Host–biomaterial interactions in mesh complications after pelvic floor reconstructive surgery

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Abstract

Polypropylene (PPL) mesh is widely used in pelvic floor reconstructive surgery for prolapse and stress urinary incontinence. However, some women, particularly those women treated using transvaginal PPL mesh placement for prolapse, experience intractable pain and mesh exposure or extrusion. Explanted tissue from patients with complications following transvaginal implantation of mesh is typified by a dense fibrous capsule with an immune-cell rich infiltrate suggesting that the host immune response has a role in transvaginal PPL mesh complications through the separate contributions of the host (patient), the biological niche within which the material is implanted, and biomaterial properties of the mesh. This immune response might be strongly influenced by both the baseline inflammatory status of the patient, surgical technique and experience, and the unique hormonal, immune and microbial tissue niche of the vagina. Mesh porosity, surface area and stiffness also might have an effect on the immune and tissue response to transvaginal mesh placement. Thus, a regulatory pathway is needed for mesh development that recognizes the roles of host and biological factors in driving the immune response to mesh alongside mandatory mesh registries and the longitudinal surveillance of patients.

[H1] Introduction

More than one in ten women will undergo one or more surgeries for pelvic organ prolapse (POP) or stress urinary incontinence (SUI) during their lifetime.[1,2] Symptoms of POP commonly include the presence of a vaginal lump or bulge and/or the sensation of heaviness or dragging in the vagina and SUI refers to the involuntary loss of urine associated with exertion.[3] Historically, a range of native tissue procedures have been used to treat both conditions, utilising dissolvable sutures and patients' own tissues to restore anatomy. Such techniques for POP, for example uterosacral ligament suspension of the vaginal apex, are often associated with a high rate of failure, with recurrence rates as high as 70% at 5 years.[4] Native tissue procedures for SUI, such as autologous fascial sling and colposuspension, are both associated with the morbidity of open abdominal surgery.[5] The desire to reduce failure rates of native tissue POP surgery and avoid the morbidity of native tissue SUI procedures led to the exploration of utilising biomaterials to augment such pelvic floor reconstructive procedures. The application of these biomaterials for the treatment of SUI in the form of the synthetic mid-urethral sling has been largely successful; however, transvaginal placement for prolapse has been more controversial, probable as a result of the large volume of implant and surgical dissection required to support the vaginal wall reconstruction.[5,6] Indeed, all mesh augmented procedures for POP and SUI are now recognized as having morbidity specifically attributable to such biomaterials.

Synthetic biomaterials have received particular attention for their use in the treatment of POP and SUI owing to their homogenous properties (more uniform chemical composition and more reliable strength and degradation) and the ability to manipulate their mechanical properties, such as stress and stiffness, with polypropylene (PPL) mesh being the most commonly used synthetic material.[7–9] Synthetic mesh implants have been widely used to support the abdominal wall in abdominal hernia repair since the 1960s[10], and in the 1990s to early 2000s, transvaginally inserted mid-urethral PPL mesh became the gold standard for the treatment of SUI and POP.[11]. PPL mesh is comprised of non-absorbable monofilament PPL woven into a mesh structure and its material properties depend on many factors in the manufacturing process, such as the molecular weight of PPL and the type of weaving which influences the stress and strain of the mesh.[12] Novel materials, such as polyvinylidene difluoride and polytetrafluoroethylene have emerged as replacements for PPL mesh and are thought to have improved biocompatibility and be more resistant to degradation, but the available evidence of the outcomes from surgery using these materials compared with PPL is limited by small participant numbers and short follow-up duration.[13–15]

Synthetic meshes for the treatment of POP are inserted either transvaginally or transabdominally; the mode of insertion has distinct effects on complication rates and adverse events.[11,12,16–18] Results from large-scale clinical trials have generally supported the use of mid-urethral PPL mesh for the treatment of SUI and the transabdominal placement of mesh for the treatment of POP, but the transvaginal placement

of mesh for the treatment of POP remains contentious with a greater number of women presenting with severe complications than in those women treated with transabdominal mesh.[17,19–21] Consequently, uncertainty regarding the use of PPL mesh exists in the medical community, with ongoing litigation and the involvement of political and regulatory bodies.[22] In response to safety concerns and regulatory conditions, many mesh products, particularly those used in transvaginal POP repair, have been discontinued.[23–27]

A successfully implanted biocompatible biomaterial will induce a regulated host immune response for its specific application, remain relatively undetected by the immune system, and integrate with the patients' tissue.[28] By contrast, an unresolved, chronic inflammatory response can contribute to complications including pain and tissue damage that occur in some patients following material implantation.[29] Mesh biocompatibility is dependent on the tissue response to the material, therefore, the same material can be biocompatible in certain applications or even in certain patients, but not in others. The underlying mechanisms leading to an adverse host response to PPL mesh in patients, particularly those undergoing transvaginal POP repair, are unclear.[20]

The host response to mesh in patients with POP has received less research focus than the human host response to mesh in the abdominal wall or animal host response to mesh in the pelvic floor.[30–33] An understanding of the human host-mesh interaction is necessary to understand the causes and progression of complications in this patient group. The host response to any implanted material includes factors that relate to the host, such as their age or body mass index (BMI), the biological niche within which the material is implanted, as well as biomaterial-specific properties, such as surface degradation or porosity, that influence the immune response.[34]

This Review will summarize the understanding of these factors that contribute to inflammation and mesh complications in the pelvic floor, especially in women in whom mesh is implanted transvaginally, as an improved understanding of mesh complications will enable the future development of mesh with increased efficacy and safety. Notably, although mesh associated complications are recognized in all forms of mesh-augmented procedures, they are particularly high in those procedures that involve transvaginal placement for the treatment of POP, a procedure for which the native tissue alternative remains largely unsuccessful; consequently, much of this Review focuses on this aspect of mesh augmented pelvic floor procedures.

