

The challenge of endometriosis for female sexual health

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Introduction

The quality of sexual life plays an important role in the overall quality of life,¹ representing a primary care priority.² Sexual health is defined, according to the World Health Organization, as a state of physical, emotional, mental, and social well-being in relation to sexuality.³ Sexual function is a complex phenomenon driven by social, psychological, and biological/hormonal factors⁴ and may be impaired by medical conditions, especially when gynecologic disorders are involved.⁵

In the last years, an increasing number of evidences has shown that patients with endometriosis frequently report an impairment in sexual functioning and satisfaction.^{5,6} Endometriosis is a benign hormone-dependent disorder associated with the presence of endometrial tissue displaced outside the uterine cavity. Its pathophysiology has long been debated and involves estrogen dependency, progesterone resistance, decreased apoptosis, oxidative stress, inflammation, and neuroangiogenesis.⁷ Global prevalence is estimated to vary from 6% to 10% in women of reproductive age,⁸ even though the condition is often misdiagnosed or underrated. The main consequences of endometriosis are chronic pain (dysmenorrhea, noncyclic pelvic pain, dyspareunia, dyschezia, dysuria) and subfertility.⁹ Among pain manifestations, dyspareunia—defined as “recurrent genital pain or discomfort that occurs before, during, or after sexual intercourse, or superficial or deep vaginal penetration”¹⁰—is only one of the main sexual symptoms experienced by women with endometriosis.¹¹ Indeed, discomfort during sex and/or difficulties to conceive often lead to poor intimacy and a negative cycle of reduced sexual arousal, desire, ability to orgasm, and satisfaction in affected women.¹²

Despite sexual concerns being a common and debilitating issue for women with endometriosis, they have been underestimated both in research and in clinical care.¹³ One of the reasons is probably that they represent a challenging topic for discussion for health care practitioners (HCPs) and patients.¹⁴ The quality of patient-HCP communication on sexual issues is poor, as patients and doctors are often reluctant to discuss sexual problems.¹⁵ On one side, patients experience pain minimization from doctors; on the other, HCPs underestimate

the importance of exploring potential sexual issues, leading to a significant neglect of a such an important endometriosis symptom.¹⁶ In this regard, in a recent international survey on >600 women self-identified as having endometriosis, >50% of women complaining of sexual pain were not informed by their HCPs about dyspareunia being possibly linked to endometriosis.¹⁷ Thus, sexual health represents a major challenge for patients and for clinicians dealing with endometriosis. Similarly, for a sexual medicine specialist, a deep understanding of the mixed clinical presentation of endometriosis-related symptoms and the pathogenesis of pain may help to suspect the disease among women seeking medical help for sexual issues apparently not related to endometriosis.

Assessment: the gynecologic perspective

Endometriosis is a hormone-dependent chronic inflammatory gynecologic disease that affects young and sexually active women. Gynecologists dealing with patients already diagnosed with endometriosis or with suspicious signs or symptoms should always inquire about sexual health.⁶ Dyspareunia is a complaint of 32% to 70% of women with this disease, affecting multiple domains of sexual function.¹³ It is estimated that about 2% to 4% of those who are sexually active may suffer from sexual dysfunction caused by endometriosis.¹⁸ Unfortunately, the clinical presentation of endometriosis is often heterogeneous, and symptoms may be nonspecific and common to other gynecologic or nongynecologic conditions.¹⁹ Therefore, misdiagnosis or a significant delay in endometriosis identification is frequently reported—on average 6 to 8 years after the onset of the complaints.

The advancement of imaging techniques and the increased knowledge and awareness of the disease in the last years have disclosed a new paradigm where the clinical and noninvasive diagnosis of endometriosis by ultrasound or magnetic resonance imaging has replaced histologic confirmation after laparoscopy.¹⁹ Imaging techniques, in particular transvaginal ultrasound (TVUS) as a first-line tool, are crucial for the diagnostic workup of endometriosis, aiming to explain underlying symptoms, map the disease location, and assess the severity of disease prior to medical therapy or surgical intervention.²⁰

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Table 1. Biological and psychological factors related to endometriosis that may impair female sexual function.

