Interpreting the immunohistological mechanisms underpinning pelvic mesh rejection: a systematic review of existing literature

Dr Claire Mecklem (Royal Darwin Hospital), A/Prof Kylie Mansfield (University of Wollongong), Dr Zhouren Chen (Prince of Wales Hospital)

Introduction

Pelvic mesh rejection is a recognized complication faced by women undergoing surgical treatment for pelvic organ prolapse (POP); a condition where pelvic organs descend into the vagina secondary to weakened pelvic floor ligaments and musculature (Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2021). The objective of this systematic literature review was to investigate the immunohistological response to inserted pelvic mesh and identify the underlying processes contributing to inflammation at the site of mesh insertion and subsequent complications.

Aims & Methods

The aim of this systematic literature review is to characterise the immunological mechanisms underpinning pelvic mesh rejection. PubMed, Scopus, Web of Science and Cochrane databases were searched between September and November 2023, with results refined to include females aged 18-64. Search strings included "pelvic" and "mesh" or "graft" and "gynae*" and "mesh" or "graft" and "transvaginal" and "mesh" or "graft" and "transabdominal" and "mesh" or "graft" and "synthetic" and "mesh" or "graft" and "biomaterial* or "tissue engineering" or "native tissue". Topic and abstract terms included "pelvic organ prolapse surgery" or "prolapse repair" or "urogenital repair" or "pelvic floor repair". Key words included "inflammati*" or "rejection" or "complication*" or "foreign body response" or "foreign body reaction" or "FBR" or "histopathology" or "immunochemistry" or "immun*". A total of 175 papers were screened by title and abstract, with a total of 13 studies selected for inclusion: 6 human studies and 7 animal studies. Image 1 reflects how studies were included or excluded from this systematic literature review.

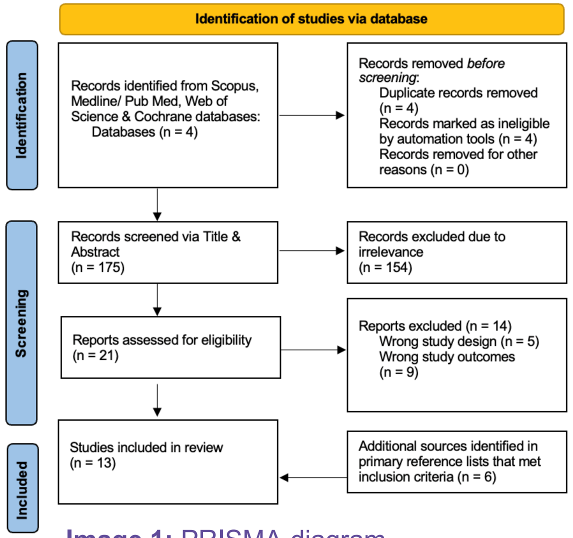
Identification of studies via database
Identification
Records identified from Scopus, Medline/ Pub Med, Web of Science & Cochrane databases: Databases (n = 4)
Records removed before screening:
Duplicate records removed (n = 4)
Records marked as ineligible by automation tools (n = 4)
Records removed for other reasons (n = 0)
Screening
Records screened via Title & Abstract (n = 175)
Records excluded due to irrelevance (n = 154)
Reports assessed for eligibility (n = 21)
Reports excluded (n = 14)
Wrong study design (n = 5)
Wrong study outcomes (n = 9)
Included
Studies included in review (n = 13)
Additional sources identified in primary reference lists that met inclusion criteria (n = 6)

Image 1: PRISMA diagram

Results

Review data reflected three key, recurrent themes: cytokine expression, inflammatory cell infiltration and tissue remodelling. It is hypothesized that these combined responses amalgamate to a foreign-body reaction triggered by insertion of polypropylene mesh, leading to inflammation, wound healing and fibrous encapsulation that contributes to host-mesh rejection. Several studies have analysed explanted mesh, identifying macrophages, neutrophils and mast cells that are well-established in acute and chronic inflammation (Dievernich et al., 2022). Various human studies (Nolfi et al, 2016; Artsen et al, 2020) have found increased expression of pro-inflammatory cytokines: including TNF-α, which is responsible for immune cell recruitment in damaged tissue and TGF-β, a potent immune regulator, which had increased expression in extracted mesh compared with adjacent vaginal wall tissue. Both these findings were similarly found in animal studies (Brown et al, 2015; Dias et al, 2016; Ai et al, 2020).

