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Repairing the female pelvic floor — when good enough is simply not good enough

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Abstract

Women commonly experience pelvic floor damage during pregnancy and vaginal childbirth and later develop stress urinary incontinence and prolapse. Polypropylene (PPL) mesh can repair abdominal hernias, but complications result when used in the female pelvic floor. In October, the Royal Society hosted a workshop to address issues surrounding pelvic floor disorders.

Pelvic floor disorders (PFD) such as stress urinary incontinence (SUI) and pelvic organ prolapse (POP) are very common and extremely embarrassing. As many as one in five women seek surgery to try to regain a normal quality of life free from the fear of leaking urine at the least exertion and the uncomfortable dragging symptoms of prolapse. Women are living longer and in the USA the prevalence of POP is projected to increase by 46% between 2010 and 2050.¹ However, despite being one of the most common age-related conditions, current treatments for PFD have unacceptably high revision and complication rates. Attention to and funding for research into PFDs has been neglected, limiting treatment options.

On October 16–17th October 2017, The Royal Society sponsored a workshop on tissue regeneration and re-engineering of female pelvic floor disorders. <https://royalsociety.org/science-events-and-lectures/2017/10/pelvic-floor/> At this meeting surgeons and scientists discussed why progress in this area has been so slow. By identifying gaps in our knowledge, we could then focus on identifying key questions (Box 1), the answers to which should improve quality of life for many women.

Dr Gloria Esegbona explained that one dilemma we have with managing PFD is that these occur within an integrated tract of tissues in the female pelvic region configured for women to reproduce. She pointed out that not all women who suffer maternal injuries of childbirth develop PFD later in life. Do some have improved capability to regenerate damaged tissues and can we impart this capability to other women? How to answer these questions and

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Further info

<https://royalsociety.org/science-events-and-lectures/2017/10/pelvic-floor/>

improve outcomes for women is a challenge and patients and surgeons need approaches they can use now.

Our knowledge of the anatomy and physiology of the pelvic floor is incomplete, and we still do not fully understand how the pelvic floor (made up of ligaments, connective tissue and muscle) functions as it responds to the demands of childbirth and ageing. Surgeons agree that pregnancy and delivery are initiating events for SUI and POP.² Although some women experience pelvic floor disorders immediately after childbirth, most women develop SUI and POP around the time of menopause, when the maternal injuries of childbirth are compounded by ageing and contributing factors such as obesity and diabetes.^{3–5}

Part of the problem is fragmentation of the field. Modern medicine is divided into silos of responsibility into which a condition that can take 20 years to develop does not fit neatly. Furthermore, over the past decade researchers have found it difficult to obtain funding to develop new materials and to work in this area, owing to refusal of some manufacturers of polypropylene (PPL) mesh to acknowledge that a problem exists. Finally, the problem has remained invisible because embarrassment has discouraged women from reporting SUI and POP. However, they are now speaking up because of the severity of the side effects associated with the use of PPL mesh⁶, which are extreme enough that they overcome reticence and embarrassment.

To predict which patients will experience the most damage from vaginal birth, James Ashton-Miller, Renato Natal Jorge, and Pedro Martins discussed how these patients can be identified using clinical predictive data and computational models of how the pelvis functions under the challenges of childbirth. Such models utilize clinical data and encompass mechanical and aetiological aspects of the development of female pelvic floor disorders. In addition, both standard and novel materials can in the future be introduced into such models to provide an *in silico* test of the benefits of new treatments prior to clinical trials. For example, widely accepted dogma states that PFD defects arise from a defective vaginal wall. James Ashton-Miller questioned this dogma as recent results from computation models suggest that defects in the paravaginal tissue — which can be corrected — might be the cause.

As summarized by Marianna Alperin, studies of animal models show that pelvic floor muscles undergo unique adaptations in preparation for the supraphysiological strains they must withstand during childbirth. These adaptations attenuate sarcomere hyperelongation and protect against pelvic muscle injury. They could potentially act as an indicator of damage or a predictor of which patients might be most at risk of developing PFD after vaginal delivery.

Extracellular matrix (ECM) is an important component of the pelvic floor and is dysregulated in POP patients such that the balance is tipped toward ECM degradation, reducing the strength and elasticity of the pelvic floor. As presented by Oksana Shynlova, vaginal fibroblasts produce the ECM and are abnormal in patients with POP, such that they decrease ECM protein synthesis and increase expression of ECM degradation enzymes with

stretch. Dr. Shynlova then suggested these abnormal fibroblasts could provide an objective index of the degree of POP and the reparative capability of the pelvic floor.