[H1] Defining mesh complications

Complication rates in patients who receive mesh for the treatment of POP and SUI vary between 5 and 42%, with a proportion developing serious, life-changing adverse outcomes.[17,19–21,23,25,35–37] The most common complications include chronic abdomino-pelvic pain and mesh exposure through vaginal tissue,

although multiple complications can occur together (Box 1).[38] The risk of a substantial complication requiring reoperation and/or mesh removal following insertion of a PPL mid-urethral sling for SUI is ~2–3%,.[20] with the risk in vaginally inserted mesh for the treatment of POP being ~12–13%.[17] When mesh is inserted abdominally for vaginal vault prolapse the risk is 2–3%, although some long-term studies utilising early microporous meshes report rates as high as 10%.[39] In an attempt to further reduce the risk of such complications, the past decade has seen the advent of uterine or cervical sparing abdominal mesh insertion procedures to reduce risk of prolapse. The limited data that are available for such procedures, such as hysteropexy, suggest that fixating mesh on the uterus rather than the vagina might further reduce the risk of mesh associated complications, to as low as 0.4%.[40]

Despite chronic pain being the most common adverse event associated with pelvic floor mesh-associated complications, the relationship between pelvic floor surgery more generally and chronic pain remains poorly understood. The aetiology of pain is complex and influenced by factors including genetics, psychological status, physical trauma and endocrine components.[41] Chronic pain that lasts for >6 months is highly prevalent in the adult population, affecting at least one in five adults.[41,42] This high population prevalence, coupled with the failure to include validated assessments of pain as outcome measures in studies of pelvic floor procedures, makes it difficult to draw conclusions about the role of mesh in chronic pain. Indeed, pain and dyspareunia are recognised features of native tissue repair of POP; a meta-analysis of 11 studies (n=764) reported similar rates between groups both with and without mesh augmentation (relative risk (RR) 0.92, 95% CI 0.58–1.47).[43] Thus, in the context of mesh, whether pain is a result of the surgery itself, the presence of the mesh prosthesis, or a pathological process related to the prosthesis remains unresolved. Proposed mechanisms for pain related to mesh prostheses, in addition to the direct tissue trauma associated with surgery, include an abnormal immune response and mesh contraction with associated myofascial disruption.[44,45] Fibrosis surrounding mesh has also been directly associated with pain after mesh placement.[46] Clinical data show that mesh removal in those patients with pain might fail to resolve symptoms for some patients, and for others can even exacerbate their pain.[35,38,47,48] This finding raises questions as to the role of the mesh prosthesis itself in the aetiology of the pain as opposed to it being attributable to surgical trauma more generally, and the efficacy and validity of mesh explantation surgery solely for the resolution of pain symptoms.

[H1] Patient-specific risk factors

Severe mesh complications only occur in a small proportion of patients, suggesting that patient-specific factors could be an important determinant of the response.[38,49,50] For transvaginal mesh placement for the treatment of POP, results from a prospective randomized study (n = 353) found that giving birth to > 2 children (odds ratio (OR) 2.64, 95% CI 1.0—6.51), smoking (OR 3.48, 95% CI 1.18–10.28), aged >65 years (OR 1.04, 95% CI 0.42–2.59), and the presence of an underlying somatic inflammatory condition (OR 5.11, 95% CI 1.17–22.23) were all independently associated with mesh extrusion or exposure.[51]

Results from one of the few long-term randomized controlled trials of mesh for POP (n = 322), the Colpopexy and Urinary Reduction Effort (CARE) study, found that concurrent hysterectomy (OR 4.9, 95% CI 1.9–12.4, $P = 0.0009$) and smoking (OR 5.2, 95% CI 1.7–16.0, $P = 0.009$) to be significant risk factors for mesh extrusion or exposure at the 2-year follow up period.[52] Outcomes from the only systematic review and meta-analysis of risk factors for mesh exposure after pelvic floor surgery (both POP and SUI) which pooled data from 25 studies including 7,084 patients, found that older patients (classified as ≥ 60–70 years depending on the study) had a significantly lower risk of mesh erosion (OR 0.96, 95% CI 0.94–0.98, $P < 0.001$) compared with younger patients, as well as an increased risk associated with having given birth to >1–2 children (OR 1.27, 95% CI 1.07–1.51, $P = 0.006$), being premenopausal or undergoing oestrogen replacement therapy (OR 1.36, 95% CI 1.03–1.79, $P = 0.03$), the presence of diabetes mellitus (OR 1.87, 95% CI 1.35–2.57, $P < 0.001$), and amongst smokers (OR 2.35, 95% CI 1.80–3.08, $P < 0.001$).[53] Results from a retrospective cohort study of women (n = 1439) who underwent mid-urethral synthetic sling insertion for the treatment of SUI identified several independent patient-specific risk factors for developing mesh erosion including older age (mean age 50.57 ± 8.33 for those women that developed complications versus 46.69 ± 7.34 for those women without complications) ($P = 0.02$) , diabetes ($P = 0.033$), current smoking ($P = 0.006$), body mass index ($P = 0.035$) and previous surgical treatment of POP and/or SUI (OR 0.16, 95% CI 0.06–0.45, $P < 0.001$); vaginal incision >2cm was the only surgical risk factor for mesh erosion (OR 0.15, 95% CI 0.08–0.31, $P < 0.001$.[54] Results from another large (n = 59, 887) retrospective cohort study included patients aged 45–63 years old found age to be the only patient factor associated with increased risk of developing mesh complications following SUI repair (hazard ratio (HR) 0.86, 95% CI 0.82–0.90).[18] Ageing has been shown to predict poor outcomes in many biomaterial applications, probably as a result of phenotypic and functional changes in the immune system and low-grade inflammatory activity that affects the host-implant relationship.[34,55] The mechanism underpinning how diabetes and smoking increase mesh complications is thought to be as a result of increased systemic chronic inflammation, whereas parity is thought to cause direct tissue injury to the pelvic floor.[51,56–58]

Reliably determining which patients are at an increased risk of developing complications following PPL mesh implantation for any use is currently not possible.[59] Most studies do not include controls and do not describe the mesh type used or its properties, making meta-analysis challenging and limiting generalizability. In order to collect comprehensive evidence about patient factors contributing to complications, monitored surgical registries are needed to longitudinally follow patients with mesh, identify meshes used, and link complications to mesh type, as well as other perioperative and patient characteristics. The Pelvic Floor Disorders Registry from the American Urogynecologic Society, set up in 2016, is an example of such a registry, recently developed to aggregate clinical data on POP, SUI, and other pelvic floor conditions, potentially yielding real-world data to influence practice in the future.[60] However, as is the case in many countries, the use of the registry remains voluntary and utility might be

somewhat limited owing to inclusion bias towards centres and clinicians already engaged in high-quality clinical care and research. Beyond the use of registries, biochemical analyses might also identify differences at a local vaginal level that could predispose some women to complications. Moreover, underlying pro-inflammatory conditions, such as obesity, diabetes, smoking, and ageing contribute to complications in other biomaterial applications, such as breast or orthopaedic implants[61,62], but have not been investigated specifically in POP or SUI mesh complications.[59,63]

[H1] Surgical risk factors

Surgical risk factors, such as the experience of the surgeon and surgical technique, have been linked to rates of mesh complications following pelvic floor reconstructive surgery.[18,53] Some clinical studies demonstrate that avoiding a vaginal incision suture line being in direct contact with the mesh material could decrease mesh exposure.[64,65] Additionally, patients who have had multiple mesh implant procedures have been associated with an increased rate of complications: in a retrospective cohort study of 59, 887 women that underwent mesh procedures for SUI, 1,252 women (2.1%) had multiple mesh sling implant procedures (of whom 1,191 (95.1%) had 2 and 61 (4.9%) had ≥3). In this group of women who had had multiple mesh procedures, the absolute risk for mesh removal or revision was 4.87% (95%CI 3.86–6.06%).[18] These women had a 4.73-fold increased hazard of this complication (95% CI 3.62–6.17, $P < 0.01$) and an absolute risk increase of 2.8% (95% CI 1.7%–4.1%).[18]