Several studies (Dias et al., Wang et al.) reported on specific aspects of the remodelling phase of the inflammatory response following mesh insertion. Authors theorised that mesh complications (ie mesh extrusion or pain) may be due to capsular overgrowth and unresolved inflammation in situ; with both studies citing increased MMP expression leading to collagen break down and fibrous exposure. This is important as in human studies majority of indications for mesh extraction were due to development of pain (secondary to mesh) or mesh exposure.

Cellular inflammatory responses were consistently observed across human and animal studies following pelvic mesh implantation. Elmer et al demonstrated significantly increased macrophage and mast cell infiltration in human vaginal tissue 12 months after mesh implantation, supporting the presence of a persistent chronic inflammatory response. Wang et al (2023) reported strong correlations between macrophage (CD68/CD163) and neutrophil (CD15) expression, with the highest neutrophil counts observed in severely degraded mesh. Increased adaptive immune cell infiltration was also identified, with Wang et al (2023) also demonstrating an association between T-cell activation (CD86) and neutrophil expression, while Eisenach et al (2021) reported increased B-lymphocyte, plasma cell, fibroblast and lymphocyte expression in vaginal tissue 12 months following mesh insertion. Following mesh explantation for pain or exposure, Tennyson et al (2019) observed increased helper, regulatory and cytotoxic T-cell populations compared with controls. Artsen et al (2019) found regulatory T-cell density was inversely associated with fibrosis, suggesting altered immune regulation may contribute to pathological tissue remodelling. Consistent with these findings, Brown et al (2015) demonstrated dense peri-fibre inflammatory infiltrates in a primate model, composed predominantly of leukocytes, including macrophages, T cells, B cells and mast cells. Collectively, these findings indicate that pelvic mesh implantation is associated with persistent innate and adaptive immune cell activation and chronic inflammation.

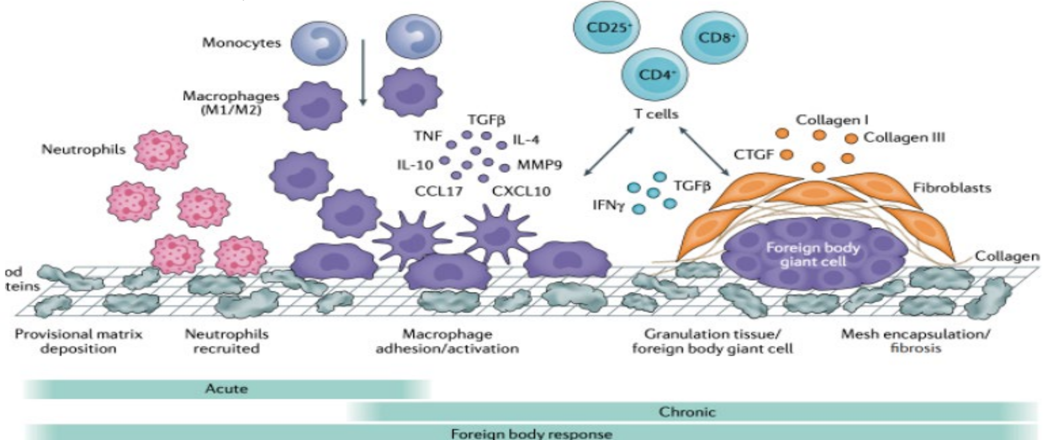
Monocytes
Macrophages (M1/M2)
Neutrophils
TGFβ
TNF
IL-4
IL-10
MMP9
CCL17
CXCL10
CD25+
CD8+
CD4+
T cells
IFNγ
TGFβ
CTGF
Collagen I
Collagen III
Fibroblasts
Foreign body giant cell
Collagen
od
teins
Key events
Provisional matrix deposition
Neutrophils recruited
Macrophage adhesion/activation
Granulation tissue/ foreign body giant cell
Mesh encapsulation/ fibrosis
Acute
Chronic
Timeline
Foreign body response