Biological factors	Psychological factors
<ul style="list-style-type: none"> • Chronic pelvic pain • Deep and superficial dyspareunia • Central sensitization of pain • Delayed diagnosis • Fertility issues • Recurrence of symptoms • Multiple surgical procedures • Coexistent mental health diseases • Coexistent chronic pain disorders • Pelvic floor muscles dysfunction • Side effects of hypoestrogenic/hypoandrogenic treatments on libido, mood, genital congestion, and vaginal lubrication 	<ul style="list-style-type: none"> • Personality traits • Fear-avoidance reaction • Lack of arousal/desire • Catastrophizing • Low self-esteem • Impaired body image • Sense of guilt • Sense of incertitude • Impaired social functioning • Reduced ability to orgasm and satisfaction • Impairment of partner relationship for sexual distress and/or fertility issues

The routine combination of pelvic vaginal examination and TVUS is an essential part of the standard primary assessment of patients with suspected endometriosis.²¹ TVUS is a dynamic tool to assess the real-time presence and localization of pain trigger points suggestive of endometriosis localizations, evoking to some extent intercourse pain. Besides, TVUS seems to be even more useful than vaginal examination alone in detecting deep endometriotic localizations.²² TVUS, following a systematic approach, allows one to examine the adnexa and anterior and posterior compartments to localize endometriosis lesions, pelvic organ mobility (ie, sliding sign), and site-specific tenderness, as sonographic “soft markers” for superficial endometriosis and adhesions.²⁰ This approach also allows one to evaluate the uterus, searching for sonographic signs of adenomyosis, a uterine disorder often associated with endometriosis and causing dyspareunia.²³

Imaging—whether TVUS or magnetic resonance imaging, with similar diagnostic performance—significantly improves the accuracy of diagnosing pelvic endometriosis, if performed by an experienced operator and combined with a detailed medical and gynecologic history and a pelvic vaginal examination.²⁴

Endometriosis phenotypes are associated with different signs and symptoms, according to the localization of lesions, even though there is not necessarily a correlation between the extent of lesions and pain intensity.²⁵ Ovarian endometriosis is normally associated with mild and moderate pelvic pain, whereas deep infiltrating endometriosis (DIE)—located at the posterior vaginal fornix, the pouch of Douglas, the uterosacral ligaments, the anterior rectal wall, and the urinary tract—is the most severe phenotype,²⁶ presenting with dyschezia, dysuria, dyspareunia, noncyclic pelvic pain, and bowel and urinary symptoms, depending on the lesions’ localization. Superficial endometriosis phenotype, located in the peritoneum, is also related to pain symptoms, including moderate to intense deep dyspareunia.²⁷ However, the advancement of imaging is showing that in most cases patients present with mixed phenotypes. Regardless, independent of the phenotype, the vicious cycle of chronic pelvic pain development²⁸ with peripheral²⁹ and central³⁰ sensitization leads to a nociplastic pain syndrome,³¹ with a number of coexistent pain disorders in endometriosis.

The presence of dyspareunia is due to mechanical pressure on lesions or to traction of scarred and retracted endometriotic tissue.³² However, for patients with endometriosis, there

is high variability in their subjective perceptions of dyspareunia, such as deep dyspareunia, introital/superficial dyspareunia, pain during and/or after intercourse, pain at orgasm, and positional pain. Deep dyspareunia may be influenced also by the occurrence of other common comorbid conditions of endometriosis, such as interstitial cystitis, painful bladder syndrome, and myofascial pelvic pain syndrome. The circle of perpetration of sexual dysfunction commonly starts with the presence of recurrent dyspareunia and the consequent fear and anticipation of pain, inhibiting the sexual response cycle.⁵ Furthermore, fertility issues worsen pain perception and sexual relationship, as distressed patients with anxiety and depression totally avoid sexual activity because of concerns about infertility and lack of support from partners rather than pain³³ (Table 1). In fact, the quality of life of women with endometriosis is affected not only by pain but also by the emotional impact of subfertility, the possible recurrence of the disease, and the uncertainty about the future related to repeated surgery and the long duration of medical therapy³⁴ (Figure 1).

