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Commentary

Current developments in endometriosis-associated pain

Lydia Coxon,[1] Lysia Demetriou,[1] and Katy Vincent[1,*]
[1]Nuffield Department of Women's & Reproductive Health, University of Oxford, Oxford, UK
*Correspondence: katy.vincent@wrh.ox.ac.uk
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Endometriosis-associated pain is burdensome to both the individual and wider society. However, current treatment leaves many with persisting pain. Here, we highlight how recent work considering endometriosis in the context of chronic pain has altered our understanding and how this has the potential to improve clinical care.

Introduction

Endometriosis is a common estrogen-dependent inflammatory disease characterized by tissue resembling the uterine lining (endometrium) found outside of the uterus, most commonly on the lining tissue of the pelvis (peritoneum), ovary, bladder, and bowel. It is thought to affect about 10% of reproductive-aged women/those assigned female at birth (AFAB). However, as there is currently no non-invasive diagnostic test, the true prevalence remains unclear. Endometriosis is classically associated with pelvic pain symptoms: dysmenorrhea, non-cyclical pelvic pain, dyspareunia, dyschezia, dysuria, and infertility. Importantly, there is increased awareness that many with the disease experience a far broader range of symptoms, including fatigue and psychological distress. It is therefore unsurprising that endometriosis, and in particular endometriosis-associated pain (EAP), significantly impacts quality of life (QoL) and is associated with work absenteeism and presenteeism.[1] Additionally, there is an enormous associated financial cost to both the individual and society as a whole, specifically healthcare costs and those associated with an inability to work or care for a family. However, until recently, there has been little research funding allocated to the disease, especially when compared to other conditions with similar prevalences.[2]

In this commentary, we highlight the recent developments in understanding EAP and consider the implications for preclinical research, clinical trial design, and clinical practice. Due to space limitations, we mainly cite reviews but would encourage the interested reader to explore the primary literature.

Multiple mechanisms underlie EAP

Historically, endometriosis has been considered purely nociceptive, with localized inflammation around the lesions giving rise to pain, and both research and clinical practice have mainly focused on these peripheral lesions. However, current understanding suggests that a large variety of factors give rise to and maintain EAP, helping to explain the well-established lack of a relationship between the extent of disease and symptom severity (Figure 1). Local pelvic mechanisms remain important, and we now better understand the role of neoinnervation within lesions and associated neuroimmune interactions.[3] The most common site for lesions is on the peritoneum, but lesions are also found within viscera. Given that the parietal peritoneum is innervated by both somatic and visceral afferent nerves—whereas the visceral peritoneum is innervated by the autonomic nervous system—and many of the associated symptoms are visceral (e.g., dysmenorrhoea, dyschezia, and dysuria), it is not surprising that visceral hyperalgesia is common, and viscero-visceral referral is likely to be an important mechanism generating pelvic comorbidities.[4] This may be particularly relevant as a sequela to endometriosis-associated dysmenorrhea. Although there is a solid knowledge base relating to the gut-brain axis, the gut microbiota's role in pain processing is still emerging, and this is an exciting area that is only just beginning to be robustly explored in the context of endometriosis.[5]

The combination of neoinnervation and pelvic inflammation along with exposure to repeated surgical interventions may explain the observation that a neuropathic-like component appears to be present in up to 40% of women with EAP.[6] More recently, there has also been interest in the third type of chronic pain, nociplastic pain, in the context of endometriosis. Altered sensory processing in those with EAP likely reflects a combination of peripheral and central mechanisms,[6] and there is increasing literature suggesting that changes in the structure and function of the brain are similar to those seen in other chronic pain conditions.[3] Using screening tools, a number of groups have identified the presence of a likely nociplastic component to EAP. Interestingly, this appears to be associated with both greater symptom burden and an increased likelihood of persistent/recurrent pain after surgery.[6] Given that nociplastic pain has been defined relatively recently, and there are not yet specific criteria to determine its presence in visceral pain, we expect this to be an area with rapidly increasing interest in the near future. It is important to remember that these pain mechanisms may occur separately or concurrently, and how best to identify them clinically and their relevance to therapeutic options are areas of great potential and interest for future research.