Concomitant procedures have also been implicated in influencing rates of mesh complications. A meta-analysis of three studies containing 835 patients undergoing concomitant POP surgery at the same time as SUI surgery demonstrated a significantly lower risk of developing mesh erosion after surgery than in patients who did not have concomitant POP surgery (OR 0.37, 95% CI 0.16–0.84, $P = 0.02$) without heterogeneity ($I^2 = 49\%$, $P = 0.14$), although there were too few studies included to conclude whether concomitant POP could be a protective factor.[53] In the meta-analysis of eight studies comparing concomitant SUI surgery at the same time as POP surgery compared with POP alone, results demonstrated no significant difference in mesh erosion.[53] A meta-analysis of 18 studies investigated whether concomitant hysterectomy with POP and/or SUI affected the risk of mesh erosion. Results from this analysis demonstrated that hysterectomy increased the risk of mesh erosion after surgery (OR 1.46, 95% CI 1.03–2.07, $P = 0.04$) with slight heterogeneity ($I^2 = 45\%$, $P = 0.02$), with no significant difference between POP, SUI or POP and SUI.[53]

Surgical experience is one of the most consistent surgical risk factors for developing mesh complications. In a retrospective cohort study of 59, 887 women who underwent mesh-based procedures for SUI, patients of low-volume surgeons (low-volume defined as being in the bottom 25th percentile for mesh

implants for SUI) had a 37% (95% CI 17–49%, $P < 0.01$) higher RR and a 0.63% (95% CI 0.36–0.92%) increased absolute risk for mesh removal or revision than in patients treated by high-volume surgeons (HR, 0.73 95% CI 0.65–0.83).[18] No difference was found in SUI outcomes between urologists and gynaecologists with the same experience, which suggests that procedure-specific knowledge and experience is important for treating SUI, rather than a specific type of operative training.[18] Similarly, results from a meta-analysis of six studies showed that patients operated upon by a senior surgeon had a significantly lower risk of mesh erosion after surgery than those operated upon by junior surgeons (OR 0.42, 95% CI 0.30–0.58, $P<0.001$) without heterogeneity ($I^2 = 46\%$, $P=0.10$).[53] However, only one of the six studies specified how senior versus junior surgeons were defined, namely that senior surgeons were consultants and junior surgeons were fellows, but even then, the relative case load or years of experience were not specified.[66]

Taken together, these findings suggest that surgical technique and surgeon experience has a role in the rate of mesh complications after POP and SUI procedures. In particular, the number of mesh-based procedures, concomitant hysterectomy, and being operated on by a less experienced surgeon seem to increase the rate of mesh complications after pelvic floor reconstructive surgery.

[H1] The host immune response to mesh

Implanting any material during surgery causes tissue injury and induces a host immune response to both the injury itself and the implanted material. The host response to the material if often termed the foreign body response (FBR). [67,68] The acute phase of the FBR initiates immediately upon surgical implantation with the adsorption of blood proteins to the material surface.[69,70] In the following minutes and hours, innate immune cells including neutrophils and monocytes are recruited in response to chemotactic cues, attach and can infiltrate porous materials (Figure 1). Adaptive, innate lymphoid, and stromal cells including fibroblasts and endothelial cells interact to orchestrate the chronic phase of the FBR in the days and weeks after implantation.[71] These multiple cell populations that can respond adaptively to the biological and mechanical cues in their environment, act in temporal concert to drive phenotypic shifts in cell behaviour, leading to the transition from acute to chronic inflammation, and tissue remodelling. The FBR culminates in the fusion of macrophages to produce foreign body giant cells (FBGCs) and the formation of a collagen-rich fibrous capsule that acts to isolate the material from the host (Figure 1).[72] In some instances, the response to a material implantation can lead to unresolved inflammation owing to the inability to phagocytose the foreign body, which can drive capsule overgrowth, scarring, and tissue contraction, which might contribute to mesh complications including pain and implant extrusion.[11,73,74]

Importantly, the FBR is an inherent biological response following insertion of any material into the body that can enable both tolerance (the absence of negative patient outcomes) and integration (efficacious

effects of the implant through restoration of tissue and patient function).[34,73,75] Modifying the FBR can, therefore, reduce capsule formation and enhance implant integration.[73] However, both tolerance and integration are in sharp clinical contrast to the response experienced by some patients with PPL meshes for the treatment of POP and SUI who suffer complications that are probably driven by a persistent, disrupted, and unresolved inflammatory FBR between host and material.[34,75] This chronic inflammatory response initiated by mesh insertion will be modulated by patient risk factors and surgical technique alongside the biomaterial properties of the mesh itself.[76,77]

[H2] The FBR to PPL mesh

A chronic FBR has historically been attributed to the persistence of M1 macrophages and extensive FBGC formation, but the presence of these cells alone is not indicative of an adverse FBR .[75,78] Within the abdominal tissue niche, excisional tissue from patients without complications after abdominal hernia repair with PPL mesh has substantial fibrosis, FBGC presence, and infiltration of predominantly M1 macrophages alongside low levels of lymphocytes and M2 macrophages. This suggests that presence of M1 macrophages and FBGCs alone does not result in an adverse FBR to PPL mesh.[79].[68] In breast implants excised for exchange or replacement surgery, IL-17 secreting CD4+ T cells and γδ-T cells and stromal cell senescence are associated with extensive fibrosis typical of the FBR.[31,68,80] Inhibition of either IL-17 signalling or stromal cell senescence prevents this fibrotic response when synthetic materials are implanted in mice. Although the role of senescent cells and IL-17 has not been interrogated for PPL nor within the pelvic floor niche, this finding indicates the complex interplay of both immune and stromal cells in biomaterial performance and the FBR, even in the absence of an adverse tissue response.[74] Materials that reach a steady state of tolerance within the adjacent host tissue are classically associated with a predominantly M2 macrophage response, minimal scarring or capsule formation and a quiescent population of resident inflammatory cells. This finding is in contrast to the postulated excessive fibrosis and immune activation seen in patients with adverse responses to implanted materials.[31,68,80]

