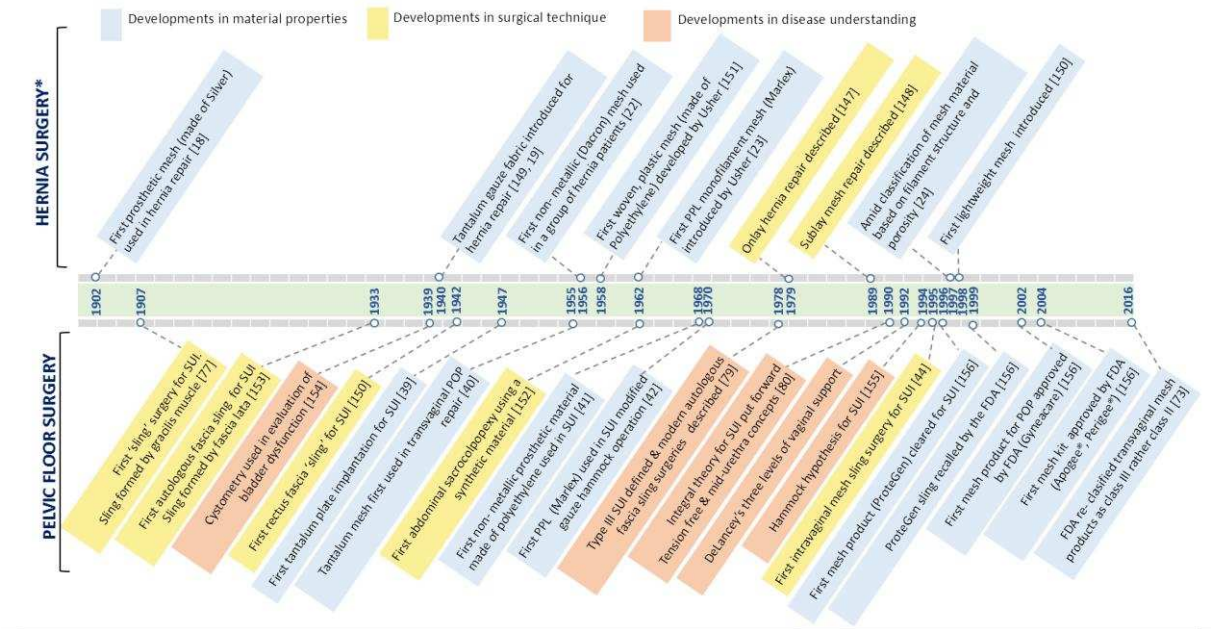

Figure 1. Milestones in development of the polypropylene mesh as a material used in pelvic floor repair. In hernia surgery, mesh material evolved over many years from a metal wire to a lightweight plastic mesh made of polypropylene (PPL). In parallel to the modifications in material properties of the mesh, the surgical technique of mesh positioning was also modified. In pelvic floor reconstruction, the materials were adopted for use in the pelvic floor after they were first used in hernia repair. Synthetic mesh was first approved for use in stress urinary incontinence (SUI), then for pelvic organ prolapse (POP). The anatomical and functional basis of SUI seems to have been well-studied before mesh was introduced, whereas for POP, the structural pathophysiology was described by DeLancey [85] only a decade ago. (*only mesh augmented incisional hernia repair procedures as they are related to mesh positioning are included here). [18, 19, 22, 23, 24, 39, 40, 41, 42, 44, 73, 77, 79, 80, 147 148 149 150 151 152 153 154 155 156]