The clinical presentation of those with EAP is complex

Recent literature highlights the varied symptomatology of endometriosis and its overlap with other medical conditions,

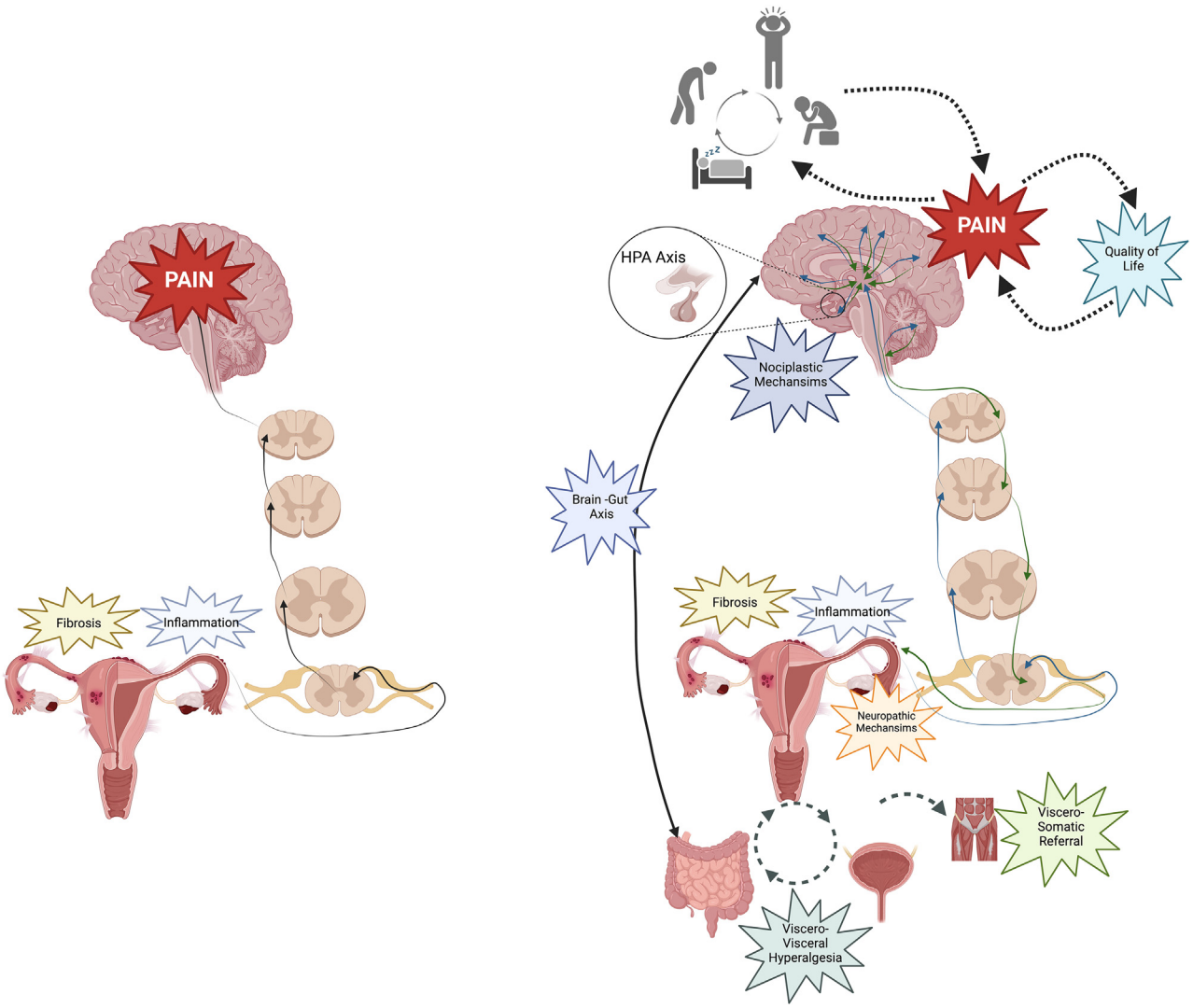

Figure 1. Illustration of the historic (left) and current (right) understanding of pain mechanisms in EAP

Importantly, there is increasing understanding of the fact that EAP can involve nociceptive, neuropathic, and nociplastic mechanisms and of the importance of viscero-visceral hyperalgesia between pelvic organs, the gut-brain axis, and the hypothalamic-pituitary-adrenal (HPA) axis in pelvic pain. Furthermore, there is a bidirectional relationship between pain and psychological distress (such as anxiety and depression), fatigue, and sleep, which further complicates the picture and can contribute to the impact of EAP on quality of life (QoL) more broadly.