Biological analysis of pelvic floor tissues and PPL meshes removed from patients with complications from POP repair can provide crucial insights to the mechanisms that lead to unresolved inflammation and mesh complications. Work in this area is limited, with no studies comparing PPL meshes that were tolerated compared with those meshes inducing an adverse response in patients with POP or SUI. However, some studies have examined explanted PPL mesh and vaginal tissue from patients treated for POP or SUI who had mesh removal because of pain or exposure.[29,46,63,81–84] These studies often combine patients with SUI and POP, so understanding how responses differ between biological niches is not always possible. Typical of the FBR, a fibrous capsule and a dense cellular infiltrate of predominantly macrophages has been observed around the excised tissues (Figure 1). Higher levels of both M1 and M2 macrophages have been observed in the tissues from patients with PPL mesh complications than in vaginal biopsy specimens from women who underwent benign gynaecological surgery without mesh, as well as associated increased levels of the pro-inflammatory chemokine C-X-C motif chemokine 10

(CXCL10), the cytokine tumour necrosis factor α (TNFα) and the pro-remodelling chemokine C-C motif chemokine 17 (CCL17).[29] Consistent with the literature in abdominal hernia PPL mesh[33], the ratio of M1:M2 macrophages has been suggested as an important driver in developing a pro-inflammatory or anti-inflammatory tissue phenotype[29,83,85] . Explantation of pelvic floor PPL mesh in the majority of studies discussed is as a result of complications arising 1–144 months after initial implantation, suggesting the onset of an adverse FBR can occur anywhere from a few weeks to several years after surgery, which could indicate different types of FBR and consequent complications.

Patients with complications from transvaginal PPL mesh for the treatment of POP can present with pain or exposure, but most studies in the mesh literature examine explanted mesh and tissue from patients who had mesh removed because of a primary complaint of either pain or exposure; thus, these symptoms do not always occur together.[86] Mesh-tissue complexes from patients in either pain or exposure groups have demonstrated similar histological properties (such as extent and location of fibrotic tissue), but studies examining immune cell populations suggest that these two symptoms could represent different pathophysiological responses to mesh.[46,63] In PPL mesh and tissue explanted from women with a primary report of pain following pelvic surgery, a progressive fibrotic response has been observed, characterised by a high proportion of collagen type I and III fibres and high levels of transforming growth factor β (TGFß).[29,46,63] The percentage of profibrotic and/or remodelling M2 macrophages was found to positively correlate with the amount of interleukin 4 (IL-4) and interleukin 10 (IL-10) in these patients, consistent with tissue deposition and encapsulation.[29] Patients who had mesh removed for either pain (n=17) or exposure (n=20), had higher levels of helper T cells and regulatory T cells, compared with controls (n=21), $P<0.001$. However CD8+ cytotoxic T cells were only more abundant in patients with exposure compared with controls ($P=0.032$), and compared with those patients with pain ($P=0.034$).[63]

A hypothesis for the aetiology of pain in some patients is contraction or shrinkage of the mesh implant, owing to mechanical loading and fibroblast-induced contraction as part of the FBR.[8,38] However, in patients with pain after mesh implantation, conservative management or mesh removal does not resolve symptoms in 15–49% of patients.[86,87] A reduction in T regulatory cells and an increase in TGFß have been associated with persistent pain following mesh removal,[46] which highlights that inflammation and active fibrosis can be sustained even in the absence of mesh. Future longitudinal studies that interrogate patient factors that might drive refractory cases of pain and the immune and cellular responses that characterise the FBR will be important to effectively treat these patients.

[H2] Biological niche-specific responses

Complication rates for pelvic floor applications of mesh are substantially higher in transvaginal than transabdominal placement.[12] These contrasting outcomes could be attributed to the distinct tissue niches of the abdomen and vagina. In patients undergoing PPL mesh implantation for abdominal hernia repair,

the gold-standard sublay technique has reduced complication rates.[88,89] The sublay technique implants the mesh under the rectus muscle and over the peritoneal fat and posterior sheath of the rectus muscle. The greater distance from the skin by using the sublay technique than in other techniques minimises tissue damage and risk of seroma.[90]Thus, the extent of tissue damaged during surgery might considerably affect patient outcomes following mesh implantation in other areas.

Transvaginal insertion of mesh uses an incision to place the mesh in direct contact with anterior and posterior external vaginal adventitia, which can induce tissue injury response.[91]Additionally, placement of the inserted mesh in contact with the external vaginal adventitia might further influence the local cellular environment through altering the mechanical properties of the wall and through interactions of native tissue with the mesh itself, potentially leading to prolonged alteration in the tissue properties and cell behaviour of the vagina.[5,6] By contrast, transabdominal surgical insertion for the repair of POP avoids surgical disruption of the vagina as mesh placement is within the extraperitoneal space with reduced or no contact with external vaginal adventitia. The vaginal walls present a unique biological niche: distinct mucosal tissue with a considerable immune and stromal cell population that can contribute to the FBR.[92–94] Vaginal-resident immune cells include macrophages, natural killer (NK) cells, T cells and plasma cells, with a bias towards immunoglobulin G (IgG) secretion when compared with extra-vaginal mucosal epithelia.[93,95,96] A vagina-specific resident lymphocyte population of cervical langerhans cells, CD14+ dendritic cells. CD14- dendritic cells and CD14+ macrophages further define the vaginal niche.[78] These epithelial and sub-epithelial lamina propria resident antigen presenting cells all drive CD4+ T cell activation towards secretion of Th1 cytokines, enabling an adaptive innate response against stimuli.[78] In premenopausal women, the vaginal environment is subject to hormonal changes during the menstrual cycle and pregnancy, with oestradiol levels correlated with number of T regulatory cells.[97,98] In post-menopausal women (who more commonly suffer from POP), the number of T regulatory cells is reduced, and is comparable with pre-menopausal women in the luteal phase of the menstrual cycle, suggesting increased immune activation in the vagina.[98] Hormonal effects on abdominal niches are less likely to be as important in patients with transabdominal hernia repair or transabdominally inserted mesh for POP. Immune and stromal cell response to the tissue injury after transvaginal mesh insertion might further be altered by the acidic environment of the vagina with its unique lactobacillus-dominated microbiome, with one study reporting alterations in relative amounts of lactobacillus, streptococcus, staphylococcus and gardenerella species between controls and patients with PPL mesh for POP exposure.[99,100] The distinct innate and adaptive immune activity in the vagina compared with the tissues disrupted by transabdominal POP and abdominal hernia repair could, therefore, contribute to the complications associated in some patients with POP treated with transvaginal PPL mesh.

