

Comprehensive endometriosis care: a modern multimodal approach for the treatment of pelvic pain and endometriosis

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Abstract: Endometriosis is a prevalent gynecological disease, leading to chronic pain and inflammation, affecting 1 in 10 individuals presumed female at birth. The diagnostic journey is often arduous, marked by neglect of the right diagnosis and prolonged wait times, significantly compromising the quality of life among those affected. This review provides a nuanced exploration of endometriosis-associated pain management, encompassing medical, surgical, and holistic approaches, all guided by accurate and refined diagnostics. Our paramount goal is to empower physicians as key figures in confronting this intricate challenge with a patient-centric approach, ultimately aiming to improve treatment and quality of life. Acknowledging each patient's unique needs, we emphasize the importance of tailoring a spectrum of options informed by current literature and insights gleaned from our experience in a high-volume tertiary endometriosis center. It is imperative to recognize endometriosis as a complex and chronic disease, often occurring with co-morbid conditions and nuanced complexities, necessitating a long-term personalized multimodal approach for each case. In addition, incorporating principles such as patient autonomy, profound respect for diverse experiences, and practical education on treatment choices is pivotal in enhancing treatment outcomes and overall patient satisfaction.

Plain language summary

Navigating the landscape of endometriosis: a comprehensive approach to pain management and patient-centered care

Endometriosis is a common gynecological condition characterized by persistent pelvic pain and inflammation, impacting approximately one in ten individuals assigned female at birth. Diagnosis often entails a challenging journey, with many experiencing delays in obtaining the correct diagnosis and treatment due to various factors, significantly affecting their quality of life. This review delves into the intricate landscape of managing pain associated with endometriosis, encompassing medical interventions, surgical procedures, and holistic therapies. Our primary aim is to equip healthcare providers with the tools and knowledge necessary to effectively address this complex issue, prioritizing patient-centered care to minimize delays in diagnosis and treatment initiation. Recognizing the individuality of each patient's needs, we advocate for a tailored approach informed by current evidence and clinical experience from specialized endometriosis centers. Furthermore, we underscore the importance of patient autonomy, respecting diverse perspectives, and providing comprehensive education on treatment options to optimize treatment outcomes and patient satisfaction.

Keywords: endometriosis, management, pain, treatments

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Introduction

Endometriosis is a heterogeneous, full-body, inflammatory disease affecting 1 in 10 individuals presumed female at birth globally.¹ Recently, a study in Australia has demonstrated estimates of disease prevalence, which have increased to one in seven women.² The disease is characterized by the abnormal growth of endometrial-like cells, including stroma and epithelium, outside the uterus, typically within, but not limited to, the pelvic cavity.^{3,4} Endometriosis is associated with hallmark pain-like symptoms, including dysmenorrhea (painful menstruation), dyspareunia (pain with intercourse), persistent pelvic pain, and infertility,^{4,5} alongside traditionally, less “classic” manifestations, including urological, gastrointestinal (GI), musculoskeletal, and neurological symptoms. In all, it is widely appreciated that endometriosis negatively impacts the quality of life, with unique experiences among those affected.⁵⁻⁷

There is currently no complete cure for endometriosis,⁸ though past and recent developments have enabled the management of both the symptoms and the disease itself.⁹ Traditional medical treatments of endometriosis have relied on menstrual/ovulatory suppression and/or surgical treatment of the disease.¹⁰⁻¹³ Unfortunately, many of these treatments have proven inadequate due to their transient nature and recurrence of disease and symptoms,^{14,15} as well as potentially facilitating unwanted side effects, which may further reduce the quality of life.^{9,16,17} As such, there has been an exponential interest in evaluating the efficacy of complementary and alternative medicine (CAM) management strategies, such as heat, cannabis, and diet.^{18,19} Some CAM strategies may be provider guided (e.g., acupuncture or physiotherapy), while others are patient-driven self-management strategies (e.g., heat or mindfulness). To add to the complexity of endometriosis, it is often present with other chronic pain conditions or medical co-morbidities, which exacerbate or confound symptoms, presentation, and quality of life.²⁰⁻²² It is essential to recognize that a holistic approach, incorporating conventional treatments such as hormone therapy and surgical interventions alongside complementary and alternative approaches, plays a vital role in improving the overall health and quality of life of people with endometriosis.

Even though the disease and symptoms may be managed, endometriosis is a lifelong and

whole-body disease that requires long-term and malleable, multimodal treatment strategies.^{5,23} Considering the traditional stepwise approach to current treatment strategies and the lack of practitioner-provided education for patients regarding treatments, autonomy is often lost, limiting the success of current treatment and management. This review aims to assess modern multimodal treatment approaches for endometriosis while considering nuances associated with the patient's life course.

Summary of current clinical care pathway

The clinical pathway for endometriosis must begin with the initial recognition of clinical presentation at a primary care level.²⁴ Generally, patients present with hallmark symptomatology such as dysmenorrhea. However, some present with symptoms like chronic pelvic pain or infertility, or symptoms that are traditionally even less taught to be associated with endometriosis, such as GI^{25,26} and urological symptoms,^{27,28} which may complicate and lengthen the diagnostic process.^{24,29,30} When a patient presents themselves in adolescence or early reproductive years, the diagnostics journey is even more complex, as symptoms may be more cyclical in nature.³¹ Patients who have undergone an extensive diagnostic delay without adequate care, subject to repeated debilitating symptoms and negative impacts on quality of life, may present with chronic, non-menstrual and menstrual pain.²¹ Societal factors and poor awareness of endometriosis remain among the field's most pertinent limitations,⁶ facilitating the diagnostic delay through *normalization*. Even though menstrual health literacy is low, often yielding misconceptions of what is a normal amount of pain with menstruation,³² patients often experience the frustrating phenomenon of having their symptoms normalized or overlooked by healthcare providers, and due to societal pressures instilled by family and friend groups.⁶

When endometriosis is finally recognized as a possible diagnosis, patients are typically prescribed hormonal medications (e.g., oral contraceptive pills) and/or non-steroidal anti-inflammatory drugs (NSAIDs) to reduce pain, generally without a precise diagnosis.^{24,33} The focus is more on suppressing the symptoms rather than truly exploring the origins or resolving the underlying process.^{24,33} Most primary care examinations and

investigations (e.g., bloodwork, imaging) are “normal,” whereby no pathology is identified despite the patient’s report of symptoms.^{24,34} In some cases, hormonal medications and/or NSAIDs may adequately relieve the symptoms. However, patients typically respond poorly to these treatments with side effects and symptom recurrence.³⁵ Most importantly, there is a lack of focus on how this might or might not be suitable for a patient’s life course.²³ Patients may be exposed to several alternative hormonal medications, following the classic stepwise first-line, second-line, third-line approach, for symptom relief, still without a clear diagnosis or a clear understanding of what exactly they are treating with these medications.

