

Endometriosis and mental health disorders: identification and treatment as part of a multimodal approach

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Endometriosis is a disease marked by more than just pain and infertility, as it transcends the well-characterized physical symptoms to be frequently associated with mental health issues. This review focuses on the associations between endometriosis and anxiety, depression, sexual dysfunction, and eating disorders, all of which show a higher prevalence in women with the disease. Studies show that pain, especially the chronic pelvic pain of endometriosis, likely serves as a mediating factor. Recent studies evaluating genetic predispositions for endometriosis and mental health disorders suggest a shared genetic predisposition. Healthcare providers who treat women with endometriosis should be aware of these associations to best treat their patients. A holistic approach to care by gynecologists as well as mental health professionals should emphasize prompt diagnosis, targeted medical interventions, and psychological support, while also recognizing the role of supportive relationships in improving the patient's quality of life. (*Fertil Steril*® 2024;121:370–8. ©2023 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, mental health, depression, anxiety, sexual dysfunction

Endometriosis is a common gynecological disorder characterized by the presence of endometrial-like tissue outside the uterine cavity. It is a highly prevalent disease that affects up to 15% of women of reproductive age and up to 50% of women with infertility (1). Apart from the well-known physical symptoms, emerging evidence suggests a link between endometriosis and mental health, particularly depression and anxiety symptoms, but also sexual dysfunction (2–4). In addition, endometriosis may be associated with eating disorders (5). These mental health problems are associated with a lower quality of life (QoL) in patients with endometriosis, contribute to the complexity of the disease, and pose a

challenge to effective treatment (6). This review aims to summarize and evaluate the existing literature on the association between endometriosis and mental health issues. Our goal was to summarize to what degree women with endometriosis suffer from these problems compared with women without endometriosis, what the possible etiologies are (diagnostic delay, chronic pelvic pain [CPP], and sensitization), and how to identify women at risk to encourage them to seek out multimodal therapy options.

MATERIALS AND METHODS

A systematic literature review was performed from January 2003 to October

2023 in PubMed and Cochrane. The following key words were used: “endometriosis” AND “depression,” OR “depressive symptoms” OR “psychological distress” OR “anxiety” OR “emotional well-being” OR “sexual function” OR “eating disorders” OR “disordered eating.” Duplicates were removed and the remaining studies were screened by three independent investigators. Only full-length original articles in the English language were included. Articles were included when they reported on an association between endometriosis and anxiety, depression, eating disorders, or sexual function using a validated screening tool. Endometriosis was diagnosed using imaging techniques and/or surgery and/or clinical criteria (International Classification of Diseases [ICD] code). Anxiety, depression, eating disorders, or sexual function were assessed using a validated multiitem scale or registered diagnosis using the ICD code. Symptomatic women with endometriosis were either compared with pain-free endometriosis patients,

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healthy controls without pain, or CPP patients without endometriosis. We focused on the most recent meta-analyses and large cohort and case-control studies for this narrative review.

RESULTS

Endometriosis and Anxiety

Multiple studies have investigated the association between endometriosis and anxiety symptoms. Most studies use validated anxiety scales to measure outcomes, such as the Self-Rating Anxiety Scale, the Spielberger State-Trait Anxiety Inventory, and the Beck Anxiety Inventory, most of which are self-administered. Several key themes emerge from the studies.

Studies consistently show that women with endometriosis are more likely to experience anxiety symptoms compared with the general population. According to the World Health Organization, approximately 6% of women worldwide suffer from anxiety, although this figure ranges from 10% to as much as 87.5% for women with endometriosis, according to two recent systematic reviews of studies by van Barneveld et al. (2) and Szyplowska et al. (3). This wide range can be explained partially by the different outcome measurements used as well as the different patient populations included. In fact, some studies focused on women with endometriosis-related pelvic pain or CPP, whereas others focused on endometriosis patients with infertility.

Recently, Sarria-Santamera et al. (7) aimed to describe different clusters of women with endometriosis on the basis of their comorbidities using a large electronic primary care database of diagnostic codes. Comorbidity cluster analysis is an emerging statistical procedure that characterizes chronic diseases using a data-driven technique with no a priori theory applied to how one may expect comorbidities to cluster. Individuals sharing the same comorbidity profile or falling into the same comorbidity cluster may share similarities in their disease pathogenesis and clinical characteristics. They found the most common cluster was characterized by endometriosis with anxiety and musculoskeletal disorders (back pain and tendinitis), with the prevalence of anxiety approaching 38%. These results imply that in women with endometriosis, their psychological state may amplify the perception of pain or that the chronic pain state of endometriosis induces anxiety symptoms.