Transabdominal or transvaginal PPL meshes for the repair of POP are implanted within a damaged tissue environment that will be biologically distinct from that of patients undergoing transvaginal treatment for

SUI. Even comparing transvaginal insertion of mesh for POP and SUI, POP involves a larger incision throughout the vagina, increased tissue dissection, higher mesh volume overall, and a higher mesh volume in contact with the vaginal environment than in mesh placement for the treatment of SUI.[5,6]. Furthermore, factors such as age, increased parity, BMI and grade of prolapse are thought to increase the risk of developing complications in response to PPL mesh implantation, as they are associated with local and systemic changes in the immune and stromal cell environment.[11,101–103] Most patients with POP are peri-menopausal or post-menopausal at the time of initial surgery, therefore, the majority of patients (even those patients who do not develop complications) will be subject to inflammaging, which is a low-grade, chronic, systemic inflammation established during physiological ageing.[104,105] Notably, CD4+ T cells from 60 year olds compared with 30 year olds, preferentially activate towards a Th17 associated profile, with the associated increase in IL-17 that can increase the FBR to synthetic materials and might, therefore, affect the response to PPL mesh.[106] The effect of age on propensity to suffer complications following PPL mesh insertion for POP and SUI is inconsistent, with studies showing both increased and decreased likelihood of adverse events with ageing. However, ageing probably affects interactions between mesh and the mechanical, cellular, cytokine and lipid mediator environment at the implant site.[107,108] The effects of age on the FBR remain to be delineated, but recruitment of macrophages to PPL mesh is delayed in young adult compared with aged mice, suggesting temporal changes in the FBR.[109]

The process of inflammaging is also associated with changes in tissue architecture, increased tissue stiffness, low-grade chronic inflammation, increased cell senescence, and a reduction in macrophage efferocytosis.[105,110,111] Pelvic tissues from patients with POP also show increased senescence, consistent with inflammaging, and infiltration of mast cells and neutrophils, compared with patients without POP, although studies across the severity of mesh-related POP complications are lacking. However, these studies suggest that the pelvic environment is already inflamed even prior to mesh exposure and this may impact tissue response to PPL mesh.[112,113] Given the role of tissue remodelling, stromal cell senescence and immune cells in the FBR, and the effect of host characteristics including mode of tissue damage, age and BMI on local and systemic inflammation, considering these factors when evaluating current and future uses of biomaterials for the treatment of POP is important.

The FBR exists on a spectrum that spans integration, tolerance and adverse responses that can lead to implant complications. To prevent adverse responses to PPL in the treatment of POP, an understanding of the drivers of the extreme and polarized negative response experienced by a subset of patients is crucial. However, the ability to assess the host and niche factors driving negative patient outcomes in some, but not all patients, will rely not only on excisional tissue from patients with complications, but also from those patients with successful outcomes to understand the biology of the healthy pelvic floor. In an ideal control group, a tissue biopsy would be performed before mesh implantation and followed longitudinally, to ascertain baseline drivers of tissue response in women that develop complications and

those women that do not. Investigating mesh removed from patients with and without adverse responses (for example, pain and/or exposure) is important to determine to what degree these complications exist on the same pathophysiological spectrum. Adoption of well-controlled studies using multimodal cellular analysis alongside clinical surveillance would enable substantial improvements in mesh evaluation and development.

[H1] Influence of biomaterial properties

The host response to a biomaterial is influenced by material properties (Figure 2). Surface material properties (for example, surface degradation and local mechanical properties) as well as bulk material properties (for example, porosity and surface area) are influenced by the chemistry of PPL mesh. These properties directly affect how cells interact with mesh and the degree of integration between host tissue and mesh.

[H2] Oxidative stress

Oxidative stress occurs when the production of reactive oxygen species (ROS) surpasses the antioxidant capacity of cells and tissues.[114] ROS contribute to the recruitment and the function of leukocytes and macrophages, highlighting the importance of oxidative stress in the orchestration of inflammation and fibrosis.[115] The role of PPL surface degradation contributing to oxidative stress and its effect on the host response to mesh is an area of interest, although the evidence is currently limited.[12,116] A relationship between oxidation of PPL and surface degradation might exist, but ROS can also directly act as chemo-attractants and signalling molecules to influence the immune response to the material (Figure 2, part a).[45,55,72,114,116,117] Notably, oxidative stress can occur independently of material processes, for example through macrophage production.[8,114]

Surface degradation implies that a loss of material occurs on the surface of the mesh, but its tensile strength remains largely intact.[118] Surface degradation of PPL mesh by oxidation has been shown in vitro[119] and in vivo[45,116,120], and is thought to be exacerbated by movement-induced friction between the mesh and tissue.[121] Explanted mesh implants have been shown to have extensive surface cracks, thickening of the outer layer of degrading PPL, and entrapment of inflammatory cells and matrix in the cracks.[116] However, a potential major confounding factor in studies of explanted mesh is the use of formalin fixation prior to analysis, as the cracked layer that has been identified as degraded polymer has also been shown to be an adsorbed protein-formaldehyde coating.[122] Moreover, merely the adsorption of proteins to the PPL surface could account for some reports of mesh cracking in which surface irregularities are observed.[119] Adsorption of proteins to biomaterials by the Vroman effect provides additional biological, chemical and topographical cues to cells. The composition of the adsorbed proteins

and the orientation and conformation of individual proteins has been reported to alter immune and stromal cell attachment and gene expression, therefore, acting to regulate the FBR.[69,123,124] The chemistry of a biomaterial influences the composition and conformation of the adsorbed protein layer.[125] Thus, the evidence is unclear as to whether these observed cracks are merely adsorbed proteins or formaldehyde causing surface irregularities, or whether the adsorbed protein layer indeed influences biomaterial surface degradation by changing the accessibility of biomaterial-resident functional groups.

[H2] Local mechanical properties

As PPL meshes used for POP repair have been repurposed from hernia applications they have not been specifically designed for the mechanical environment of the pelvic floor.[12] PPL meshes are considerably stiffer than the vaginal tissue they are in contact with.[126,127] Stiffness – the ability to resist deformation under load – is an important property for meshes to sustain physiological loading. However, if the mesh is much stiffer than the surrounding tissue, the mesh bears the majority of the load and shields the tissue, a process known as stress shielding (Figure 2, part b).[128] In human studies of vaginal mesh explanted because of complications, teardrop-shaped fibromatas encapsulated mesh fibres.[63] The shape of this response is thought to be the result of repeated micromotion of a stiffer mesh against a softer vagina that results in injury, inflammation, and tissue remodelling.[63] Alongside mediating mechanical effects including micromotion, material stiffness can have direct effects on cell behaviour. Effects of stiffness are material-dependent, although increased stiffness can alter macrophage polarisation, driving pro-inflammatory cytokine release from immune and stromal cells.[129,130]Results from animal studies have demonstrated that stiffer materials increase the thickness of the fibrous capsule in the minimally-loaded subcutaneous sites in mice, suggesting both a biological and mechanical effect of material stiffness on host response.[131] Without adequate loading, vaginal tissue in non-human primates undergoes a maladaptive remodelling response, characterized by a defective extracellular matrix and poor inflammatory resolution, which could help explain why exposure and extrusion occurs in some patients.[126,127]