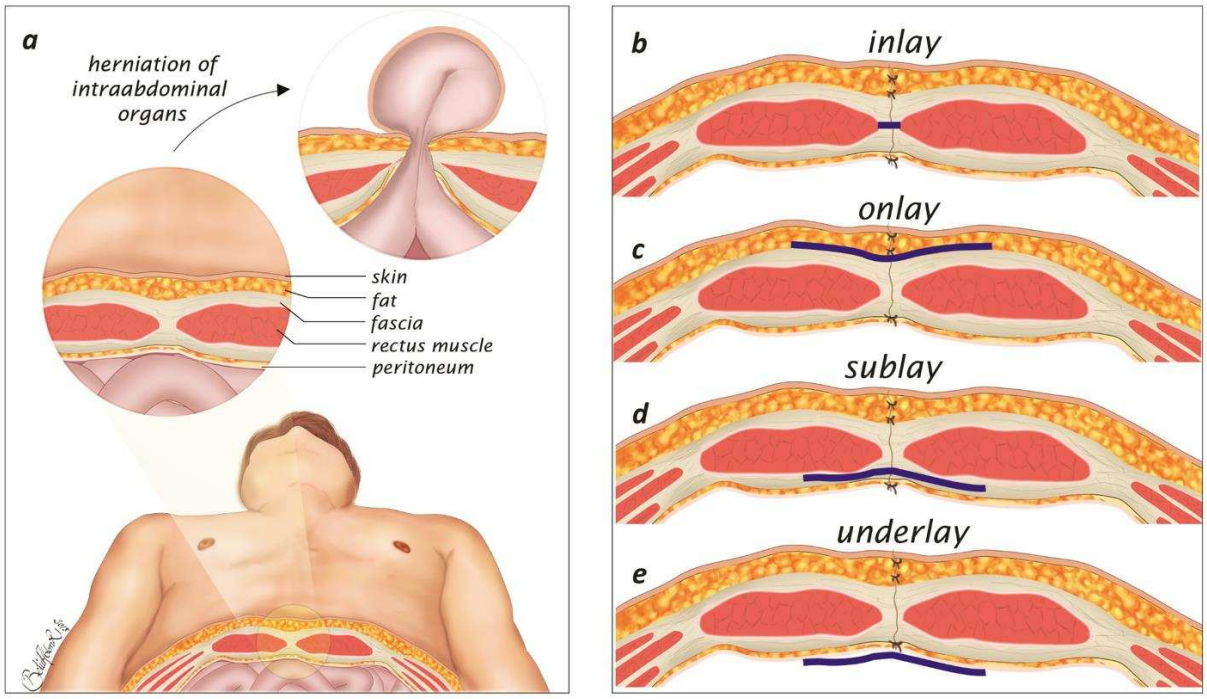

Figure 2. Mesh positioning in relation to muscle and fascia in incisional hernia repair. (A) A cross-section of anterior abdominal wall with a fascia defect causing herniation of the intestine. (B) Inlay mesh implantation to fit in the gap created by the fascia defect. This method was largely abandoned owing to high recurrence rates. (C) Onlay placement of mesh material to overlie and reinforce the fascia repair. (D) In the sublay technique, the mesh is placed on a well-vascularized wound bed underneath the muscle and is in between two strong fascial layers. This technique is considered the current gold standard and is associated with reduced complication and high success rates. (E) The underlay technique started to be used after widespread use of laparoscopic surgery. In this method, a mesh with antiadhesive properties would be preferable to a polypropylene mesh to prevent attachment of intra-abdominal organs.