Nonetheless, endometriosis may be associated with adenomyosis, a gynecologic condition defined as the presence of endometrial glands and stroma deep within the myometrium,^{35,36} whose symptoms are heavy menstrual bleeding, severe dysmenorrhea, dyspareunia, and infertility.^{23,37} Given the association between endometriosis, especially DIE,³⁸ and adenomyosis in 30% to 45% of cases, dysmenorrhea and dyspareunia are frequently explained by the presence of this uterine disorder rather than endometriosis itself.³⁹ For instance, after surgical treatment for DIE, patients with coexistent adenomyosis do not experience a reduction in pain symptoms, including dyspareunia, when compared with those with only endometriosis. This suggests the significant contribution of adenomyosis in determining gynecologic pain, affecting also the efficacy of endometriosis treatment.⁴⁰ Indeed, a recent study reported that patients with DIE and associated adenomyosis showed greater impairment in overall and sexual quality of life as compared with those with isolated DIE.⁴¹ Moreover, adenomyosis is relatively common among women <30 years old⁴²; thus, it should be routinely considered a cause of dysmenorrhea or dyspareunia, even in the absence of endometriosis lesions.⁴³

The modern management of endometriosis includes pharmacologic and/or surgical⁷ treatments or assisted reproductive technology for the infertility issues.⁹ Clinical