The diagnostic journey could include referrals to several obstetricians/gynecologists (OBGYNs) prior to reaching a gynecologist with a higher level of expertise in endometriosis, who may be more equipped to assist the patient in managing the disease.⁵ Along this path, patients may experience several surgeries for diagnosis and/or treatment, with variable benefits yet consistent exposure to risk.^{36–38} Patients may also undergo repeated untargeted surgeries, including hysterectomies or oophorectomies (inducing premature iatrogenic menopause) without ample consideration of a patient’s life course, still with limited relief and potentially facilitating additional negative consequences.^{36–38} By the time a patient presents at an advanced specialist level, endometriosis may truly become something more, a disease of the nervous and myofascial systems inducing central sensitization and/or a disease involving the bowel or bladder, directly with growths of tissue or indirectly via cross-sensitization.^{39,40} In some instances, endometriosis may compromise fertility,^{41,42} leading to patients giving up on family building among those who have this as a personal priority. A nuanced and multidisciplinary evaluation beyond traditional gynecological issues may be what is needed to pave the way for a customized approach to management.^{43–45} However, in reality, barriers exist to the implementation of a multidisciplinary approach—cost, time, health-care system limitations, providers’ knowledge of endometriosis, and lack of knowledge about pain and organ systems outside of their main specialty, and often, the resignation of the patient to live in pain.^{13,46–49} Managing this condition should be viewed as a continuous journey, often involving collaboration with multiple specialists, rather than an isolated, discrete endeavor.^{43–45} It should

start early and continue progressively over the patient’s life course.²³

Considerations throughout the clinical care pathway

Painting the picture—the initial presentation

Before management should even be discussed, the initial contact should encompass a detailed rapport between the patient and the physician, developing a dynamic relationship and trust, aiming to improve clinical outcomes.^{50,51} Here, the narrative should involve *validation* and *exploration* of patient concerns, including symptoms, goals, expectations, and feelings.^{52,53} To provide adequate care, the rapport should further consolidate the patient’s history pertinent to endometriosis, including all symptoms, demographics, past diagnoses, surgical history, hereditary factors, and social and psychological aspects.^{54–55} Alongside clinical features, equally important, the physician should also consider a patient-centered approach, identifying desires and goals,^{57,58} whether it be the management of symptoms, education, fertility, their careers, and/or other priorities important to the individual patients.

Imaging and a thorough understanding of anatomy play a critical role in the treatment of endometriosis, providing a detailed and accurate evaluation that is essential for developing targeted and personalized treatment plans. An initial physical exam, which includes assessing pelvic floor muscle (PFM) properties, such as tonicity, strength/weakness, “smudging,”⁵⁹ and site-specific tenderness,^{60,61} may elucidate additional abnormalities pertaining to the nervous and musculoskeletal systems, which may further guide patient treatment and management. Following a physical examination, advanced non-invasive imaging techniques are employed to thoroughly examine all pelvic compartments.^{62–65} Imaging may help determine the location, severity, and state of adhesions associated with endometriosis and identify non-endometriosis-related abdominal and pelvic pathologies. Diagnostic imaging has proven particularly effective for diagnosing ovarian endometriosis (OE) and has shown significant advancements in identifying deep endometriosis (DE) through ultrasound and MRI.^{65–69} While superficial endometriosis (SE) remains challenging to diagnose non-invasively, recent improvements in imaging techniques have

enhanced its detection accuracy. By integrating a physical assessment and advanced imaging into the clinical care pathway, healthcare providers can ensure precise diagnoses, which are crucial for implementing effective and individualized treatment strategies for endometriosis.⁷⁰

It is important to emphasize that in cases where advanced diseases like DE and OE are not evident on imaging despite clinical suspicion, consideration should be given to the possibility of SE, which cannot be ruled out at this time on any non-invasive imaging modality. In such instances, acknowledgment of patient symptoms is of the utmost importance, as normal imaging may yield feelings of invalidation.⁷¹ Depending on the patient's symptomatology, history, and goals, surgery as a diagnostic test can be considered,⁷² with potential added therapeutic value if endometriosis is identified and surgically treated.⁷³ Alternatively, not all people pursue surgery as a diagnostic test.⁷⁴ This aligns with the guidelines of many countries—based on symptoms, history, and goals; instead, patients may focus on different therapeutic strategies, particularly empirical medical treatments for endometriosis.

In addition to a comprehensive clinical assessment and advanced imaging diagnostics for endometriosis, it is imperative to evaluate patients for commonly coexisting conditions diagnosable on imaging systematically.⁷⁵ This includes, but not limited to, polycystic ovarian morphology/syndrome (PCOM/PCOS), adenomyosis, fibroids, intracavitary pathology, and ovarian and tubal cystic lesions (e.g., hydro- and hematosalpinges, ovarian cystic lesions).⁶⁵ From a clinical history and examination perspective, non-gynecological disorders should also be considered, like irritable bowel syndrome, bladder pain syndrome (formerly interstitial cystitis), myofascial pelvic pain, and autoimmune diseases.