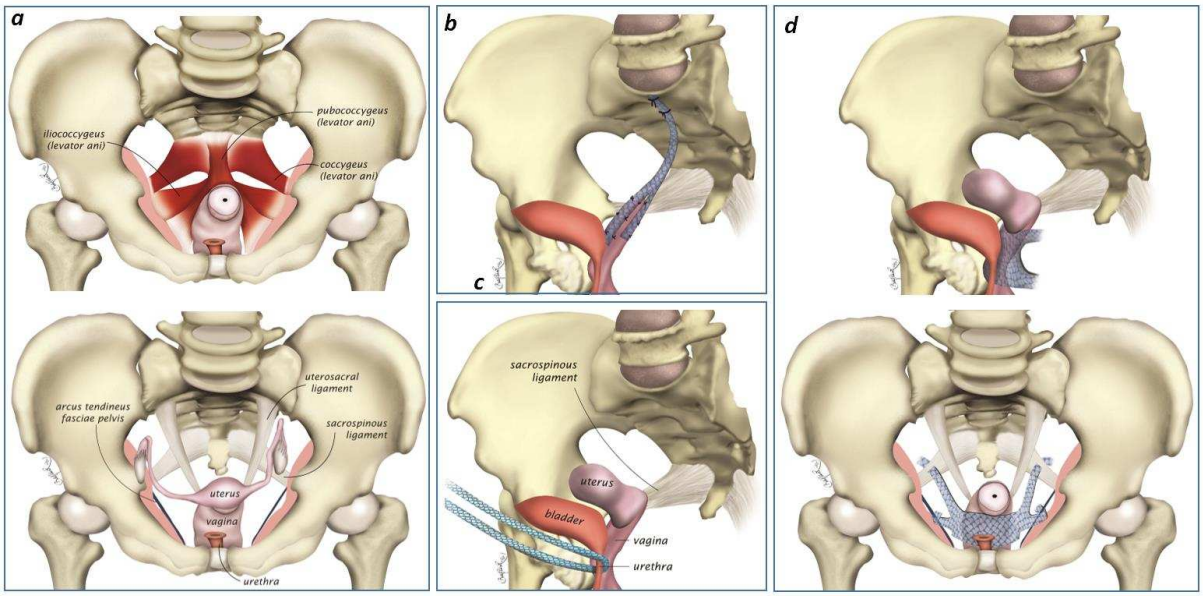

Figure 3. The most common sites of surgical mesh implantation in the pelvic floor. (A) Anatomical features commonly involved in pelvic floor surgery: pelvic floor muscles and uterosacral ligament (level I support), sacrospinous ligament and arcus tendinous fascia pelvis (ATFP) (level II support). The rectum is not included and the uterus is removed when necessary to obtain improve visibility. (B) Transabdominal placement of polypropylene (PPL) mesh to treat pelvic organ prolapse (POP) (sacrocolpopexy operations). In these operations, the mesh is secured in a fixed position and mainly experiences a unidimensional downward force. (C) Transvaginal implantation of PPL mesh at the level of the midurethra to treat stress urinary incontinence (SUI). Here, a retropubic midurethral sling is depicted. (D) Transvaginal placement of PPL mesh for POP repair, 45° lateral view and 30° anterosuperior view. Many variations of these operations exist; here, the tissue plane in which the mesh is implanted in mesh-augmented anterior colporraphy procedures (upper image) and how the mesh kits be can be used to fix the mesh to the sacrospinous ligament and/or the ATFP are shown. In both cases, multi-axial forces are acting on the mesh and a large area of the mesh stays in close proximity to vaginal skin, making it prone to bacterial colonization. These factors all might have contributed to occurrence of mesh related complications.