Endometriosis-associated pain and anxiety. Severe pain, a hallmark symptom of endometriosis, is strongly linked to increased anxiety. Women who suffer from pain that is more severe tend to report higher levels of anxiety, as summarized in the systematic review by van Barneveld et al. (2). In fact, one study reported no significant differences on a psychometric test for anxiety between women with asymptomatic endometriosis and a control group, although those with endometriosis and pain had higher anxiety (6). These findings were confirmed by Guillemot et al. (8), who assessed psychological state, including anxiety, using validated self-administered questionnaires in >1,000 women with endometriosis, dividing them into subgroups according to reported daily pain, cyclical pain, or pain-free. They found all out-

comes (body image, self-esteem, and QoL), but especially anxiety, correlated to the degree of pain, with 68.4%, 57.5%, and 29.6% of women reporting anxiety, respectively. Anxiety symptoms often have a detrimental impact on the overall QoL for women with endometriosis. The chronic nature of the disease and its associated symptoms can be emotionally distressing. In their systematic review, Kalfas et al. (9) evaluated the literature on the association of psychosocial factors with pain intensity and severity as well as health-related QoL in women with endometriosis. Not only did the investigators find that catastrophizing and anxiety were the factors most consistently associated with greater pain, but they also found that anxiety was among the factors related to worse health-related QoL in women with endometriosis.

Chronic pelvic pain and anxiety. Several plausible mechanisms have been proposed to explain the observed association between endometriosis and anxiety. Chronic pelvic pain, a hallmark of endometriosis, is suggested to play a central role in exacerbating anxiety symptoms. As-Sanie et al. (10) used neuroimaging with functional magnetic resonance imaging to study insula neurotransmitter concentrations and intrinsic brain connectivity to other pain-related brain regions. They found that women with endometriosis and CPP had elevated neurotransmitter levels and greater connectivity to pain-related regions, the latter of which positively correlated with anxiety. Women with endometriosis but no CPP showed no differences in anxiety compared with controls. In addition, the psychosocial impact of a chronic, often debilitating condition, including disrupted daily activities, impaired QoL, and challenges in maintaining relationships, likely contributes to increased anxiety levels.

Genetic predisposition and anxiety. There has been some indication that an underlying genetic predisposition may play a role in the development of mental health disorders, including anxiety, in women with endometriosis. In a genome-wide association study, Koller et al. (11) showed a consistent genetic correlation with anxiety in linkage disequilibrium score regression (LDSC) analysis and significant associations for anxiety (odds ratio [OR] 1.39, 95% confidence interval [CI], 1.13–1.65) in Mendelian randomization (MR) analysis (11–14).

Adjustment to receiving diagnosis. A shorter time from diagnosis was associated with increased anxiety in a cross-sectional study evaluating predictors of psychological distress in women with endometriosis (15). Although the subjects suffered from few symptoms, most likely because of the high prevalence of hormonal therapies, they nonetheless were prone to anxiety, especially shortly after receiving the diagnosis. These results provide support for the idea that being diagnosed with endometriosis, which involves becoming aware of having a chronic disease with no definitive cure and is often associated with infertility, is a disruptive and stressful event for women.

The uncertainty surrounding the prognosis of endometriosis, fertility concerns, and the management of symptoms often leads to psychological stress and anxiety (16). Facchin et al. (17) conducted interviews and administered the Hospital

Anxiety and Depression Scale (HADS) to women with endometriosis. They found that women who were able to adjust to their illness and saw the diagnosis as a short disruption fared much better than those who experienced a complete disruption to their lives because of endometriosis. Such disruption in women with endometriosis was a major source of distress and anxiety. Women whose female identity was very negatively affected by the prospect of having infertility reported specific anxiety disorders, such as recurring panic attacks that started after the diagnosis of endometriosis and were connected to the fear of infertility.

Healthcare providers who treat women with endometriosis should ask about anxiety symptoms, especially in newly diagnosed patients, those suffering from infertility, and those with chronic pelvic pain. Clinically available tools such as the Patient Health Questionnaire (PHQ)-4, PHQ-7, and Generalised Anxiety Disorder Questionnaire have been recommended by guideline groups for screening for anxiety, although the Endometriosis Health Profile-30 is a more extensive questionnaire assessing the QoL used in clinical research settings (18–22). Although research data are scarce, studies have suggested that women who undertake psychological counseling show lower postintervention anxiety values and a significantly higher QoL compared with a nonintervention control group (23). Surgical therapy has been shown to improve overall mental health as measured by QoL questionnaires, although anxiety per se has not been evaluated (24). There is a lack of data to demonstrate that psychological counseling or treatment of anxiety improves the pain of endometriosis.