To address the complex interplay of factors influencing patients' perspectives on diagnostics and treatment, clinicians should prioritize building rapport, fostering trust, and educating patients while emphasizing patient autonomy throughout their diagnostic and treatment journey. Recognizing the impact of religious or cultural background, sexual trauma, and past experiences with healthcare, clinicians can support patient-centered approaches, such as allowing patients to insert speculums during vaginal examinations,

thereby respecting their life history and personal preferences.

Multidisciplinary and life course approaches to management

A crucial discourse revolves around implementing a comprehensive life course approach to treating and managing endometriosis.²³ Endometriosis is a chronic and potentially lifelong disease, with enduring effects and plausibility for recurrence remaining throughout the patient's life.^{76,77} Subsequently, treatment and management should foster a long-term plan, considering and tailoring strategies relative to patients' life course and respective goals. For example, a patient in premenopausal years may request symptom management, fertility preservation, and education about endometriosis. Comparatively, a patient in perimenopausal years who may have undergone repeated treatments, such as previous excision of endometriosis or an array of hormonal therapy, may foster a dialogue pertaining to alternative strategies and supportive care.^{78,79} Although natural alleviation of symptoms may occur as hormonal fluctuations associated with the menstrual cycle diminish, the menopausal period may bring unique challenges. Symptoms such as persistent pelvic pain, irregular bleeding, and dyspareunia may persist or evolve, continuing the negative impact on overall quality of life.^{78,79} Patients with endometriosis have been reported to continue to have serious issues well into menopause, such as bowel obstruction.⁸⁰ Though poorly understood, hormonal shifts associated with this period may further introduce variability in the severity and presentation of endometriosis symptoms, necessitating a nuanced and multidisciplinary approach.

Autonomy and education

The clinical care pathway must embrace and integrate patients' autonomy at every step of their journey. By doing so, healthcare professionals adhere to ethical principles and lay the foundation for the robust patient-physician relationship.^{81,82} Patient autonomy stands as a cornerstone in acknowledging the individuality of each patient, recognizing that their experiences and priorities are highly distinct. What may be the most appropriate course of action for one patient might prove unsuitable or less effective for another. Embracing patient autonomy empowers individuals to actively participate in

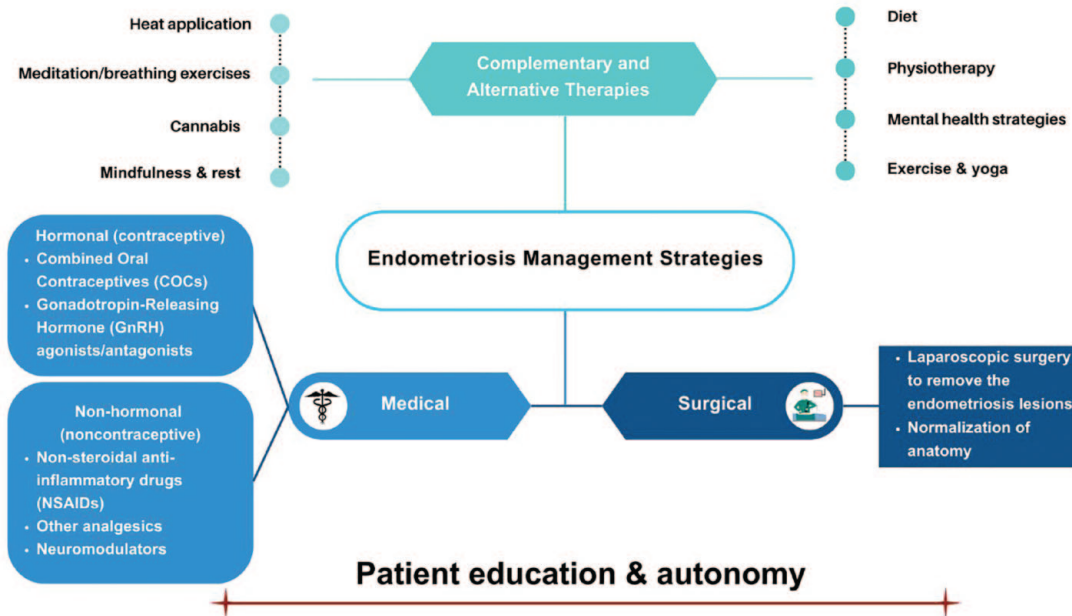


Figure 1. Endometriosis management strategies. The figure demonstrates our proposed “buffet approach” for the management and treatment of endometriosis, including medical, surgical, and complementary approaches based on patients’ goals and preferences.

making decisions about their treatment, ensuring that their chosen plans align with their unique values and preferences and, in turn, promote the treatment plan’s success.⁸¹ Patient autonomy may also be promoted by considering individualized patient factors, health determinants, and inequities.^{81,83,84} For example, a patient in rural areas or without access to insurance may be unable to access treatment and management, where alternative or creative approaches may be required, such as the use of online pain programs, telemedicine consultations, and community-based support programs.

Autonomy may be lost in managing endometriosis through paternalism,⁸⁵ where medication may be prescribed without a discussion and/or consideration of alternative treatments. Similarly, surgical interventions for endometriosis may be scheduled without a comprehensive discussion regarding the chosen method of treatment or potential concurrent gynecological pathologies, potentially compromising the effectiveness of the treatment. Patient autonomy may be maintained by offering and discussing various treatment options rather than by following a rigid stepwise (also known as colloquially “ladder”) approach. This is done while always keeping patient safety and priorities in view. This patient-centric

approach allows individuals to choose treatments that align with their beliefs and preferences.

Alternative to the traditional stepwise approach, presenting multiple options may be referred to as the “buffet approach,” as we describe in Figure 1, where patients are presented with currently available treatment options that best suit their preferences, guided by the physician discussing the benefits and limitations of each option. This analogy emphasizes the idea that patients are free to select from a diverse range of treatments, and may choose multiple options at a time, promoting a more personalized and comprehensive health-care experience. The goal should be to create a supportive environment where patients feel empowered to make informed decisions about their health, fostering a partnership between healthcare providers and individuals seeking care.