Image 2: Foreign Body Response. Taken from Abhari et al., 2021

Discussion

The mechanisms behind the inflammatory response leading to mesh rejection are complex and challenging to unravel. In human studies, the primary indications for mesh removal were pain (reported in 4 of 6 studies) and mesh exposure (also reported in 4 of 6 studies). Most pelvic mesh removed due to complications exhibits physical deformities, with mesh shrinkage, contraction, or retraction being more prevalent in women experiencing pain (Svabik et al., 2011; Rogowski et al., 2013). Although the mechanism behind pain generation remains unclear, the results of this review suggest it may arise from chronic inflammation leading to tissue remodelling with fibrotic encapsulation resulting from a persistent foreign body response (Image 2). The mesh triggers an inflammatory response, initially recruiting pro-inflammatory cytokines and activating matrix metalloproteinases (MMPs) that degrade the surrounding extracellular matrix (ECM). Tissue damage leads to tissue infiltration with inflammatory cells including macrophages, mast cells and neutrophils. Over time this then activates the acquired immune response. T cells and B cells then initiate collagen deposition hereby encapsulating the mesh to further protect the host. Mesh then gradually shrinks, exerting tension on surrounding tissues (such as the vaginal wall) and leading to pain. This hypothesis is supported by findings of Velemir et al., 2010 and Eisenberg et al., 2014, who describe removed pelvic mesh shrinkage exceeding 50% of the size originally inserted. On the other hand, mesh exposure may be precipitated by increased tissue breakdown secondary to increased MMP expression, as reflected in the study by Nolfi et al (2016). In usual healing scenarios, inflammatory cells and wound cells are triggered to release MMPs, which subsequently break down the ECM. However, when pelvic mesh is introduced, increased expression of MMPs is seen, that can then be followed with pro-inflammatory macrophage infiltration and subsequent tissue breakdown.

Strengths & Limitations

A significant limitation identified with this review was the discrepant duration between human studies (1-44 months) and animal studies (3 months). In human studies there was also a lack of "true control" group as mesh is seldom removed in those who do not experience complications. However, majority of studies did include a control group, be it autologous or matched control, which also improved result validity; adding strength to comments made about general findings. Moreover, as the study design is a systematic literature review, all included literature has been rigorously peer reviewed; increasing the credibility of claims and reliability of synthesized findings.

Conclusion & Implications for Clinical Practice

The precise mechanism underlying pelvic mesh rejection remains unclear despite multiple studies analysing the foreign body response to mesh at a cellular level. Findings from the included reviews suggest fibrous encapsulation as a host-protective mechanism possibly responsible for pain. Alternatively, mesh exposure may be characterized by increased matrix metalloproteinase (MMP) expression, leading to tissue degradation. The lack of suitable alternatives to pelvic mesh remains met with restriction via the Therapeutic Goods Administration; prohibiting its use for surgical repair of pelvic organ prolapse within Australia. This is in spite of the low levels of pelvic mesh rejection identified by articles included in this review as well as and larger reviews such as PROSPECT (2017) and Reid et al (2023). Should a feasible alternative mesh be created, it is imperative that longitudinal population studies be undertaker prior to the product becoming commercially available so as to avoid the numerous complications that pelvic mesh initially created for some patients.