Most of the understanding of mechanical properties of the pelvic floor is based on animal studies or small tissue biopsies of humans, neither of which recapitulate the complex biomechanical environment of the human vagina.[12] Studies suggest that the tensile properties of mesh permanently change under loading, raising questions about the biomechanical suitability of some meshes to vaginal placement.[8] Commercially available vaginal meshes have been shown to be vulnerable to mechanical failure after 3 days of dynamic loading.[132] This irreversible deformation under dynamic loading could influence mesh exposure or extrusion and result in chronic inflammation and fibrosis.[133–135] In addition, surgical attachment of mesh to vaginal tissue using sutures provides discrete points of attachment to the vagina and points of increased load.[8] These point regions (mesh-tissue-suture interface) with high force transmission are thought to contribute to a host maladaptive remodelling response, potentially forming a site of exposure

or extrusion.[8,136] By contrast, areas of mesh that are under less tension undergo mesh wrinkling or buckling and associated pore collapse, resulting in a mechanically inferior tissue with concentrated regions of inflammatory cells, which could predispose to mesh exposure.[8,136,137]

[H2] Mesh porosity

The porous area of mesh serves as a scaffold for the subsequent ingrowth of fibrous tissue.[138] The overall porosity of mesh and pore size are factors that have been shown to influence the extent of tissue ingrowth into mesh, vascular ingrowth, collagen deposition, infiltrated cell types, and the extent of scarring.[8,12,126,139] Biomaterial porosity is a potent regulator of immune and stromal cell activation and differentiation. Mesh porosity is often described using the Amid classification, which is a widely used classification system for the physical properties of biomaterials for abdominal wall hernia repair.[140]

In hernia repair, if the mesh pores have a small diameter (<10μm), bacteria can infiltrate but macrophages and neutrophils cannot enter the pores, leading to higher rates of surgical infection.[140] Meshes with pore diameters >1000μm enable effective tissue integration (characterized by the quality of tissue around mesh fibres). Pore diameters < 1000μm are also associated with increased fibrotic responses.[140,141] In the pelvic floor, if the pores between the fibres are too small (although it is unclear what diameter is too small), the surface of the fibres can become encased by a granulomatous inflammatory reaction as part of the FBR.[142,143] Highly fibrosed tissue over mesh probably contributes to contracture and pain, and can complicate the removal of mesh; leading to permanent damage of the surrounding tissue.

PPL meshes are manufactured with a range of overall porosities and pore diameters, although how the pores change under physiological loading must be considered. Meshes used for transvaginal applications can be loaded in a uniaxial direction, which can cause pore collapse leading to mesh deformation and problems with tissue integration.[8,29,126,139] Thus, although pore diameter has a role in mesh-tissue interactions, how pores change under physiological loading must also be considered (Figure 2).

[H2] Mesh surface area

Evidence from the vaginal and hernia mesh literature suggests that mesh surface area (the volume of mesh polymer in contact with tissue) could be proportional to the magnitude and type of the FBR generated.[19] Both animal and human studies have shown that reducing the volume of mesh implanted reduces the risk of extrusion or exposure.[29,137,144,145] This finding could help explain the worse outcomes of transvaginal mesh for the repair of POP, where a higher volume of mesh is used than that for the treatment of SUI. In a rat abdominal hernia repair model, the M1:M2 macrophage ratio was increased with high-weight meshes with small pore diameter compared with with lightweight meshes with large

pore diameter.[145] In humans with PPL mesh removed for a primary complaint of mesh exposure (n=15) or pain in the absence of exposure (n=12), there was a two-fold increase in M1 macrophages *(P*=0.003) and a 2.27-fold increase in M2 macrophages *(P*<0.001) around areas of mesh knot compared with areas with a single mesh fibre. [29] In a retrospective case-control study including 133 cases and 261 controls with PPL mesh for POP, mesh volume was also found to be an independent predictor of mesh exposure (OR 6.73, 95% CI 1.12–40.63).[137]

[H1] **Potential issues in mesh development**

Device design and development is an iterative process and regulatory guidance facilitates the development of safe and effective devices; however, ultimately the responsibility for the device lies with the manufacturer. To retrospectively pinpoint specific failings that lead to device failure and recall is challenging, but some inadequate regulatory processes around device indications for use, methods of preclinical testing and post-market surveillance might have enabled unsuitable devices to reach the market. Notably, regulatory guidance differs based on location of intended sale.

[H2] Changing mesh indications

Different FBRs to mesh in the abdominal wall and pelvic floor highlight the importance of using materials that are designed for the target environment. Transvaginal PPL meshes for the treatment of POP were mostly classified as moderate-risk devices and received regulatory approval via the US FDA 510k route, by proving substantial equivalence to a predicate device already on the market (PPL meshes used for hernia repair and later PPL mid urethral slings for the treatment of SUI).[146] This change in indication for use, although appearing minor, means that meshes used for POP repair were not specifically designed with the target tissue in mind; leaving the use of the device open to unperceived risks from unanticipated host tissue-material interactions. The 510k route is widely criticised by the institute of medicine and the media, partially because proving equivalence is loosely defined:[147,148] Manufacturers are required to provide product information, such as thickness of material, pore size, tensile strength, suture pull-out strength, tear resistance, and mesh stiffness and demonstrate that it is comparable with the predicate device. However, several studies have demonstrated that PPL meshes approved by the 510k route are substantially different from their predicate device.[149–151]Meshes that were approved by the FDA based on equivalence have substantially different pore sizes and surface areas compared with their predicate device. [151] Predicate creep with mesh submissions has also been observed, where numerous small changes over a period of time have led to the development of a device very different from the original predicate device.[149,150] When 61 meshes were traced back through a chain of equivalence claims, only two unique devices (approved in 1985 and 1996) were found.[152] Neither of these devices had supporting clinical trial data at time of approval and empirical evidence from randomized trials was only available on average 5 years after approval. In response to concerns about lenient mesh regulation, the

FDA and European Union regulatory bodies in 2016 changed the classification of mesh to higher-risk devices, which are subject to more rigorous preclinical testing than moderate-risk devices.[153,154]

[H2] Unspecific pre-clinical testing

Before approval by a regulatory body, a biomaterial must undergo a risk-based exercise to evaluate the biological status of the device. Where unknowns and/or risks are still present following a review of the biological evaluation, the manufacturer might consult the International Organization for Standardization (ISO) guidance to help select a series of preclinical tests to evaluate the gaps identified. Key guidance for the evaluation of biological safety of medical devices is the ISO 10993 series (Box 2), which describes a range of in vitro and in vivo testing options that can be utilised to help provide evidence for device safety and efficacy.