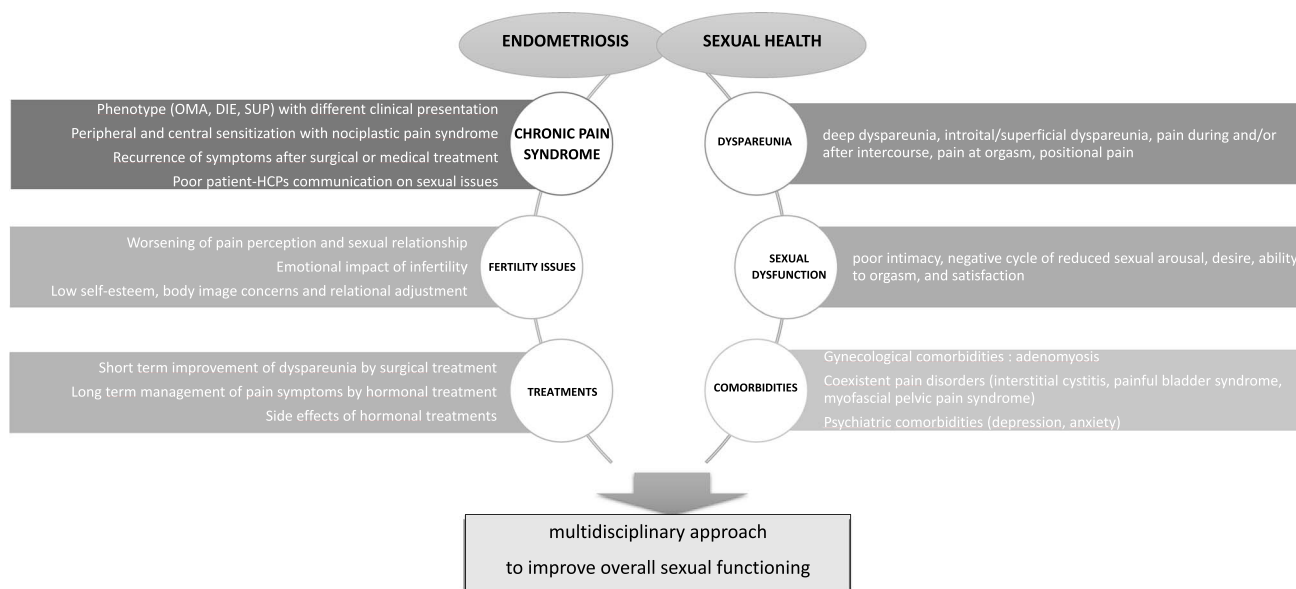


Figure 1. Comprehensive sexual health assessment in patients with endometriosis. DIE, deep infiltrating endometriosis; HCPs, health care practitioners; OMA, ovarian endometriosis; SUP, superficial endometriosis.

studies are exploring whether the available treatment options may improve the patient's sexual function but not necessarily lead to a definitive resolution of the sexual issue. In fact, endometriosis entails a significant psychological impact, impairing self-esteem, body image, or self-efficacy and social functioning, predisposing also to a high risk for mental health diseases.^{44,45} For this reason, the ideal treatment should be conducted by a multidisciplinary team, with the aim to improve overall sexual functioning and not only to reduce the painful symptoms during intercourse⁴⁶ (Figure 1).

Assessment: the sexual medicine perspective

In a sexual medicine setting, women or couples may show up for sexual symptoms after being diagnosed with endometriosis—as referred by their general practitioner, gynecologist, or other specialist—during the diagnostic process or before any diagnostic conclusion. Unfortunately, due to common diagnostic delays, patients may report that sexual complaints have been present for months or even years before consultation.

Despite the complex scenario of sexual function in women with endometriosis, the key symptom that has to guide the sexual HCP is, undoubtedly, deep dyspareunia. It has been well established that infiltrating lesions, scarred endometriotic tissue, or pelvic inflammation triggers pain during coitus. The first challenge in this process is that “dyspareunia” is no longer a female sexual dysfunction according to the last edition of the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition),⁴⁷ being included in the wider category of genitopelvic pain/penetration disorder. Conversely, in the *International Classification of Diseases, 11th Revision*, dyspareunia is still listed separately as a noninflammatory disorder of the female genital tract related to an identifiable physical cause.⁴⁸

If the patient experiencing deep dyspareunia has not been previously diagnosed with endometriosis, it is crucial that this be considered the main possible direct etiology. When a sexual pain history is obtained, midcycle spotting or pain,

pain worsening in specific positions with deep thrusting, and painful periods are suggestive of endometriosis. According to a recently proposed categorization, other gynecologic disorders related to deep dyspareunia are genitourinary syndrome of menopause, pelvic organ prolapse, pelvic inflammatory disease, pelvic congestion syndrome, fibroids, uterine positions, and adenomyosis.¹¹ In addition, nongynecologic conditions may occur with painful sex, and they appear to be extremely heterogeneous: urologic (interstitial cystitis/painful bladder syndrome, recurrent urinary tract infections), gastroenterologic (irritable bowel syndrome, inflammatory bowel disease), myofascial pain syndrome, and psychiatric disorders (including depression and anxiety).^{45,49,50} In clinical practice, overlap of 2 or more of these predisposing factors is a common finding. Given the multifaceted nature of sexual-related pain, interdisciplinarity is essential in all phases of the process of care, including initial evaluation (Figure 1).

Regarding the impact of endometriosis on other sexual domains, the quality of available evidence is poor, with only a few controlled trials using gold standard validated questionnaires for the assessment of sexual function and distress.^{51–53} Sexual questionnaires, including the Female Sexual Function Index⁵⁴ and the Female Sexual Distress Scale–Revised,⁵⁵ may be effectively used by all gynecologists during preliminary assessment to outline women's sexologic profiles, as well as to facilitate patients' expression of thoughts, feelings, complaints, or questions regarding their sexual lives. Specific questionnaires created to assess different aspects of sexual function in women with endometriosis are lacking. Recently, an Italian group validated the Subjective Impact of Dyspareunia Inventory, a brief tool designed to assess the impact of endometriosis-related dyspareunia from a multidimensional perspective.⁵⁶