In conjunction with prioritizing autonomy, the role of education cannot be understated when presenting treatment options. Providing patients with comprehensive and accurate information about potential therapies, including their benefits and risks or strengths and limitations, minimizes the possibility of the nocebo effect.^{86,87} Although this concept has seldom been explored in endometriosis, patient education is vital in reducing

pain and improving recovery.^{88,89} This phenomenon arises when pre-existing negative beliefs or stigmatization surrounding a treatment negatively influence its efficacy. By providing patients with accurate, appropriate, factual, and unbiased information, healthcare providers can help dispel misconceptions and instill a more positive and open mindset toward the proposed treatments, optimizing the potential for successful outcomes.^{86,87,90} Equally valuable, pain education plays a crucial role in endometriosis management, serving as a valuable treatment strategy.⁹¹ Enhancing patient's understanding of the condition and its complexities empowers individuals to actively engage in their care, fostering improved coping mechanisms and potentially reducing the overall impact of pain.^{43,91}

Complementary and alternative management of endometriosis

The use of patient-driven self-management care to alleviate the symptoms associated with endometriosis is highly prevalent, making it imperative to consider these strategies as part of patient care.^{18,92,93} However, it is essential to acknowledge that the effectiveness and the mechanisms by which self-management strategies work remain to be elucidated. Addressing this knowledge gap is crucial for optimizing patient outcomes and improving their quality of life.

Recent studies suggest that among self-management strategies, heat application, rest, and meditation/breathing exercises were the most widely adopted.¹⁹ Interestingly, cannabis usage, heat therapy, and dietary modifications surfaced as the most effective means of managing self-reported pain.^{19,94} Conversely, emotional-focused strategies like relaxation, mindfulness, acceptance, and fostering a positive attitude have not received adequate exploration in the context of endometriosis.¹⁹ Nonetheless, it is essential to acknowledge that mental stress has been well-established to influence pain perception and exacerbate pre-existing conditions, as supported by various studies linking health anxiety and stress with endometriosis-related pain.^{95,96} Alongside self-management strategies, patient-centered care may be supported by allied healthcare professionals, including dietitians, pelvic floor physiotherapists, and psychologists.⁹⁷⁻⁹⁹ Patients may also seek alternatives, such as osteopathy, acupuncturists, and physiatrists.

Diet and endometriosis

The role of diet in influencing endometriosis symptoms and progression has garnered increasing attention, yet the full impact of dietary choices on endometriosis remains to be fully elucidated.¹⁰⁰ Given the chronic inflammatory nature of the disease, numerous studies have centered around investigating the potential benefits of adopting an anti-inflammatory diet to improve endometriosis symptomatology.¹⁰¹⁻¹⁰⁴ There is growing evidence to suggest that inflammatory diets characterized by the consumption of red meats, trans fats, and coffee may exacerbate symptoms, while diets rich in anti-inflammatory foods, such as vegetables and omega-3 polyunsaturated fatty acids, have shown promise in reducing symptom severity.¹⁰²⁻¹⁰⁵ However, controversy remains as studies have similarly shown an inverse association between fruits, meat, and endometriosis risk.¹⁰²⁻¹⁰⁵ Still, this may be linked to the estrogen-like activity of pesticides, dioxins, and dioxin-like chemicals.^{100,102}

Approximately 90% of patients with endometriosis experience GI-related symptoms (i.e., bloating, pain, constipation, and diarrhea), irrespective of bowel involvement.^{25,26,97} Similarly, there is a threefold increased risk of developing Irritable Bowel Syndrome (IBS) among people with endometriosis.⁹⁸ Although the mechanism by which the two enigmatic diseases coexist remains unknown, studies have suggested the possibility of intestinal dysbiosis^{99,106} of gut microbiota or inflammatory causes.⁹⁸ Regardless, dietary changes may be valuable to improving symptoms and targeting co-morbid GI-related diseases, though this remains to be elucidated. Similarly, diet therapy may be considered in the presence of DE of the bowel, especially for those who choose to forego bowel excision due to surgical risks.

Recent research has expanded our understanding of how dietary interventions can impact endometriosis symptoms. For instance, a study demonstrated in an immunocompetent mouse model that a high-fat diet exacerbates endometriosis outcomes by increasing systemic inflammation and oxidative stress, suggesting the negative effects of high dietary fat intake.¹⁰⁷ Similarly, it has been suggested that people with endometriosis use dietary modifications, such as reducing gluten and dairy, to manage symptoms, with significant reported improvements in GI disturbances and fatigue.¹⁰⁸ In addition, when focusing

on the nutritional practices of individuals with endometriosis, positive patient adherence to the low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet highlights its potential benefits for managing GI symptoms.¹⁰⁹ Significant dietary changes post-diagnosis have been further supported, with many women reporting improved symptoms and quality of life after adopting gluten-free and anti-inflammatory diets.¹¹⁰

It is essential to note that the current body of research comprises non-randomized controlled trials (RCTs), leading to considerable heterogeneity in diet types, measured outcomes, studied populations, and overall study designs. As a result, while several studies have suggested a potential association between diet and pain perception among individuals with endometriosis, establishing a causal relationship has proven challenging. Further rigorous research incorporating RCTs (ClinicalTrials.gov identifiers: NCT04259788, NCT05387161, NCT05411549, NCT05714189), and standardized methodologies are necessary to better understand the true impact of dietary interventions on endometriosis management. Such efforts will pave the way for more personalized and evidence-based dietary recommendations, offering enhanced support and improved quality of life for those with endometriosis.