adding to the complexity surrounding diagnosis and treatment of EAP.[6,7] Not all patients with EAP describe the classic triad of dysmenorrhea, non-cyclical pelvic pain, and dyspareunia, and moreover, not all patients with this triad will be found to have endometriosis.[6] EAP had already been highlighted as a chronic overlapping pain condition, and comorbid pain conditions are commonly described by those suffering with EAP, both in the pelvis (e.g., irritable bowel syndrome, bladder pain syndrome) and more distant areas (e.g., migraine, fibromyalgia).[6,7] Furthermore, endometriosis is also commonly comorbid with other non-painful conditions such as asthma, chronic fatigue, depression, and anxiety.[1,6] Although there are likely to be a variety of mechanisms underlying comorbidity, recent large genetic studies have demonstrated genetic associations between endometriosis and other chronic pain and inflammatory conditions and shed light on biological pathways common to these conditions.[8]

The complex clinical presentation of endometriosis and its comorbidities, along with diagnostic challenges and often negative interactions with healthcare professionals, combine to have a significant impact on both QoL and psychological well-being for those with EAP.[7,9] For any chronic pain condition, it is important to remember the bidirectional relationship between chronic pain and psychological distress, rather than assuming that pain is secondary to poor mental health. This may be particularly true for endometriosis, where the associated symptoms are intimate, and diagnosis is challenging and usually delayed. The increasing volume of robust research exploring these relationships and potential interventions can only be positive.

However, a recent review does highlight the need for better psychological models of EAP, as a traditional fear-avoidance model, as conceptualized for musculoskeletal pain, may not be fully relevant.[9]

Importantly, there has been increased awareness over recent years that endometriosis can be present in adolescence and be associated with just as severe symptoms as in adulthood. Moreover, it's impact on QoL is also significant during adolescence, limiting physical and social activities and thus impacting both physical and mental QoL.[1] While not yet fully understood, it is important to remember that the future impact of experiencing repeated/chronic pain in adolescence is likely to be considerable given the important biological and social changes during this time (e.g., neuroplasticity, education, and growing independence).

Relevant preclinical models need to be reconsidered

Our increased understanding of the complexities of endometriosis, and in particular EAP, highlights that the classical approach to the development of preclinical models of endometriosis, where endometriotic lesions are recreated in animals, is no longer sufficient to capture/reflect the multiple mechanisms that are involved and the varied disease symptomatology. Recent reviews have highlighted how infrequently pain has been assessed as an end point in these available models.[10] Given the importance of preclinical models in disease understanding and drug development, there is an urgent unmet need for the development of novel EAP models and relevant paradigms to assess the far-reaching impacts of pain. We expect this to be an area of considerable advances in the next few years as groups with significant expertise in pelvic visceral pain increasingly explore EAP and develop models/methodologies that achieve these aims.

It is increasingly clear how important and common dyspareunia is for those with EAP,[1,6] and this is a symptom particularly poorly considered in preclinical models. Although there are preclinical endometriosis models where sensitivity to vaginal distension can be demonstrated, it remains to be seen whether this can be reversed with therapeutic strategies and whether that translates into clinical efficacy given the complex nature of female sexual pain.

Improved recommendations for clinical trial design

Moving forward, the advances in our understanding of EAP described above need to be reflected in the design of clinical trials in order to be translated into meaningful therapeutic options for those suffering with EAP (Figure 2). This is relevant both when considering how we collect outcomes but also who we recruit to clinical trials.

A wide variety of clinical trials have been undertaken in EAP, and there are currently 18 relevant Cochrane reviews. However, a recent systematic review highlights how poorly pain is assessed in these trials.[11] Considering the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations for the design of pain trials, this review highlights that although pain itself was an outcome in 98.4% of studies, other important measures such as physical and emotional functioning were much less commonly assessed (29.8% and 6.8%, respectively). Combinations of more than two pain-relevant outcomes were also rarely assessed, thus failing to capture the biopsychosocial nature of pain. Importantly, even for pain severity, there was no consistency in the tools used to measure this outcome, making future comparisons and meta-analyses challenging. Although a core outcome set (COS) for endometriosis does exist,[12] this does not fully align with IMMPACT recommendations, capturing only pain intensity, QoL, adverse events, and patient satisfaction with treatment; other recommended domains relate to fertility/pregnancy outcomes. Once again, this highlights the need for clinicians and researchers from different areas (e.g., women's health and pain) to work together rather than remaining siloed.