Endometriosis and Depression

There is a body of evidence linking endometriosis to depressive symptoms and depression. A variety of screening and diagnostic tools have been used for the assessment of depressive symptoms. The most commonly depressive symptoms were assessed using the HADS and Beck Depression Inventory. In several studies, information about the diagnosis of endometriosis and depression was retrieved from medical records (ICD codes).

Depressive symptoms were reported in 9.8%–98.5% of patients with endometriosis, compared with 6.6%–9.3% of controls, on the basis of a recent systematic review (3). As in anxiety, this wide range can be partially explained by the different outcome measurements used as well as the different patient populations (infertile, symptomatic, and CPP) included.

The literature on the topic is not entirely consistent, as a few studies have failed to find a higher depression rate in endometriosis patients compared with healthy controls (25–27) and also in pain-free endometriosis patients compared with healthy controls (6, 10).

Risk factors for depression. The greatest association was found between endometriosis-associated pain (including CPP, dysmenorrhea, dyspareunia, and dyschezia), depression, and anxiety (2). Several studies showed higher levels of depression in symptomatic endometriosis patients compared with asymptomatic endometriosis patients and controls (6, 28, 29). In the presence of CPP, depression was reported in up to 86%, compared with 28% without pain (30). Women

with endometriosis were 1.48 (95% CI, 1.44–1.53) to 5.06 (95% CI, 3.57–7.16) times as likely to have clinically recognized depression (31–33). Women who have endometriosis in combination with other chronic diseases are especially at risk for depression (29, 33).

Although some evidence suggests that younger age (<35 years) is an additional risk factor for developing depression in the presence of endometriosis (33), other studies reported that the risk for depression with endometriosis is independent of age (32). Geller et al. (29) attempted to formulate a prediction model for depression in women with endometriosis. These investigators found that the association between depression and anxiety was mediated by negative body image, self-criticism, and pain intensity, as well as being especially pronounced in women with women with endometriosis and an additional chronic illness.

Other possible risk factors for depression in women with endometriosis included sleeping disturbance and fatigue, body image disturbances, prior use of gonadotropin-releasing hormone agonists, and oral contraceptives (28, 34, 35). Suffering from moderate to severe fatigue was associated with depression, anxiety, poorer sleep quality, poorer sexual functioning, and worse gastrointestinal QoL in an intensity-dependent manner (35).

Inconclusive results exist about the association between endometriosis-related infertility and depression: two studies reported no differences in the level of depression in infertile compared with fertile endometriosis patients (OR, 0.7; 95% CI, 0.4–1.4) (36, 37). On the other hand, Skegrod et al. (38) found a moderate correlation between depression and infertility (0.519) in a small study sample of 79 patients with endometriosis. Lower rates of depression have been reported in women who have had a prior pregnancy (33).

Genetic predisposition and depression. As in anxiety, Koller et al. (11) reported also a genetic predisposition for depression in patients with endometriosis. They found both a significant association and correlation between endometriosis and depression using MR (OR, 1.09; 95% CI, 1.08–1.11) and LDSC, respectively (11).

Screening for depression. There are currently no specific recommendations regarding screening methods for depression in (inter-) national guidelines. The National Institute for Health and Care Excellence (NICE) points out, that endometriosis is a long-term condition with physical, sexual, psychological, and social impact requiring long-term support (39). For these reasons, clinicians who treat women with endometriosis should ask about depressive symptoms, especially in symptomatic endometriosis patients, those with CPP, and those who suffer from other chronic diseases. Frequently used tools include the Beck Depression Inventory and HADS (40, 41). The guidelines for the German-speaking countries recommend screening with the PHQ-4 and PHQ-9 (18, 19, 21). In the European Society of Human Reproduction and Embryology guideline, the possible elevated risk for depression in endometriosis patients is not addressed, but it is mentioned that nonmedical strategies, including psychological interventions, should be discussed in symptomatic women (1).