Physiotherapy

The pelvic floor is composed of muscles (levator ani, coccygeus, obturator internus, piriformis, and arcus), ligaments, and connective tissues that provide support to the pelvic organs and viscera, including the bladder, uterus, and rectum.¹¹¹ There is a substantial presence of PFM dysfunction among people with endometriosis and persistent pelvic pain.^{39,60,112,113} Dysfunction of the PFMs in endometriosis is multifaceted, with varying presentations, including hypertonia/spasming, hypotonia, and incomplete relaxation of the PFMs.^{60,114} Although the mechanism of the dysfunction in endometriosis is still unknown, it is likely multifaceted, composed of cellular components, such as inflammatory and neurogenic changes, and physiological components, such as adhesions, sensitization, and psychological factors. Together, PFM dysfunction may be the direct cause or share a similar mechanism with gynecological symptoms associated with endometriosis

and highly prevalent urinary and GI symptoms.¹¹⁵ Upon robust clinical evaluation and recognition of PFM dysfunction among people with endometriosis, pelvic floor physiotherapy (PFP) is suggested to target the symptoms and pain.

In evaluating the effectiveness of PFP, studies have evaluated pain symptoms and PFM function associated with endometriosis. A pioneering pilot study conducted by Raimondo *et al.*,¹¹⁶ suggests a significant reduction in superficial and deep dyspareunia scores among patients undergoing PFP. Assessing the muscles directly with three-dimensional (3D)/four-dimensional (4D) perineal ultrasound, mean levator hiatus area (LHA) at rest, contraction, and Valsalva were significantly larger post-therapy, suggesting an improved tone.¹¹⁶ The same study suggests a high level of satisfaction in the therapy, with 100% of patients being satisfied or very satisfied.¹¹⁶ The findings were later confirmed in a RCT, with PFP improving LHA on Valsalva maneuver, superficial dyspareunia, persistent pelvic pain, and PFM relaxation.¹¹⁷ However, this study was conducted among 50 patients, solely with DE, limiting the generalizability among all phenotypic presentations. A meta-analysis evaluating the effectiveness of PFP in improving quality of life and pain associated with endometriosis suggests that among the studies included, PFP was able to improve pain intensity and physical function of the PFM among those with endometriosis.¹¹⁸

The use of PFP may be adopted among those with endometriosis and should be considered in the clinical care pathway among all patients who experience dyspareunia and highly prevalent pelvic floor and musculoskeletal symptoms. The therapy may act as a management and education tool, whereby patients are taught about their physiology and pain sensory pathways, further promoting education and health outcomes. PFP may be further used to mitigate the phenomenon of cortical smudging,⁵⁹ where patients have a poor ability to map the sensory input of their PFM. Despite the limited evidence, current literature and mechanistic reasoning support the PFP management strategy in improving both symptoms and functionality and tone of the PFM.^{117,119,120} It should be further noted that several studies have suggested the practicality of using ultrasonography in conjunction with PFP to gauge and monitor improvement.^{117,119,120} Considering health inequities and determinants, PFP may not be

covered by insurance providers, leading to the inability or discouraging patients from pursuing therapy. In such cases, modifiable programs may be considered, such as biweekly sessions with periodic follow-ups. Similarly, free resources may be recommended, such as online therapy sessions and yoga.

Cannabis

Among the most effective self-management strategies in improving endometriosis-associated symptoms and improving quality of life,^{19,94} cannabis remains a momentous and increasingly explored topic. Irrespective of its wide use, the mechanism by which cannabis alleviates symptoms remains poorly understood. The entire body is saturated with components of the endocannabinoid system (ECS), which orchestrate physiological and cognitive processes.^{121,122} Within the ECS, cannabinoid receptor-1 (CB1) remains the most abundant, alongside CB2 and transient receptor potential channels.^{121–123} Endogenous cannabinoids, including the widely studied 2-arachidonoyl glycerol and arachidonoyl ethanolamide (anandamide; AEA), alongside their respective receptors, play crucial roles in various processes, including immune system modulation, appetite, pain sensation, mood, memory, and fertility.^{124–127} Exogenous cannabinoids, including but not limited to tetrahydrocannabinol (Delta-9-THC) and cannabidiol, act on these endogenous pathways, eliciting their local or systemic effects.¹²³

The use of cannabis has been shown to improve gynecological symptoms (dysmenorrhea, dyspareunia, persistent pelvic pain), GI symptoms (nausea, dyschezia), depression, sleep, stress, and libido.^{94,128} From a large retrospective cohort, inhalation was the most common form of administration (67.4%), with pain being the most targeted symptom,⁹⁴ yet GI symptoms demonstrate the greatest self-reported improvement.⁹⁴ Studies evaluating transpolydatin and palmitoylethanolamide, endogenous fatty acid amide that binds to two distinct receptors in the ECS, have shown a significant reduction in endometriosis symptoms, including overall pain scores, dysmenorrhea, dyspareunia, and dyschezia.^{129,130} However, it should be noted that there is a substantial lack of high-quality studies evaluating the effectiveness of cannabis in endometriosis, mainly using murine models.

The ECS has been found throughout gynecological structures, including ovaries, fallopian tubes, and uterus, playing a crucial role in embryo transfer and blastocyst implantation.¹³¹ Studies suggest higher AEA in peritoneal fluid among people with endometriosis and a reduction in CB1 receptors in ectopic tissue, suggesting rescued ECS signaling and promoting a hyperproliferative response.¹³² However, most studies suggest there is no difference relative to controls.^{19,94,128} Despite the scarcity of evidence, mechanistically, it is likely that the effects of exogenous cannabinoids directly act on CB receptors located on sensory and sympathetic neurons, in turn reducing endometriosis-associated symptoms.¹²⁴ However, this remains to be elucidated beyond animal models.

Mental health strategies

The implication of endometriosis on mental health has been widely accepted, with negative impacts on nearly all aspects of quality of life.^{133,134} The origin of this altered mental health state among people with endometriosis goes beyond the direct consequences of the disease. It may manifest systemic failures on social and medical levels, including lack of information, inadequate treatments, diagnostic delay, normalization of symptoms, and overall poor experiences with healthcare providers.⁶ These facets lead to reduced quality of life, including physical, psychological, social, education, employment, sexual, and financial impacts.^{6,133} Recent meta-analyses and systematic reviews have identified common themes associated with endometriosis and mental health, including a higher prevalence of anxiety (up to 79%) and depression (up to 86%) among people with endometriosis.¹³⁵ Similarly, persistent pelvic pain, a sequelae of endometriosis, is associated with a substantially increased prevalence of anxiety and depression.^{133,136} A longitudinal study suggests that people with endometriosis are at higher risk of developing major depression and anxiety disorders later in life.¹³⁷ It should be further noted that mental health consequences may affect a patient throughout their life course, potentially requiring nuanced and personalized approaches.