Despite these limitations, there is a universal consensus—and it is apparent to HCPs dealing with this population—that all domains of sexual function suffer the detrimental effect of the disease. In fact, fear and anticipation of pain act as powerful inhibitors of the sexual response cycle, resulting in reduced

desire and lubrication difficulties.¹² Nevertheless, other correlates of endometriosis, beyond dyspareunia, may impair sexual functioning and satisfaction. These include chronic nonsexual pain, subfertility, surgical and hormonal treatments, low self-esteem, body image concerns, and relational adjustment (Table 1). In this regard, mini-invasive surgery performed for diagnostic or therapeutic reasons can exert a negative influence on the patient's sense of femininity and self-esteem as a woman (Figure 1). Hormonal treatments, especially those inducing chronic hypoestrogenism, such as continuous low-dose contraceptive pills or gonadotropin-releasing hormone agonists, have been reported to be associated with sexual disturbances due to the lack of the physiologic cyclic changes in estrogen and androgen levels.⁵⁷ High-dose progestins have also been found to alter sexual function, even though they improve dyspareunia.⁵⁸ These factors represent major points to consider when treating women with already diagnosed endometriosis who are presenting with sexual dysfunction (ie, low desire and insufficient lubrication). In addition, emerging evidence underlines the association between deep and introital dyspareunia, hinting the co-occurrence of endometriosis and other conditions, such as vulvodynia and provoked vestibulodynia⁵⁹; these may share common pathophysiologic mechanisms and influence each other. Therefore, women with endometriosis and deep dyspareunia should also be asked about superficial pain. Another interesting issue is the debated association between endometriosis and cardiovascular risk factors, such as enhanced atherogenic lipid profile and hypertension,⁶⁰ which could add another layer of complexity by predisposing affected women to vasculogenic disorders of genital arousal.⁶¹

In summary, when approaching women with known or suspected endometriosis in a sexual medicine setting, it is essential to avoid focusing only on deep dyspareunia and neglecting other aspects of sexual functioning and overall quality of sexual life (Table 1).

Management of endometriosis targeting the improvement of sexual function

Medical treatment and surgical treatment are both valuable options to improve sexual outcomes in a medium- to long-term period in patients with endometriosis, although the extent and duration of the positive effects have been poorly defined.⁴⁶

Hormonal treatments, such as progestins and gonadotropin-releasing hormone analogs and antagonists, are effective on various endometriosis-related pain,⁷ including dyspareunia, even though poor evidences are available on improvements on global sexual functioning. Previous studies suggested that dienogest decreased the intensity of deep dyspareunia among women with DIE,⁶² the compound was effective for long-term treatment,⁶³ and enhanced sexual function, albeit without restoring levels to normal.⁶⁴ Combined estrogen-progestins and other progestins, such as norethindrone acetate, have also been shown to manage endometriosis-related dyspareunia.^{65–67} However, in some patients, hormonal therapies do not seem to be effective for the specific outcome of deep dyspareunia. It has been hypothesized that this could be due to incomplete suppression of lesions, hormonal changes that worsen the pain through reduced lubrication or other local mechanisms (ie, in provoked vestibulodynia), exacerbation of mood disorders in susceptible individuals, and heterogeneity