Improvement of depression. Few data exist on the improvement of depressive symptoms following treatment in endometriosis patients. In the study by Farshi et al. (23), endometriosis-associated depression did not change significantly after an 8-week-long psychological counseling program. Conversely, the reduction of CPP did not reduce depressive symptoms in women with endometriosis (42). The meta-analysis by Arcoverde et al. (24) showed significant improvement in mental component score after surgery for all types of endometrioses (OR, 0.21; CI, 0.04–0.38) and significant improvement in mental health (OR, 0.39; CI, 0.03–0.74) after surgery for deep infiltrating endometriosis (DIE) (24). There is a lack of data on how the treatment of endometrioses specifically influences depression.

Endometriosis and sexuality. Sexual dysfunction is an often-overlooked problem for women with endometriosis, although the topic has gained increasing attention in recent years. A review of the literature showed that the most frequently used questionnaire for the assessment of female sexual function was the Female Sexual Function Index (FSFI) (43). Other frequently used tools included the Female Sexual Distress Scale-Revised (FSDS-R) (44) and the Sexual Satisfaction Scale for Women (45). A variety of validated questionnaires were used to assess different psychological and relationship aspects related to sexual function.

The prevalence of sexual dysfunction in women with endometriosis was as high as 32%–79%, compared with 17.6%–40% in controls (4, 46–48). The wide range in the reported prevalence is explained partially by the fact that some studies evaluated only sexual dysfunction or the presence of dyspareunia, although others also assessed sexual distress and/or sexual satisfaction. All domains of sexual function, specifically, desire and arousal, orgasm, satisfaction, and pain, were affected by endometriosis (46).

Pain and sexuality. Pain, especially dyspareunia, was reported in up to 79% of patients (47–49); however, the results regarding its impact on sexual function were inconclusive. Some studies reported dyspareunia to be one of the main determinants of sexual dysfunction (46, 50, 51). In their prospective study, Dior et al. (46) found significantly reduced scores in the FSFI total score and pain subdomain, which improved partially after surgery for DIE. However, this study included no other questionnaires, possibly failing to identify other factors influencing sexual function. This is supported by two small studies that found dyspareunia to be a significant negative predictor for sexual function measured using FSFI—representing one factor alongside anxiety, depression, sleep quality, BMI, level of education, and stage of endometriosis (50, 51). Other studies that used questionnaires to assess sexual distress in addition to FSFI found that dyspareunia alone does not predict sexual dysfunction (47, 49, 52). Despite a higher prevalence of genito-pelvic pain in endometriosis patients versus controls, Rossi et al. (47) reported similar total scores in FSFI. However, sexual distress measured using FSDS-R was significantly higher in patients with endometriosis, and they declared more negative emotions toward sexuality (47). The investigators conclude that “endometriosis patients

seem to be more sexually distressed than dysfunctional.” Similarly, in a small cross-sectional study by Zarbo et al. (49), neither dyspareunia nor chronic pain predicted sexual distress, although negative beliefs predicted sexual distress significantly.

The complex interaction between pain, sexual function, sexual distress, and psychological aspects is highlighted by a prospective study by Fritzer et al. (53), who evaluated pain scores, sexual function (using FSFI), and distress (using FSDS-R) as well as psychological parameters before and after surgery in 96 patients with DIE or peritoneal endometriosis. Even though pain scores during and after intercourse decreased significantly after surgery, FSFI total scores did not change significantly. This study points also to the influence of the stage and location of endometriosis. In fact, sexual distress improved postoperatively in cases of DIE, but not in women with peritoneal endometriosis and vaginal resection. However, frequencies of interrupted sexual intercourse, feelings of guilt toward the partner, being afraid of pain before and during sexual intercourse, and feelings of being a burden for the relationship decreased significantly in both patients with peritoneal endometriosis and DIE.

Mental health and sexuality. Consequently, factors in addition to pain likely play a comparably important role in determining sexual function in women with endometriosis. Among the psychological factors, depression and anxiety were the most studied (2, 46, 50, 51, 54, 55). De Graaf et al. (56) found that depressive symptoms were significant negative predictors for sexual functioning with an OR of 0.761 (51). Moreover, depression seems to negatively influence female sexual satisfaction (56). According to a prospective cohort study, depression might also have a negative impact on the response to dyspareunia treatment. In this study, higher depression scores at baseline were predictive of persisting dyspareunia at a follow-up after 1 year (55). Fewer studies have reported on the influence of anxiety on sexual function. In a cross-sectional study with 220 women with endometriosis, anxiety—together with sleep quality, pelvic pain, and depression—was among the four major mediators of sexual dysfunction (50). According to a cross-sectional study by Fairbanks et al. (57) involving 245 patients with endometriosis, the more severe the depression and anxiety, the greater the impairment of sexual function.