Managing these negative psychological impacts among people with endometriosis is complex and multidimensional, likely requiring direct psychosocial management as well as targeting

fundamental systemic issues, such as appropriate education about endometriosis. Of the few management strategies that exist, cognitive behavior therapy (CBT) is a merging technique, directly targeting anxiety and depression.¹³⁸ CBT provides people with endometriosis the ability to identify and question their thoughts and beliefs related to their psychological health.^{139,140} Although several highly anticipated studies, including RCTs, are emerging, preliminary findings suggest CBT in those with endometriosis significantly reduces stress, anxiety, and depression.¹⁴¹ Beyond emerging techniques, a widely explored management strategy among people with endometriosis includes mindfulness-based interventions. Studies have suggested that mindfulness-based interventions can improve symptom severity directly, significantly reducing all endometriosis-associated and pelvic pain symptoms immediately post-treatment.¹⁴² In addition, improvements were maintained longitudinally when comparing 1- to 6-year Endometriosis Health Profile follow-up scores post-mindfulness-based psychological intervention.¹⁴³ The findings illuminate the importance and long-term benefits of mindfulness-based therapies among people with endometriosis.

Interdisciplinary care

Though endometriosis has traditionally been treated using simple, gynecology-focused approaches, it has become increasingly apparent that a multidisciplinary approach is required at all care levels. When a physician presents treatment options, multidisciplinary and holistic approaches should be equally considered adjunct and personalized relative to patient factors and desires. If a patient continues to respond poorly to conservative and holistic treatments and all options have been exhausted, specialized pain centers or programs and additional medical specialties, including gastroenterology and urology,^{43,44} should be consulted or potentially reconsulted if they have already been involved in care. Pelvic pain programs, psychiatric interventions, and group therapies may also be suggested to assist in managing symptoms and provide comfort for individuals facing similar challenges.

Conclusively, self-management strategies are widely used within the endometriosis community and warrant consideration in a clinical context. Despite the challenges in evaluating their efficacy

due to current biases in existing studies, promising evidence indicates that these strategies may offer relief comparable to placebo or hormonal therapies for alleviating endometriosis symptoms. Patients will likely use these management strategies with or without the support of clinicians. Thus, it is crucial for medical professionals to be supportive of these management strategies. When indicated, practitioners should encourage these strategies to empower individuals dealing with endometriosis, linking their support to the establishment of a trusting and open relationship with patients.

Traditional treatment approaches

Hormonal medication

Hormonal medication is broadly considered a “first-line” approach in managing endometriosis, though it should be discussed alongside other options with consideration of patients’ life course and goals.¹⁴⁴ There are several classifications of hormonal therapies used in the management of endometriosis, though most work by suppressing the menstrual cycle, reducing estrogen levels, and controlling ectopic growth.^{144,145} The estrogen-dependent nature of endometriosis has been widely appreciated, with an increase in local autocrine estrogen production and estrogen receptors in ectopic and healthy tissue.^{144,146,147} Given the dependency, most treatments available target estrogen production or the binding of estrogen to its receptor to suppress the menstrual cycle and limit the bioavailability of estrogen, which facilitates ectopic growth.^{144,155} Combined oral contraceptives (COCs) typically contain a combination of synthetic estrogen and progestin hormones. These hormones work synergistically to prevent ovulation, thereby reducing estrogen levels in the body.¹⁴⁸ Suppressing the hormonal fluctuations associated with the menstrual cycle may alleviate cyclic pain symptoms.^{145,149} In patients with central sensitization, suppressing ovulation may also alleviate ovulation-associated pain. Numerous clinical studies have demonstrated the effectiveness of COCs in relieving endometriosis-related pain and symptoms. Ideally, continuous use of COCs (i.e., no placebo pills or days off the pill) can result in lighter and shorter menstrual periods, even completely suppressing menstruation, minimizing the inflammatory impact of endometriosis lesions, and reducing cyclic pain.^{149–151}

Alongside the estrogen-dependent nature of endometriosis, the progesterone-resistant nature of endometriosis has been appreciated.^{146,152,153} In normal circumstances, progesterone, a natural hormone produced by the ovaries during the second half of the menstrual cycle, plays a crucial role in regulating the growth and shedding of the uterine lining. However, in endometriosis, the ectopic growth exhibits reduced responsiveness to progesterone's effects.^{146,154,155} This diminished sensitivity to progesterone leads to the uncontrolled growth and survival of endometriosis. Progesterone resistance in endometriosis is a complex and multifaceted phenomenon involving altered hormone signaling pathways, genetic factors, and changes in the microenvironment of the affected tissues.¹⁵⁶ However, the origin and role of progesterone resistance remain to be elucidated, limiting the development of progesterone-specific effective treatment strategies.^{152,153} That said, progestins are a standard treatment among those with endometriosis and function by mimicking the action of progesterone. When progestins are administered, they help to regulate the hormonal fluctuations that occur during the menstrual cycle, causing a reduction in the growth and activity of ectopic growth.¹⁵⁷ By suppressing the growth of these abnormal tissues, progestins effectively alleviate the symptoms of endometriosis and help to thin the endometrial lining (reducing menstrual bleeding and uterine-specific pain with menstruation), which can alleviate symptoms and reduce the overall extent of the condition.^{150,158} As with any medical treatment, individual responses may vary, and healthcare providers may recommend different progestin-based therapies or regimes, carefully considering perceived benefits, side effects, and contraindications of use.