Appropriate testing would typically be carried out by an outsourced contract research organisation with good laboratory practice (GLP) certification.[155] These measures ensure that the outcomes of device testing can be appropriately controlled and compared, that test results can be widely understood and that the conditions of the test and underpinning documentation can be trusted. However, in striving for standardization in preclinical testing, much of the specificity relating to the intended clinical use of the device can be lost. For example, during cytotoxicity testing (ISO 10993-5), standardized cell lines with well characterized cytotoxicity responses are used. These tests are useful as a pilot test for toxicity and as a tool to reduce the burden of animal studies for some devices, but these cell lines reveal very little about how the device will respond within the native tissue of the implantation site.[156] In the case of mesh for the treatment of POP, many of the differences in cell-material response between the abdominal and vaginal niche would be missed by using these standardized cell lines. In addition, depending on the device structure, testing is commonly performed in an indirect manner (via liquid extract or indirect contact), rather than culturing cells directly on the device itself, further removing the test from the biological environment in which the device will be used. These generic in vitro tests can ensure that a device is not grossly unsafe, but have limited ability to predict in vivo outcomes.[156] In the case of mesh, a lack of specific preclinical testing for use in the repair of POP in relevant vaginal environments could have contributed to their unsafe repurposing from abdominal hernia applications.

In vivo evaluations (where required) are covered largely by ISO 10993-6 (Biological evaluation of medical devices – Part 6: Tests for local effects after implantation) and ISO 10993-11 (Biological evaluation of medical devices – Part 11: Tests for systemic toxicity).[157,158] For permanent implantable devices such as PPL meshes for the treatment of POP, in vivo biocompatibility testing responsibility is placed on the device manufacturer to justify the selected in vivo animal model. The choice of which animal is generally

limited to the availability of standard models provided by GLP testing facilities, which can reduce clinical relevance of the model. Most laboratory animals are quadrupeds and subject their tissues to different magnitudes of loading from humans.[159] Moreover, the placement of materials at the intended site of clinical implantation is not required in animal models, confounding the ability to make direct comparisons with humans as mesh-tissue constructs in the vagina are exposed to highly specific mechanical forces and biological niche.[30,160] Thus, animal studies are not true studies of biocompatibility. An important area of future work is the development of more relevant preclinical tests that can be used to predict in vivo outcomes:[161] for example, the effect that cyclical loading has on pore diameter and surface stiffness, or how the acidic vaginal environment impacts the surface properties of PPL mesh and what cells are exposed to, are relevant questions to improve decision making about mesh safety and predictions about clinical outcomes.

[H2] Post-marketing surveillance

The limitations of using predicate devices illustrates the need for post-marketing surveillance including mandatory registries for meshes. Without adequate long-term monitoring, no substantial evidence is available to show that the devices will truly perform effectively and safely. Some patients require mesh removal as a result of severe complications years after implantation;[29,46,63,81–84] although patients can report adverse events to regulatory agencies, most patients do not know what type of mesh they have, meaning their report cannot be linked to a specific device.[25,162,163]A patient mesh registry that would enable long-term surveillance of meshes would be helpful to gather useful information about mesh outcomes.[149,164]Implant registries have been set up for other medical devices with histories of complications, such as hip[165] and breast[166] implants. Denmark has had a mesh database (the Danish Urogynaecological Database (known as the DugaBase)) since 2007 that mandates the entry of implanted prosthesis in addition to further clinical data such as patient characteristics and prior surgical history.[167] The Australian government has pledged funding for an Australasian mesh-specific registry, similar to pre-existing National Clinical Quality Registries that are used for orthopaedic and breast implants[168], and the New Zealand government has explored funding an equivalent.[169] Such prospective registries might enable comprehensive data collection about adverse event profiles of prostheses, linking specific devices to patient outcomes to prevent the retrospective identification of high-risk devices observed with the gynaecological mesh controversy.

[H1] Conclusions

The use of transvaginal PPL mesh for the treatment of both POP and SUI has caused debilitating complications in some women, including chronic pain and vaginal exposure and extrusion. Patients that experience complications often exhibit a chronic host inflammatory response to mesh. In some instances, the FBR can lead to unresolved inflammation contributing to the ongoing complications experienced by patients.

The mechanism leading to inflammation and mesh complications is not clear but will be influenced by the interaction between the patient (host factors), surgeon, tissue niche, and mesh material properties (Figure 3). Not enough information is available to determine which patients are at increased risk of developing complications; however, some evidence supports that patients with underlying pro-inflammatory conditions such as diabetes, smoking and ageing are at increased likelihood of developing adverse outcomes following mesh implantation. Surgical factors, such as a less experienced surgeon, concomitant hysterectomy, and the patient having a large number of previous mesh-based procedures, increase the rate of mesh complications. Future longitudinal studies from the time of surgery would enable identification of host and surgical factors that might be predictive of complications or an adverse response to mesh implantation.

Studies that have examined explanted transvaginal mesh and tissue from women with complications following mesh treatment for SUI and POP have shown regulated inflammation with a fibrous capsule and a dense cellular infiltrate of predominantly macrophages. However, future studies must be powered to discern between SUI and POP treatments, and between mode of mesh insertion in POP. Differences in the abdominal and vaginal biological niche, in particular the distinct immune and stromal cell environment and microbiome, probably contributes to differences in the innate and adaptive immune activity in these tissues, and the extent to which mesh can integrate successfully with the tissue. The ability to assess host and niche factors driving negative outcomes in some patient groups will rely on analysing explanted tissue from patients both with complications and those patients with successful outcomes. Mesh surface and bulk material properties are further modulators of the FBR. Meshes with large pore diameters, low surface area, and low local stiffness could be less likely to induce an adverse FBR, but these factors have not yet been evaluated in a longitudinal controlled study. The effect of PPL oxidation on the host immune response and movement-induced friction in the pelvic floor niche also warrants further investigation.

Finally, limited preclinical evidence in the pelvic floor, despite its unique biological environment, and lack of long-term surveillance are issues that have contributed to a poor understanding of transvaginal mesh complications. Changes in indications for mesh use, without transparent preclinical and clinical testing, have further clouded the reasons for poor outcomes in some patient populations. Preclinical tests that could improve prediction of in vivo outcomes in the pelvic floor are needed, such as tests that are

relevant to the biological environment of the vagina and the mechanical loading environment of the pelvic floor. Many patients show signs of chronic inflammation years after implantation, and so the routine use of mandatory mesh registries would enable longitudinal surveillance of meshes. These registries would produce prospective data and link outcomes to patient characteristics and mesh type, in order to determine who is most likely to benefit from mesh and conversely who is at risk of complications. This information could also inform the development of improved materials and better strategies for their evaluation and use.

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Key points

- Current evidence suggests that risk factors for developing complications following transvaginal mesh placement include pro-inflammatory conditions such as patient age, smoking, and diabetes, as well as surgical technique and experience.

- Explanted mesh following transvaginal POP repair from women with complications shows poorly regulated inflammation with a fibrous capsule and a dense cellular infiltrate of predominantly macrophages.

- Differences in the abdominal and vaginal biological niche probably contribute to dissimilar immune responses to PPL mesh and consequently the extent to which mesh can integrate.