Regeneration can be facilitated by treatment with stem cells either alone or as a supplement to an ECM or synthetic scaffold. Margot Damaser and J. Koudy Williams explained that in most cases the regenerative effect of stem cells is via their secretions, creating the possibility of treating only with cellular secretions or other cell-derived materials.⁷ The use of endometrial-derived cells is being explored by Caroline Gargett while Margot Damaser is testing if cell-derived microsomes can stimulate tissue regeneration and prevent development of PFD. The idea of early treatment prior to Stage IV POP development was further explored by K.D. Sievert who rhetorically asked if we would wait until Stage IV to treat cancer.

Sheila MacNeil reminded workshop attendees of a 2017 consensus statement⁸ written by gynaecologists, urologists, and urogynaecologists, which concluded that surgeons are probably performing the right type of operations but with a suboptimal material. This observation raises the question of which materials surgeons should use and is reflected in the fact that some experienced surgeons have reverted to using patients' native fascia when available and if the patient's health allows it. The 2017 consensus statement concluded that patients with PFD need new materials that do not cause severe adverse effects.⁸

Three groups at the workshop reported on developing next-generation materials for repair of PFD. One approach, discussed by Stephen Badylak and Pamela Moalli, is based on materials designed from acellular ECM. Badylak described how native collagenous tissues can be used to stimulate tissue regeneration rather than scar formation, introducing to the workshop the fundamental role of the immune system in rejection or acceptance of foreign materials, potentially leading to tissue regeneration. Another approach, described by Sheila MacNeil, is based on a mesh of FDA-approved polyurethane fibres that respond well to repeated distension and are well tolerated by the immune system in animals.⁹ A further option based on the use of recombinant human collagen combined with autologous cells derived from the patient's endometrium was proposed by Caroline Gargett.

How to introduce new materials was a great topic of discussion — newly designed biomaterials are rarely fully optimized when they are first developed; instead biomaterials are designed and tested critically in the laboratory, eliminating materials that fail at that stage. Regulatory bodies then normally require that animal models be used to evaluate potential toxicity and efficacy. However, neither of these was addressed at the time of introduction of PPL mesh for repair of the female pelvic floor. Application for PFD was instead justified based on its successful prior use in the abdominal muscle (achieved over a decade of eliminating initial high density materials which caused inflammation and contraction), a very different environment from the female pelvic floor with very different requirements and outcomes.

Several groups are now working with animal models to test new materials for treatment of PFD. This type of study, more than any other was needed but missing when PPL meshes were introduced for use in the pelvic floor. Jan Deprest described his extensive experience

developing preclinical animal models to study many aspects of POP and to evaluate materials before they are implanted into patients. Both he and Caroline Gargett have begun using sheep as a relevant and accessible model for evaluating material to be introduced into the vagina for PFD. Dr. Deprest has shown that PPL meshes which do well in the abdomen cause PFD when implanted in the vagina of the same animals-definitively demonstrating the vagina is not the same environment as the abdomen.¹⁰

To conclude the meeting, Sohier El Neil stated this is a field desperately in need of collaboration between clinicians and scientists to tackle these challenges. Molecular and cellular effects of surgeries need to be considered along with the systemic effects of treatments since scientific research is the foundation of personalized medicine. Increased awareness of the problem is also needed, not only in scientific and clinical circles but also among the greater public. For too long PFD have been invisible – now it is time to own the problem and tackle it.

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Box 1 |**Key questions in tackling pelvic floor disorders**

- Can we predict which patients will experience most pelvic floor damage during vaginal birth and what can we do about it?
- How can computational models of the pelvic floor help?
- Can tissues that have responded to extreme demands undergo successful regeneration?
- What can we learn from animals about how tissues adapt during pregnancy?
- Do the symptoms of stress urinary incontinence (SUI) and pelvic organ prolapse (POP) occur because of a defective vaginal wall?
- When patients have developed pelvic floor disorders can this be detected in the fibroblasts of the vagina?
- Do we need to alter the surgical approach to the management SUI and POP or do we need materials that have been specifically designed for the environment of the pelvic floor?
- Can we develop next-generation biomaterials to be introduced with or without cells to provide long-term mechanical support for the pelvic organs without associated adverse effects?
- Do we need to add cells to a mesh material to stimulate a tissue regeneration response or will cell-derived materials be sufficient?
- How do we provide a really strong evidence base for the introduction of new materials for the management of SUI and POP?