In combination with both estrogen and progesterone, the last form of hormonal medication discussed is gonadotropin-releasing hormone (GnRH) agonists/antagonists. In line with estrogen dependency and progesterone resistance, GnRH agonists suppress the production of estrogen and progesterone, creating a temporary menopausal state.^{159,160} GnRH antagonists act similar to GnRH agonists but offer a faster onset of action and reduced risk of estrogen flare-up. While highly effective, their use is limited to short-term due to the potential for bone density loss, cardiac vascular disease, and cognitive effects.^{161,162} With

recent interest in long-term endometriosis-specific treatments, novel alternatives have been developed, including GnRH receptor antagonists in combination with estradiol and progestin, with clinical trials suggesting improvement in endometriosis-associated pain.¹⁶³ The included add-back allows for a longer, safer duration of use, where risks may be mitigated. Although the treatment has shown promise as a tolerable regime in improving endometriosis-associated symptomatology, the effectiveness of these strategies relative to current hormonal therapies remains to be elucidated.¹⁶⁴

The use of intrauterine devices (IUDs), particularly levonorgestrel-releasing IUDs (LNG-IUDs), is a prevalent and debated hormonal treatment for endometriosis. The benefits of LNG-IUDs include a significant reduction in the recurrence of painful periods and an overall improvement in pain symptoms and quality of life for many people with endometriosis. Several studies highlight these positive outcomes, with LNG-IUDs effectively reducing dysmenorrhea and the size of endometriotic lesions.^{165,166} In addition, LNG-IUDs have been shown to provide a long-term therapeutic option with fewer systemic side effects compared to other hormonal treatments such as GnRH agonists.¹⁶⁷ However, the contentious aspects of IUD use in endometriosis treatment stem from side effects such as irregular bleeding, bloating, and potential hormonal imbalances, which can lead to patient discomfort and discontinuation of the treatment.¹⁶⁸ Moreover, the evidence supporting the efficacy of LNG-IUDs remains limited, with some studies indicating a need for further high-quality randomized controlled trials to confirm these findings.¹⁶⁵ Overall, while LNG-IUDs offer a promising option for managing endometriosis symptoms, the balance between their benefits and potential side effects necessitates careful consideration and personalized patient care.

Nuances in hormonal therapy

In addressing the concern regarding hormonal treatment for endometriosis, it is essential to acknowledge both its benefits and limitations. While hormonal therapy can effectively suppress symptoms associated with endometriosis, it may not provide a complete resolution of the condition and can be associated with adverse effects,

including, though not limited to, weight gain, mood swings, decreased libido, and bone density loss. In addition, hormonal treatments may not align with every patient's preference or goal for managing their condition. Given the chronic nature of endometriosis and the diverse experiences of patients, including factors such as impacts on quality of life and symptomatology, as well as the intersectionality of religious and cultural backgrounds, transgender identities, and differing reproductive goals, it is imperative to consider alternative treatment modalities alongside classic treatments.^{13,169}

The interplay between endometriosis and other gynecological conditions, such as PCOS, underscores the importance of considering the broader hormonal milieu. The presence of concurrent gynecological pathologies may influence the efficacy of treatment modalities, necessitating personalized approaches.¹⁷⁰ For instance, in the context of PCOS, characterized by heightened follicular and estrogenic activity, a lower dosage of GnRH antagonist may be considered to alleviate symptoms. Hormonal therapy also assumes a pivotal role as an adjunct to surgical interventions, both pre- and post-operatively. Pre-operatively, GnRH analogs may be utilized to shrink cysts, facilitating improved surgical outcomes.¹⁷¹ Similarly, post-operative administration of GnRH analogs has been shown to diminish the risk of disease recurrence,¹⁷² though it is possible that it has been more so beneficial for symptom recurrence as GnRH analogs can simultaneously (and potentially unknowingly) treat adenomyosis, fibroids, or PCOS.

Many patients with endometriosis have likely undergone previous hormonal therapies with varying degrees of success and side effects.^{173,174} Given the high prevalence of mental health issues among this population, careful consideration of treatment history is paramount.¹³⁶ Strategies such as the use of IUDs or low-dose hormonal therapy, which minimize systemic hormonal exposure, may mitigate mental health risks.^{175–177}

Despite the widespread adoption of hormonal medication as a primary non-invasive treatment for endometriosis, its efficacy in preventing symptom recurrence is debated.^{178,179} Patient-specific studies suggest hesitancy in accepting hormonal therapy due to concerns about side effects and stigma. Thus, comprehensive patient education is

essential to dispel misinformation, such as misconceptions about the causes of endometriosis or the efficacy of certain treatments, while assuring patient safety and exploring alternative treatment avenues. In addition, it is important to acknowledge and address potential biases that practitioners may hold, which could influence their position of power as educators. To circumvent these issues, clinicians should engage in ongoing training to recognize and mitigate their biases, fostering an open, patient-centered dialogue that prioritizes accurate information and shared decision-making.¹⁸⁰ Clinically, a gradual approach to tailoring hormonal therapy is recommended, as adverse effects typically diminish within 3 months.^{16,181–183} Rushed prescription practices may limit future treatment options, underscoring the importance of cautious and informed decision-making. By involving patients in these decisions and respecting their preferences, clinicians can enhance patient autonomy and ensure a more personalized and effective treatment plan.

