

Short Commentary

Beyond the Lesions: Unraveling the Multifactorial Nature of Endometriosis and Chronic Overlapping Pain

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Endometriosis has a long and complex history in the field of medicine, with its etiology and treatment being sources of debate for many years. This estrogen-dependent neuro inflammatory disease is marked by the presence of endometrial-like tissue outside the uterus, affecting approximately 10% of women of reproductive age. The disease's symptoms are varied, with pain being a defining characteristic, including dysmenorrhea, painful intercourse, chronic pelvic pain, and bowel and bladder pain. These symptoms can be profoundly debilitating, adversely impacting quality of life and psychological health [1].

Compounding these challenges is the staggering reality that diagnosis can take 10 years or more, prolonging the suffering of those affected and underscoring the urgent need for greater awareness and more efficient diagnostic methods for the disease. Adding to its existing burden, endometriosis remains incurable, with treatments based on the suspected etiology of the pelvic pain and primarily focused on symptom relief. While such treatments can benefit those whose pain is driven by peripheral mechanisms, therapies that primarily target the periphery are often only effective for individuals experiencing anatomically localized pain. In fact, nearly 50% of medical and surgical treatments are unsuccessful, leaving patients with ongoing pain even after the suppression or surgical removal of endometriosis lesions. Moreover, there is little correlation between the extent of the disease and the severity of pain experienced, suggesting that factors beyond the lesions themselves may play a significant role in the pain associated with endometriosis. Over the past two decades, a growing body of evidence has supported this notion, indicating that endometriosis is not merely a disease defined by the presence of endometrial lesions but one that is also mediated by central nervous system factors, including altered sensory processing as well as structural and functional changes in the brain [2-7].

In recent years, endometriosis has increasingly been recognized as a heterogeneous condition that often coexists with other organic pain disorders. Collectively referred to as chronic overlapping pain

conditions (COPCs), these disorders frequently occur together and include endometriosis, vulvodynia, irritable bowel syndrome, temporomandibular disorder, chronic fatigue syndrome, interstitial cystitis/painful bladder syndrome, fibromyalgia, tension-type and migraine headaches, and chronic low back pain. COPCs predominantly affect females and exhibit a high degree of co-prevalence. Although the underlying causes of these conditions remain poorly understood, they are generally believed to share common pathophysiological mechanisms, with alterations in central nervous system processing likely contributing to the pain experienced. Substantial evidence suggests that a higher prevalence of these conditions is associated with more frequent and prolonged pelvic pain episodes, increased pain severity, impairments in daily activities, reduced treatment efficacy, and declines in psychological functioning and quality of life [8-10].

It is estimated that over 95% of patients with endometriosis report having at least one overlapping pain condition. Unfortunately, these comorbidities are often resistant to singular treatments and may even exacerbate pelvic pain severity and reduce therapeutic effectiveness. Despite this understanding, endometriosis has traditionally been classified and treated as a peripheral disease, focusing on the removal or suppression of endometrial lesions—an approach that has yielded suboptimal outcomes [11].

Why do these treatments often fall short? Given the heterogeneity of endometriosis and its common overlap with other pain conditions, one possibility is that our treatment efforts are not appropriately targeted, failing to address centrally mediated factors that impact endometriosis pain, including the multimorbidity of the disease. Recognizing this gap, our team recently conducted a study examining the prevalence of COPCs in a sample of 525 women with chronic pelvic-abdominal pain (CPP), 25% of whom also reported endometriosis. Not surprisingly, compared to women with just CPP, those with endometriosis reported more adverse pain outcomes including greater pelvic pain severity and interference, as well as a higher degree of burden associated with their pelvic pain. They also reported a higher prevalence of COPCs, including fibromyalgia, chronic fatigue syndrome, and temporomandibular disorder. Even

more striking, approximately 25% of women with endometriosis reported three or more COPCs, compared to only 12% of women with just CPP. Interestingly, a higher prevalence of COPCs was linked to more adverse pain outcomes, regardless of an endometriosis diagnosis. These findings align with previous data showing that as the number of pain diagnoses increases, symptoms become significantly more severe. More importantly, our results underscore the substantial burden that multimorbidity places on patient functioning [12,13].

Given the impact of co-occurring pain, screening and treatment of COPCs in endometriosis could be crucial steps toward improving clinical care. However, achieving effective treatments for these comorbidities is often complex, as providers frequently encounter challenges stemming from limited resources and inadequate education about endometriosis and chronic pelvic pain, making it difficult to systematically assess and manage multiple pain conditions. Additionally, patients with endometriosis often endure long, fragmented care across multiple medical specialties, with many providers lacking extensive training in pain management and focusing on treatment from their own medical lens. Unfortunately, this approach often overlooks the multidimensional nature of the disease, potentially neglecting the central mechanisms driving endometriosis pain [14].

Patients with comorbidities often face an array of challenges that can significantly hinder treatment. To make meaningful strides in disease management, it is crucial that we prioritize endometriosis care and expand the focus of treatment beyond the lesions. The presence of COPCs should be a key consideration in patient management, as those with multiple pain comorbidities likely require a broader and more comprehensive spectrum of therapeutic targets to effectively manage their symptoms. Alongside pharmacological management, this could include supportive counseling or psychotherapy to address maladaptive beliefs and emotional distress that often accompany pain, integrative and complementary therapies (e.g., yoga, mindfulness), self-management strategies (e.g., physical activity, stress management), and physical therapy to treat myofascial pain and dysfunction.

Given the decades of research demonstrating that endometriosis is not merely a disease of lesions, it is time we consider other contributing biological, psychological, and social factors that affect patient functioning and well-being. We desperately need a paradigm shift in both the management of endometriosis and the way patients are informed about the disease and their treatment options. This transformation could enhance patient care and provide a more holistic approach to pain management. Not only could this offer a vital opportunity to alleviate the profound burden of endometriosis, but it may also dramatically improve the overall quality of life for those affected.

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