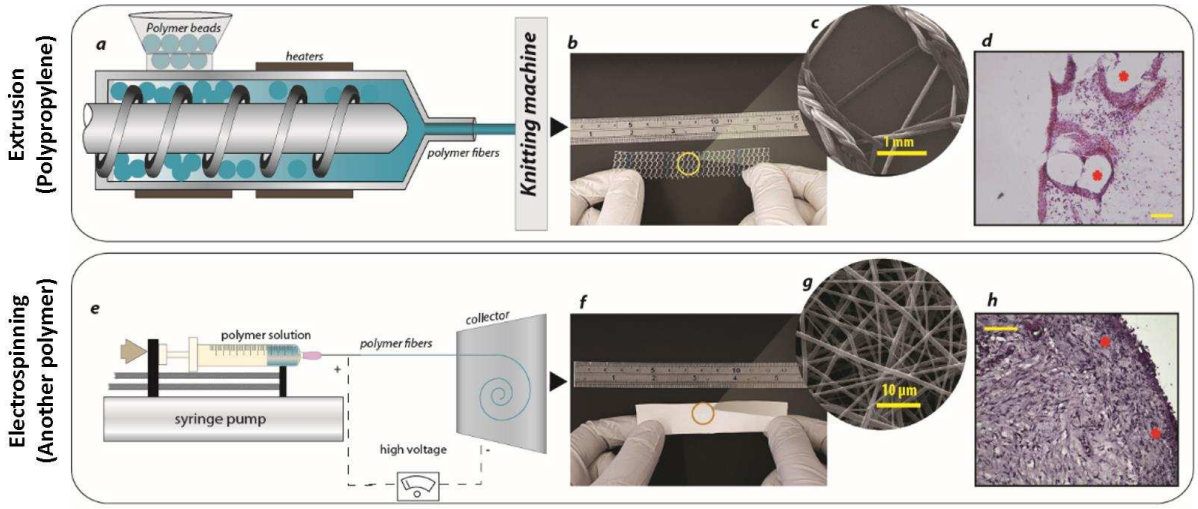

Figure 4. The industrial process used to produce monofilament polypropylene (PPL) mesh compared with a tissue engineering process called electrospinning. (A) Polymer extrusion process to produce the monofilament PPL mesh. (B) The end product of extrusion process gross view, (C) electron microscopic view and (D) the resultant tissue response to the PPL. (E) Electrospinning of another polymer to produce (F) an electrospun mat with (G) microsized and nanosized fibres with micropores in electronmicroscopic view. (H) Tissue sections of the electrospun mesh show excellent tissue infiltration. (*the mesh in tissue sections).