Real-world data highlight both the heterogeneity and the complexity of those experiencing EAP. As already described, comorbidities are common,[7,8] yet the presence of comorbidities is standardly an exclusion criterion for participation in a clinical trial, which calls into question the relevance of results to the wider clinical population. Moreover, it is well established that there are issues relating to access to both diagnosis and treatment of endometriosis in relation to race/ethnicity, gender, and class.[1] These disparities are reflected in research cohorts and clinical trial populations, potentially missing an opportunity to better understand the disease and to find treatments that are effective and acceptable to all. We hope that the current drive toward inclusive patient and public involvement and engagement (PPIE) within all stages of the research cycle will move this forward, and we are certainly aware of a number of currently recruiting clinical trials in EAP with PPIE members as active partners since the conception of the project/funding applications.

Pain-informed clinical practice

Despite the increasing volume of basic/clinical science literature demonstrating that for a large proportion of individuals, EAP is not purely nociceptive, current clinical recommendations continue to focus on treatments targeting the lesions, either by surgery or hormonal suppression.[13] There is, however, an increasing awareness that this leaves between a third and a half of women with persistent/recurrent pain and in line with this a desire to re-evaluate standard treatment strategies and/or consider those focused more on pain and QoL. A Cochrane review of surgical trials in endometriosis concludes that "compared to diagnostic laparoscopy only, it is uncertain whether laparoscopic surgery reduces overall pain associated with minimal to severe endometriosis".[14] Given the risks associated with surgery and the potential to generate neuropathic and other forms of post-surgical pain, we await with interest the results of the ESPRiT2 trial, which used robust, randomized, controlled clinical trial methodology to compare diagnostic laparoscopy to laparoscopic treatment of superficial peritoneal endometriosis.

A variety of small studies have begun to explore psychological and physical therapeutic approaches to the management of EAP.[6,13] Although they appear promising, it is too early to be certain of the benefit of these individual approaches. Many women are initially not keen about the idea of a psychological approach, and