The relationship between depression and sexual function seems to be bidirectional. In fact, Roomaney et al. (58) found that in women with endometriosis, the quality of their sexual relationship was a significant predictor of the symptoms of depression.

A few studies investigated possible psychological risk factors for sexual dysfunction, in addition to the aforementioned depression and anxiety. One study analyzed the impact of fatigue on patients with endometriosis and found an association between fatigue and poorer sexual functioning (35). A correlation between trauma and stress-related symptoms as well as dissociative symptoms has been observed also in a small cross-sectional study (59). Significantly higher levels of pain catastrophizing as well as alexithymia have been reported among women with endometriosis (46, 60), factors that might enforce their sexual distress.

On the one hand, psychological aspects are important factors in the pathogenesis of sexual dysfunction in women with endometriosis. On the other hand, sexual dysfunction and/or sexual distress also have important psychological consequences.

A cross-sectional study by Sullivan-Meyers et al. (37) explored the relationship between sexual distress and body image in 471 women with a surgical or clinical diagnosis of endometriosis. The investigators observed a high prevalence of both sexual distress and body image disturbance, affecting 83.0% and 77.3% of participants, respectively. High sexual distress was significantly associated with lower body appreciation, higher body image distress, and lower self-compassion.

Patients described feelings of loss of control over their own bodies, worthlessness, hopelessness, lower feelings of femininity, and lower self-esteem (46, 60), resulting from sexual dysfunction.

Relationships and sexuality. Moreover, sexual dysfunction can have a negative impact on the psychosocial and sexual well-being of the partners of women with endometriosis and therefore compromise the relationship. In fact, relationship problems secondary to sexual dysfunction have been reported in 15%–34% of women with endometriosis (46). Interestingly, in women with endometriosis, sexual problems seemed to have a greater negative impact on relationship happiness than in control women (61). In a cross-sectional study with 105 women with endometriosis and their partners, Pereira et al. (62) found that women's sexual satisfaction had a direct effect on their own and their partner's marital satisfaction. The interdependence between endometriosis-related pain (IEP), psychological well-being, and sexual satisfaction of both partners was highlighted in a study by Schick et al. (63). They reported that high depression, anxiety, and stress scores in women were associated with higher impact of IEP on their partners, and vice versa. Moreover, less sexual satisfaction in women was associated with a higher IEP in men (63).

On the other hand, intimate relationships themselves have been shown to influence sexual function in women with endometriosis. In fact, higher couple satisfaction and perceived partner responsiveness were significantly associated with higher sexual satisfaction in the study by Kfoury et al. (56), both in women with endometriosis and in controls. Even in the case of dyspareunia, the relationship might be an important factor of influence. Women with severe pelvic pain and dyspareunia perceive a greater negative impact of their disease on their intimate relationships than women whose symptoms are less severe (64). According to Aerts et al. (65), how the partner responds to the patient's pain likewise influences the woman's experience of pain.

In summary, sexual dysfunction is a highly prevalent but often-overlooked problem in women with endometriosis. Given its influence on psychological well-being, QoL, and intimate relationships, healthcare providers should specifically investigate sexual problems in patients with endometriosis, especially in those suffering from dyspareunia, but also in patients diagnosed with depression or anxiety. Surgical and medical treatment of dyspareunia is important, but given

the complex pathogenesis of sexual dysfunction, interdisciplinary and multimodal treatment, possibly including the partner, should be considered.

Endometriosis and Eating Disorders

Only three studies have investigated whether endometriosis is associated with eating disorders. The first was a population-based register study that followed all women born in Sweden between 1973 and 1990 for diagnosed psychiatric disorders and endometriosis from age 14 years until the year 2016. 14,144 women were diagnosed with endometriosis according to ICD10 codes. Women with certain psychiatric diagnoses, among them eating disorders, were more likely to be later diagnosed with endometriosis (5). The order of manifestation observed in this study suggests that chronic pain alone might not explain the association between these two diseases. This is supported by a genetic association study including 202,276 unrelated female participants, among them 8,276 women with endometriosis and 194,000 female controls (11). The investigators reported increased odds of eating disorders (OR, 2.94; 95% CI, 1.96–4.41) in patients with endometriosis. Using the Scalable Genetic Correlation Estimator method to compute single-nucleotide variant-based heritability and genetic correlation, they found that endometriosis was genetically correlated with eating disorders.