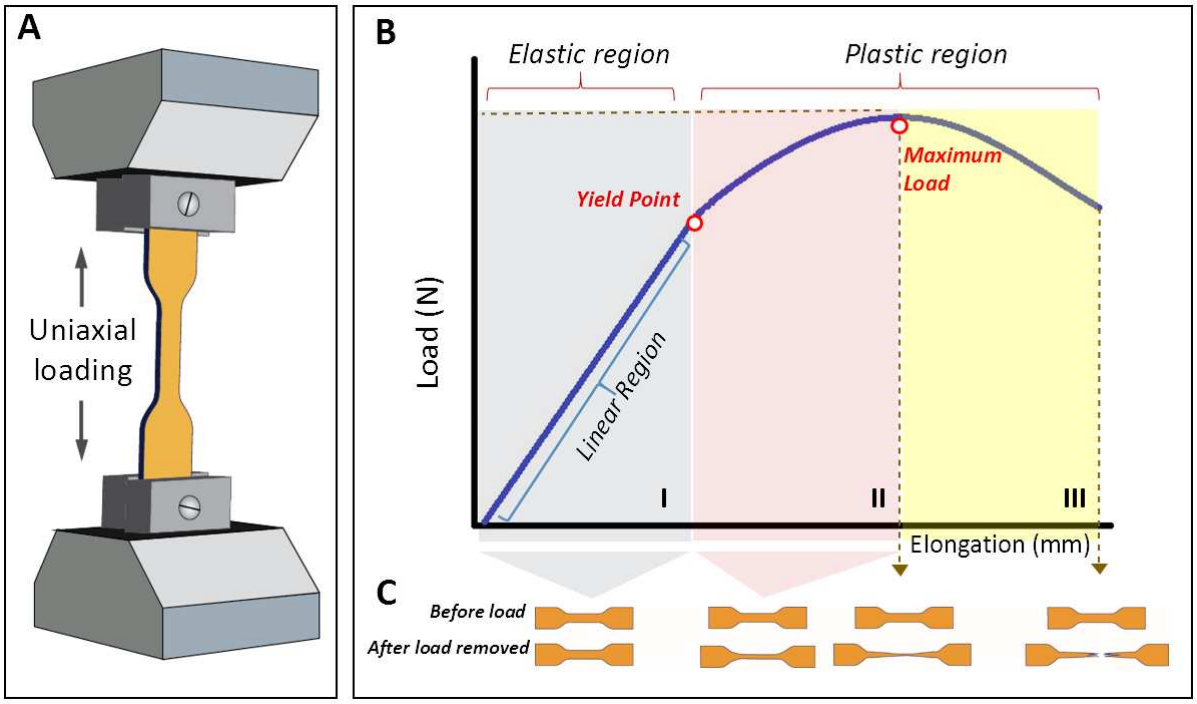

Figure 5. The basic mechanical properties of a material determined by uniaxial mechanical testing. The tensiometer setup is demonstrated in part (A). The load-elongation curve produced by this test is demonstrated in (B) with the change in appearance of the sample loaded to the tensiometer (C). The maximum 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. In region I, the material goes back to its exact size and shape after the load is removed. After the yield point (region II) plastic deformation starts and the material does not go back to its original state after the load is removed, although an obvious change in the material might not be observed. Towards the end of this region, necking of the material starts which reflects permanent deformation. Soon after the maximum load is applied the material completely fails and a fracture line can be observed. The regions are marked for graphical clarity, they do not necessarily depict the real distribution of the regions according to material elongation.

Box 1. Problems in mesh development for pelvic floor repair

1. Lack of appropriate regulations for approval of medical devices

a. Devices granted approval with no or limited clinical data

2. Lack of understanding of female pelvic floor disorders

a. Structural and functional complexity of female pelvic floor unclear

b. Pelvic floor biomechanics not well studied

c. Targets for surgical treatment generally poorly defined, particularly in transvaginal pelvic organ prolapse repairs

3. Problems related to the material

a. Surgical mesh not designed for use in pelvic floor

b. Limitations in available material processing technologies and materials at the time

c. Polypropylene considered inert; however, surface degradation occurs

4. Factors related to surgical technique

a. Proximity of large areas of mesh implant to mucosal wound

b. Implantation of mesh onto a poorly vascularized wound bed

5. Lack of relevant animal models of efficacy and safety

Box 2. Problems following widespread clinical use of the mesh for SUI and POP.

1. Lack of post marketing surveillance

2. Poor patient selection

a. Poorly defined disease subgroups

b. One-size-fits-all approach

3. Factors related to operating surgeon

a. Poor subspecialty training on management of all aspects of stress urinary incontinence and pelvic organ prolapse

b. Minimally invasive operations perceived as easy to perform

4. Extensive marketing

Table 1. Mesh success and complication rates in incisional hernia repair and the pelvic floor.

Surgery	**Composition of the proposed target tissue**	**Mechanical loading of the mesh at the site of implantation**	**Success rate* (follow-up duration)**	**Serious mesh-related complications**
Abdominal (incisional) hernia repair	Fascia	Biaxial	86.8- 88.8% (5 years)	4.5% (5 years)
SUI (Mid-urethral sling)	Mostly fascia	Uniaxial	43- 93% (>5 years)	4% (5 years)
Abdominal POP repair (sacrocolpo(hystero)pexy)	Fascia	Uniaxial	93-95% (7 years)	6-10% (7 years)
Transvaginal POP repair (Vaginal colpo (hystero)pexy; Anterior and colporrhaphies)	Fascia plus smooth muscle plus ECM (poorly defined)	Biaxial and/or multiaxial? (poorly defined)	53- 82% (7 years)	Up to 42% (7 years)

Comparisons were made related to the definition of the target tissue that is being replaced in these surgeries and the loading conditions of the mesh at the site of implantation. (*definition of success is not standard please check the references for further information)

Table 2. Comparison of polymer processing methods of extrusion and electrospinning.

Component or process	**Extruded mesh**	**Electrospun mesh**
Raw material	Polymer beads	Polymer beads
Additives	Yes	No
Liquifying process	Heating	Dissolving
Manufacturing principle	Extrusion	Electrical field
Post process	Knitting	None
Sterilization	Autoclave	Good Manufacturing Practice
Pore size	>70 micrometers	1-10 µm
Fibre size	300-500 µm	1-10 µm
Tissue integration	Poor	Excellent
Level of technology	Industrialized process	Tissue engineering process

Author contributions

N.M. researched data for the article, all authors made substantial contributions to discussions of content. N.M., B.A.D. and S.M. wrote the manuscript and N.M., C.R.C. and S.M. reviewed and edited the manuscript before submission.

Competing interests

NM, BAD, SMN declare no competing interests. CRC has been involved in the development of bio- engineered alternative to conventional synthetic sling materials with Symimetic Ltd.

Publisher's note