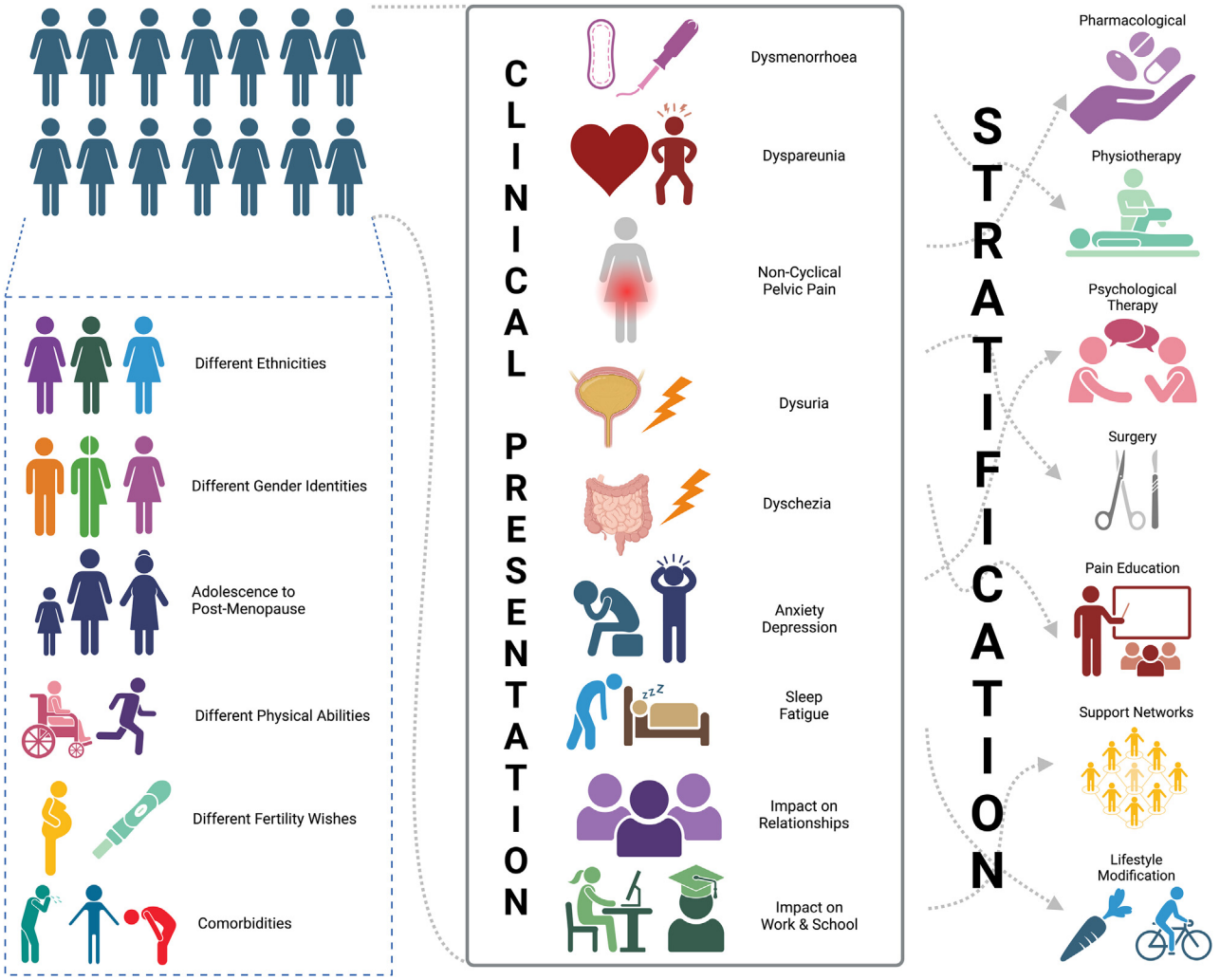

Figure 2. EAP is a complex and heterogeneous condition with both the clinical presentation and individual's priorities varying over the life course

The full breadth of this population is rarely captured in clinical trials, limiting our ability to identify acceptable and effective treatments for the wider population and hindering a move to a personalized approach to the management of this common disease.

similarly, many clinicians are wary about broaching these options, perhaps in part due to past misconceptions about the relationship between chronic pain and psychological factors as described earlier. Pain science education is likely to be helpful in positioning the role of psychology appropriately and is standard practice in other forms of chronic pain. However, it is clear that pain science education is lacking within gynecology services around the world despite the fact that it would be considered valuable by patients.[15] Clinically, the use of multidisciplinary pain management programs remains an option explored late in the patient journey, often after repeated surgical interventions. Given the success of these approaches in other chronic pain conditions, it is to be hoped that we will soon have further evidence supporting their use in EAP specifically and that healthcare systems will enable them at a much earlier stage.[6]

Conclusion

As we have illustrated, there has been huge progress in our understanding of EAP. The use of harmonized data collection tools (as available here: https://ephect.org) has facilitated collaborative projects with datasets much larger than those that could be achieved from a single center. Such collaboration has led to relatively large funding awards from both US and European grant bodies, enabling exploration of the genetics, comorbidities, and pain phenotypes of this complex disease. An understanding of EAP in the context of a chronic pain condition and the recent shift to considering it as a systemic disease rather than focusing purely on the pelvis can only be of benefit in fostering a holistic approach to the management of EAP. However, there is still much work to do to ensure that clinical trials are appropriately designed in light of this new knowledge and that regulatory bodies will accept this information. We remain a long way from a personalized medicine approach to EAP, but we are

beginning to understand what factors may be important to consider, and there is the increasing awareness that a life course approach is essential.

Importantly, public awareness of endometriosis is much greater than it was previously, and both traditional media and social media have contributed positively to this. It is hoped that greater awareness will reduce diagnostic delay and time to access pain-focused treatments, ultimately reducing some of the burden associated with EAP. However, there remains a focus on a nociceptive model of pain and a surgical approach to management, which can make alternative therapeutic approaches challenging to discuss in clinic and hard for those with EAP to engage with. It is clear that making a real impact on clinical care requires a collaborative approach, ensuring that basic and clinical scientists work together with patients, clinicians, and policy makers from diverse backgrounds and engaging with Femtech and (social) media along the way.

DECLARATION OF INTERESTS

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