RANZCOG Regional SYMPOSIUM 2026 Swan Valley

RANZCOG Excellence in Women's Health

Reference:
Abhari RE, Izett-Kay ML, Morris HL, Cartwright R, Snelling SJB. Host–biomaterial interactions in mesh complications after pelvic floor reconstructive surgery. **Nat Rev Urol.** 2021;18(12):725-738. doi:10.1038/s41585-021-00511-y.
Ai FF, Mao M, Zhang Y, Kang J, Zhu L. Experimental study of a new original mesh developed for pelvic floor reconstructive surgery. **International Urogynecology Journal.** 2020;31(1):79-89.
Artsen AM, Rytel M, Liang R, King GE, Meyn L, Abramowitch SD, Moalli PA. Mesh induced fibrosis: The protective role of T regulatory cells. **Acta Biomater.** 2019;96:203-210. doi:10.1016/j.actbio.2019.07.031.
Brown BN, Mani D, Nolfi AL, Liang R, Abramowitch SD, Moalli PA. Characterization of the host inflammatory response following implantation of prolapse mesh in rhesus macaque. **Am J Obstet Gynecol.** 2015;213(5):668.e1-668.e10. doi:10.1016/j.ajog.2015.08.002.
Dias FGF, Prudente A, Siniscalchi RT, de Vidal BC, Riccetto CLZ. Can highly purified collagen coating modulate polypropylene mesh immune-inflammatory and fibroblastic reactions? Immunohistochemical analysis in a rat model. **Int Urogynecol J.** 2015;26(4):569-576. doi:10.1007/s00192-014-2529-0.
Dievernich A, Achenbach P, Davies L, Klinge U. Characterization of innate and adaptive immune cells involved in the foreign body reaction to polypropylene meshes in the human abdomen. **Hernia.** 2022;26(1):309-323. doi:10.1007/s10029-021-02396-7.
Eisenach IA, Pichigina AK, Lapii GA, Mozes VG. Morphogenetic Aspects of the Response of Vaginal Tissues to Polypropylene Implants as the Basis of Mesh-Associated Complications. **Bull Exp Biol Med.** 2021;171(2):265-9.
Eisenberg VH, Steinberg M, Weiner Z, Alcalay M, Itskovitz-Eldor J, Schiff E, Lowenstein L. Three-dimensional transperineal ultrasound for imaging mesh implants following sacrocolpopexy. **Ultrasound Obstet Gynecol.** 2014;43(4):459-465. doi:10.1002/uog.13303.
Glazener CMA, Breeman S, Elders A, Hemming C, Cooper KG, Freeman RM, et al.; PROSPECT Study Group. Mesh, graft, or standard repair for women having primary transvaginal anterior or posterior compartment prolapse surgery: two parallel-group, multicentre, randomised, controlled trials (PROSPECT). **Lancet.** 2017;389(10067):381-392. doi:10.1016/S0140-6736(16)31596-3.
Nolfi, A. L. et al. (2016). Host response to synthetic mesh in women with mesh complications. **American journal of obstetrics and gynecology.** 215 (2), s. 206.e1–206.e8. doi:10.1016/j.ajog.2016.04.008
Reid FM, Aucott L, Glazener CMA, Elders A, Hemming C, Cooper KG, et al.; PROSPECT Study Group. PROSPECT: 4- and 6-year follow-up of a randomised trial of surgery for vaginal prolapse. **Int Urogynecol J.** 2023;34(1):67-78. doi:10.1007/s00192-022-05308-0.
Royal Australian New Zealand College of Obstetricians and Gynaecologists. (2021). Polypropylene vaginal mesh implants for vaginal prolapse. https://ranzcog.edu.au/wp-content/uploads/2022/05/Polypropylene-vaginal-mesh-implants-for-vaginal-prolapse.pdf
Rogowski A, Bienkowski P, Tosiak A, Jerzak M, Mierzejewski P, Baranowski W. Mesh retraction correlates with vaginal pain and overactive bladder symptoms after anterior vaginal mesh repair. **Int Urogynecol J.** 2013;24(12):2087-2092. doi:10.1007/s00192-013-2131-x
Svabik K, Martan A, Masata J, El-Haddad R, Hubka P. Ultrasound assessment of anterior vaginal mesh dimensions: relationship with intraoperative mesh dimensions and clinical outcome. **Ultrasound Obstet Gynecol.** 2011 May;37(5):593-7.
Tennyson L, Rytel M, Palcsey S, Meyn L, Liang R, Moalli P. Characterization of the T-cell response to polypropylene mesh in women with complications. **Am J Obstet Gynecol.** 2019;220(2):187.e1-187.e8. doi:10.1016/j.ajog.2018.11.121.
Velemir, L., Amblard, J., Fatton, B., Savary, D. & Jacquetin, B. (2010). Transvaginal mesh repair of anterior and posterior vaginal wall prolapse: a clinical and ultrasonographic study. **Ultrasound in obstetrics & gynecology.** 35 (4), s. 474–480. doi:10.1002/uog.7485
Wang H, Klosterhalfen B, Klinge U, Müllen A, Jockenhoevel S. Influence of polypropylene mesh degradation on tissue inflammatory reaction. **J Biomed Mater Res A.** 2023;111(8):1110-1119. doi:10.1002/jbm.a.37494.