of the pathways eliciting pain in endometriosis.⁵⁰ In fact, hormonal therapy affects brain areas involved in sexual response, emotions, and behavior, potentially interfering with reactions to sexual stimuli. In clinical practice, iatrogenic introital dyspareunia has been observed to improve with regular use of lubricants and off-label topical hormonal treatments applied to the vestibule (prasterone and testosterone). This is consistent with the extensive literature that describes the anti-inflammatory effect of androgens and with novel evidence indicating their potential as anti-inflammatory agents in the human vagina.⁶⁸ Endometriosis has been described as a disease characterized by an abnormally high ratio of estrogens to androgens. Androgen receptors have been detected within the lesions,⁶⁹ and low levels of androgens seem to be associated with increased pain. In this view, clinicians may try to enhance systemic androgens levels in affected women, especially in those with associated or comorbid hypoactive sexual desire disorder. This could be obtained by prescribing a hormonal therapy that maintains ovarian androgen production despite suppressing menstrual cycles (eg, levonorgestrel intrauterine devices) or a progestogen-only contraceptive that avoids an estrogen-induced increase in hepatic synthesis of SHBG (sex hormone-binding globulin), which normally results in low free testosterone levels.⁷⁰ An alternative strategy is represented by exogenous administration of transdermal testosterone, which is expected to exert a beneficial effect on desire and other sexual domains; however, this is off-label in most countries, and efficacy data on women in reproductive age, unlike those in postmenopausal women, have to be confirmed.⁷¹

A surgical approach of endometriosis may offer significant improvement in dyspareunia and quality of sex life among patients with DIE, at least in the short term (by 6–10 months from the operation),⁷² especially if combined with postsurgical hormonal treatment.⁷³ Pain scores for dyspareunia significantly decreased after surgery, and feelings of being guilty toward the partner or being a burden for the relationship significantly improved.⁷⁴ However, complete radical excision of DIE may involve high risk of intra- and postoperative major complications, such as ureteral, bladder, or bowel injuries or potential risk of pelvic denervation; thus, a highly skilled multidisciplinary surgical team is advisable, and risks and benefits should be always discussed with the patient. Overall, surgery can be considered a good option to improve dyspareunia and global sexual functioning when hormonal treatment is not effective, contraindicated, or not tolerated because of side effects or in case of attempts of spontaneous conception. Recurrence of the disease 1 to 5 years after surgical treatment is another issue that has been recently described and should be taken into account for the management of endometriosis.⁷⁵

Nonmedical treatment of sexual dysfunction in endometriosis is even more challenging, and the literature lacks studies addressing the efficacy of different approaches in this specific population. A multimodal strategy is required. Cognitive-behavioral therapy, mindfulness training, relaxation, physical therapy, and psychotherapy aimed at reducing chronic pain and restoring general psychological well-being have the potential to improve overall and sexual quality of life.⁷⁶ Nevertheless, promising results of these techniques and their combinations have been observed in terms of pain, anxiety, depression, stress, and fatigue but not regarding the

main sexual symptom, dyspareunia.⁷⁷ Sex therapy can be particularly useful in cases or couples who may benefit from sexual education—for example, modifying sexual techniques by increasing foreplay, delaying penetration, and avoiding specific positions and phases of the menstrual cycle. A partner's involvement in the therapeutic process is another neglected topic, and several reviews have highlighted the need of high-quality evidence on the partner's role on sexual outcomes. Recent data show good results obtained by pelvic floor muscle physiotherapy on superficial and deep dyspareunia.⁷⁸ Finally, the efficacy of transcutaneous electrical nerve stimulation, dietary supplements, and complementary medicine approaches on sexual symptoms has to be clarified.

Conclusions

Dyspareunia and sexual dysfunctions associated with endometriosis represent a major clinical challenge as well as an important outcome of endometriosis treatments. A comprehensive approach considering multiple dimensions of female sexuality, not just pain at intercourse, is warranted. Sexual functioning is a multidimensional phenomenon based on the interaction of multiple physical/anatomic, psychosocial, and emotional factors. Thus, the treatment of patients with endometriosis-related sexual impairments should first envisage a comprehensive sexual health assessment to correctly identify and characterize the disorder. Then, a multidisciplinary team involving the expertise of gynecologists, sexologists, and psychologists/psychotherapists should provide a comprehensive approach, where sexual functioning should be considered a major therapeutic goal for patients with endometriosis and their partners.

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