Surgical treatment

Historically, the most widely adopted method of diagnosing endometriosis was direct visualization through surgical laparoscopy or a “key-hole surgery” followed by histological confirmation.^{184,185} The predominant use of laparoscopy may be attributed to the ability to diagnose and simultaneously treat endometriosis through the excision and/or ablation of the ectopic growth.^{186,187} From a diagnostic and disease extent standpoint, several papers have been published describing, characterizing, staging, and mapping endometriosis within the pelvis, adnexa, anterior, and posterior compartments.^{4,188,189} This requires a keen eye upon surgically entering the pelvic cavity to evaluate all anatomy for diseased tissue. Depending on the severity of the disease, the pelvic anatomy may be distorted and limited in mobility due to DE and adhesions. Beyond the surgical treatment of endometriosis, laparoscopy allows for the normalization of anatomy through adhesiolysis.^{189,190}

Although laparoscopy aims to treat endometriosis by direct excision of the lesions/nodules and normalizing the pelvic anatomy, controversy remains. The primary limitation of laparoscopy is that it requires the surgeon to be able to identify and resect all diseased tissue.^{74,191} Laparoscopic excision requires specialized surgical skills and

expertise to visualize and recognize the heterogeneous presentations of the disease adequately. In some cases, endometriosis deposits or complex nodules may be challenging to visualize due to distorted anatomy or are hidden behind adhesions, potentially enabling unrecognized residual disease.^{192,193} Moreover, endometriosis may be microscopic and invisible to a surgeon's eye.¹⁹⁴ In instances of surgical treatment, microscopic remnants (potentially at surgical margins) may be present as well, calling into question whether surgery can truly consistently and entirely eradicate the disease.¹⁹⁵ This has led some authors to advocate for complete peritonectomies.^{196–198} Further, the pelvis and pelvic structures are highly neurologically innervated, carrying sensory, motor, and autonomic nerves,¹⁹⁹ crucial in orchestrating normal physiological phenomena and facilitating pain perception. Although several studies have been published illuminating the need for nerve sparing during laparoscopic excision of endometriosis, the potential for nerve damage and post-operative pain remains.^{200,201}

Similarly, given the relatively invasive nature of laparoscopy, the same technique that aims to remove adhesions may simultaneously introduce adhesions and scar tissue.²⁰² A recent meta-analysis suggests that excision of endometriosis is superior to ablation in managing long-term dysmenorrhea, dyschezia, and persistent pelvic pain.²⁰³ On the other hand, it is currently being studied whether ablation or excision of SE is better for endometriosis symptoms.²⁰⁴ In addition, the efficacy of laparoscopy alone in treating endometriosis is debatable, with studies suggesting a 6%–50% recurrence in symptoms and disease.^{15,77,204} Another notable limitation remains the regionally dependent extensive surgical wait times associated with laparoscopy and regional variations in costs, specialists, and surgical availability,^{205–208} as well as the availability of pre-surgical imaging,^{65,68,209–211} limiting patients from receiving adequate care.⁵ In cases where severe endometriosis may affect the bowel, rectum, or bladder, a multidisciplinary team may be required to adequately treat the disease.¹⁷² Considering disease severity, excision-based techniques for structures that may involve a heightened risk, such as the segmental resection for the bowel or ureteral resection for a blocked ureter, address the disease at its roots, potentially minimizing recurrence.^{192,212,213}

Nuances in surgical approaches

An array of nuanced patient-centered surgical approaches exists. Notably, there has been increasing dialogue regarding when and whether to operate relative to adopting alternative medical approaches.⁷⁴ These questions pose invaluable issues for both healthcare resources and the patient, with implications for the success of treatment and quality of life and similarly requiring extensive dialogue of risks and benefits.

A landmark discussion in the context of surgery presents among those requiring fertility preservation. For cases requiring fertility preservation, fertility-sparing surgery, such as cystectomy or ovarian cyst drainage,²¹⁴ tailors the surgery relative to a patient's life course. Among younger patients, oophorectomies and hysterectomies should be cautiously considered in the context of estrogen deficiency on overall health and pregnancy desires while adhering to patients' goals.^{215,216} For individuals seeking conception, collaborative procedures, including assisted reproductive therapy (ART) in conjunction with surgery, can be explored to optimize reproductive outcomes.^{217–219} For example, one may consider stimulation and egg retrieval before a surgery, which can harbor negative egg reserve, and eventual embryo transfer after post-operative healing. Among patients who have opted for surgery, it is currently recommended that they try for pregnancy at their earliest convenience, with an optimal period of 6 months after surgery.²²⁰ However, dialogue remains as to whether ART should be performed before or after surgery.

Considering a patient's life course, the benefits and disadvantages of early excision of endometriosis should be discussed alongside alternative treatment plans, given the chronic nature and possible recurrence rate post-operatively, potentially necessitating multiple surgeries in the future.^{92,93} For example, a patient who may present with endometriosis and central sensitization and/or nociplastic pain may not benefit from surgical excision as a solitary treatment,⁹⁰ as the origin of sensitization may be attributed to additional underlying factors, such as past or current physical or psychological trauma.⁹¹ Additional surgical factors should equally be considered, such as the duration and complexity of surgery^{94,95}; a patient may wish to avoid surgery for DE involving the bowel, given the risks and potential outcomes

associated with the procedure,^{96,100} based on their symptom experience and alternative management strategies. In recent years, there has been development in treating endometriosis using robot-assisted surgery equipped with 3D visual systems and improved spectral depth, reducing surgeon burnout fatigue and reducing any natural tremor of the surgeon.^{221–223} Given the prolonged wait times often linked with laparoscopy, particularly among those undergoing complex surgeries, alternative strategies should be implemented to address patients' needs while they await their surgical date. For such a common disease, there is a paucity in surgeons with the skill to manage large surgical volumes.

Conclusion

The management of endometriosis presents a multifaceted challenge that requires a comprehensive and patient-centered approach personalized to a patient's life course. From pharmaceutical interventions to CAMs to surgical treatments to assisted reproductive technologies, the treatment landscape for endometriosis has seen notable advancements, offering patients a range of options to address their unique needs. However, it is crucial to recognize that endometriosis is a complex and chronic condition, often demanding a combination of therapies tailored to individual cases. Moreover, integrating patient autonomy, respect for diverse experiences, and effective education about treatment choices are crucial in enhancing treatment outcomes and patient satisfaction. As research and medical understanding continue to evolve, efforts to develop innovative and evidence-based treatments will undoubtedly improve the quality of life for individuals living with endometriosis.

Declarations

Ethics approval and consent to participate

Ethics approval was not required for this study, as it is a review and did not involve the use of any patient information or images.

Consent for publication

Not applicable.

Author contributions

Ido Mick: Conceptualization; Investigation; Writing – original draft; Writing – review & editing.

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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