- Mesh with large pore diameters, low surface area, and low local stiffness might be less likely to induce an adverse foreign body response, but this supposition has not been evaluated longitudinally.

- A lack of transparency in pelvic floor preclinical testing and post-marketing surveillance are regulatory failings that have probably contributed to the inappropriate repurposing of meshes for some patient groups.

- The ability to assess factors driving negative outcomes will rely on longitudinal studies to ascertain baseline drivers of tissue response in women that develop complications and those women that do not.

Figures

Figure 1: The host immune response to polypropylene (PPL) mesh cumulating in a foreign body reaction.

Upon surgical implantation, blood proteins are adsorbed to the surface of the mesh. Innate immune cells from the blood, including neutrophils and monocytes, are recruited in the minutes, hours and days following implantation and these cells attach and infiltrate into porous PPL mesh. Monocytes can differentiate into macrophages in the days and weeks following implantation and tissue-resident macrophages and stromal cells alongside lymphoid cells are recruited in response to chemotactic cues and further contribute to the chronic immune response. The foreign body response culminates in fusion of macrophages to form foreign body giant cells and the formation of a fibrous capsule that isolates the mesh from the host. In some cases, unresolved inflammation, capsule overgrowth, and tissue contraction can contribute to implant complications.

IL, interleukin; IFN, interferon; TGF, transforming growth factor; $CD8^+$, cytotoxic T cells; $CD4^+$, helper T cells; $CD25^+$, regulatory T cells; MMP = matrix metalloproteinase; col, collagen; CTGF, connective tissue growth factor; TNF, tumour necrosis factor; CCL/CXCL, chemokine ligands.

Figure 1 adapted with permission from Mariani et al

Figure 2: Polypropylene material properties and processes that could influence the host immune response. (Part a) Oxidative stress can influence the immune response to the mesh.[55,117] Immune cell activation can cause oxidative stress, but reactive oxygen species (ROS) can also directly act as chemoattractants and signalling molecules to influence the FBR. Limited evidence supports the role of surface degradation contributing to oxidative stress. (Part b) Stiffness mismatch between mesh and vaginal tissue could drive stress shielding; repeated micromotions between the materials could contribute to mesh deformation and poor inflammatory resolution. (Part c) Large pore diameters with low surface area could be favourable for effective inflammatory cell infiltration, but pore collapse under loading could inhibit cells from infiltrating into the material.

Figure 3: Regulated inflammation and mesh complications are influenced by the complex interaction between the patient (host factors), tissue niche, and mesh material properties. The foreign body response to mesh, and extent to which the mesh will integrate with the native tissue, is influenced by factors that relate to the host, the biological niche within which the material is implanted, as well as biomaterial-specific properties.

Boxes

Box 1|Common polypropylene mesh complications following surgery for transvaginal repair of pelvic organ prolapse (POP), transabdominal POP, and transvaginal treatment of stress urinary incontinence

The most commonly reported complications are pelvic pain, mesh exposure and/or extrusion, dyspareunia, and infection.[38,48,170] Transvaginally placed mesh for the repair of POP has the highest complication rates.[17]

[bH1] Definitions

[bH2] Pain

An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.[171]

[b1] Chronic pelvic pain
[b2] Chronic or persistent pain perceived in structures related to the pelvis; often associated with negative cognitive, behavioural, sexual and emotional consequences and symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor or gynaecological dysfunction.[41]

[bH2] Vaginal exposure[a]

A condition of displaying or revealing mesh (for example, mesh visualised through vaginal epithelium). [172]

[bH2] Vaginal or urinary tract extrusion[a]

A condition in which mesh gradually passes out of a body structure[172] (that is mesh protruding into the vaginal cavity or urinary tract).

[bH2] Dyspareunia

Persistent pain during sexual intercourse. [172]

[bH2] Infection

Multiplication of microorganisms and reaction of host tissues to the infectious agents and the toxins they produce.[11]

[b1] Can present with pain, local tenderness, redness, and purulent discharge.

[f] [a] Some studies report mesh erosion. Based on the International Urogynaecological Association and International Continence Society guidelines, erosion is replaced by a term that is more clinically specific, such as exposure or extrusion.[172]

Box 2| International Organisation for Standardization (ISO) 10993 Biological Evaluation Preclinical Testing – Manufacturers approach offers guidance for the evaluation of biological safety of medical devices [161,162]

The ISO 10993 guidance does not specify what testing is to be performed, rather the onus is on the manufacturer to observe the guidance and, taking a risk-based approach, justify what testing is and is not relevant for the device in question.

[bH1] Preclinical Testing for biological evaluation:

[b1] Perform a Biological Evaluation Review (BER) of the device.

[b2] Consider the effect of raw materials, manufacturing processes, manufacturing environment and contact materials such as packaging.

[b2] Throughout the BER consider risks to the patient and end users from a biological, chemical and physical perspective, specifically for the intended defined use.

[b1] Results from the BER will form the basis of the Biological Evaluation Plan by which relevant testing can be identified to mediate the risks elucidated from the BER, and also answer the technical competencies outlined in the Design Inputs.

[b1] Perform the testing.

[b2] For a permanent implantable device (such as mesh), testing will involve cytotoxicity testing, in-vivo testing (to assess local effects and systemic toxicity), chemical analysis, degradation studies and tests for residuals (from manufacturing process and/or sterilization).

[b1] Following the testing, a biological evaluation report will be prepared to summarize the risks identified and how the testing has proven this risk is mitigated for the device. Any residual risk remaining at the end of this process must be highlighted and further reduced or justified.

Glossary

Biocompatible: Biocompatibility is the ability of a material to perform its intended function with an appropriate host immune response for a specific application.

Microporous meshes: According to the widely used Amid classification, microporous mesh refers to mesh that contains pores that are < 10 microns in size.

510k route: Refers to a premarket submission process made to the FDA, demonstrating that the device that is to be marketed is as safe and effective (that is, substantially equivalent) to a legally marketed device.

Predicate device: A medical device that is used as a point of comparison for new medical devices seeking approval through the FDA's 510k premarket clearance pathway.

M1 macrophages: classically activated macrophages typically associated with pro-inflammatory responses in in vitro studies

M2 macrophages: alternatively activated macrophages that typically induce pro-resolving and anti-inflammatory responses in in vitro studies.

Th1 cytokines: For example, IFNy and TNFa are typically associated with pro-inflammatory responses driving immune cell activation and maturation.

Vroman effect: The sequence in which serum proteins adsorb to a surface; proteins that adsorb earlier are competitively displaced by other proteins with stronger binding affinities.

Mesh knot: Refers to a dense area of mesh fibres immediately adjacent to each other

TOC blurb

Complications related to the use of mesh in pelvic floor reconstructive surgery are related to a number of factors. This Review discusses the foreign body response, the biomaterial properties of mesh, the patient-specific and surgical risk factors and the failings in mesh development, all of which have contributed to these complications.