On the other hand, Panariello et al. (66) observed that in patients with endometriosis, pain is associated with impaired eating behaviors. The investigators used several questionnaires to assess eating behaviors and associated feelings in women with endometriosis. They found significant differences between women with no pain and mild pain and women with moderate and severe pain regarding beliefs, feelings, thoughts, and behaviors toward eating. However, this cross-sectional study included only 30 patients with endometriosis and no control group and therefore needs to be confirmed by larger studies.

Another risk factor for the development of eating disorders in women with endometriosis might be the high prevalence of body image disturbance. In fact, Sullivan-Meyers et al. (37) reported that in their study population, 77.3% of patients with endometriosis suffered from a disturbed body image. However, they did not investigate whether there was an association with eating disorders.

Overall, data regarding an association between eating disorders and endometriosis are scarce. Some investigators have proposed a genetic association. Other influencing factors might be the alteration of eating behaviors by pain and the high prevalence of body image disturbance among women with endometriosis. None of the guidelines addresses screening for eating disorders in women with endometriosis. Future studies are needed to further elucidate the possible association between endometriosis and eating disorders and better identify subgroups at risk.

DISCUSSION

This narrative review summarizes the association of endometriosis with mental health disorders. The literature shows an overall high prevalence of depression, anxiety, and sexual

dysfunction in women with endometriosis, with a higher prevalence of eating disorders emerging. Most of the studies report that it is not necessarily the disease per se, but the symptoms it induces, especially pelvic pain, that are associated with a higher risk for mental health problems. This is supported by the comparisons made to asymptomatic women with endometriosis, who are less often affected by mental health problems.

The presence of CPP is an important risk factor for psychiatric disorders such as anxiety and depression (6). This might be explained partially by the negative psychosocial consequences of chronic disease, which are more pronounced in cases of persistent, often daily pain vs. sporadic, cyclic pain. However, there also seems to be a link between the pathogenesis of CPP and mental health problems at a neurologic level. It is believed that a delay in diagnosis of endometriosis of up to 8–10 years leads to long-term pain that is often inadequately treated, contributing to the development of a CPP syndrome (67, 68). In a recent comprehensive review, Mechsner (69) details how, over time, nociceptive pain evolves into a lowered pain threshold accompanied by spinal hyperalgesia and pelvic floor dysfunction, resulting in dysuria, dyschezia, dyspareunia, and CPP. Central nervous system abnormalities in pain processing have been identified in multiple chronic pain syndromes and lately also in women with endometriosis (69). These changes include elevated neurotransmitter levels in the insula and greater connectivity to pain-related regions, and they are also related to anxiety and depression. However, these alterations have been observed only in women with endometriosis and CPP but not in asymptomatic patients with endometriosis, again pointing to the causal role of chronic pain in the development of mental health problems (10).

Besides pain, there has been some indication that an underlying genetic predisposition may play a role in the development of mental health disorders in women with endometriosis. Using genome-wide association study data, Adewuyi et al. (70) assessed the relationship between endometriosis and depression, with the aim of clarifying the biological mechanisms underlying the cooccurrence of the disorders. Interestingly, they found a significant genetic overlap between endometriosis and depression with single-nucleotide polymorphism effect concordance analysis, a positive and highly significant correlation between the two traits with LDSC analysis, and MR analysis suggesting a causal effect of depression on endometriosis. The investigators conclude that these genetic analyses support a causal association between endometriosis and depression and confirm the comorbidity of the two conditions. In a subsequent genome-wide association study likewise using multiple large biobanks and diagnostic codes, Koller et al. (11) evaluated the comorbidity of endometriosis with anxiety, as well as depression and eating disorders. Endometriosis was associated with an increased OR between 3.35 and 5.02 of having those disorders concomitantly. Using the Scalable Genetic Correlation Estimator method to compute single-nucleotide variant-based heritability and genetic correlation, the investigators found that endometriosis was genetically correlated with depression, anxiety, and eating disorders. Once again, LDSC

analyses showed a consistent genetic correlation between anxiety and depression, and MR analysis showed significant associations for depression (OR, 1.09; 95% CI, 1.08–1.11) and anxiety (OR, 1.39; 95% CI, 1.13–1.65), with inadequate power to evaluate the outcome of eating disorders (11). Taken together, these studies provide evidence of a shared genetic etiology for endometriosis and mental health problems.

Considering the high prevalence of mental health problems and the important role of CPP, early diagnosis of endometriosis and effective treatment of endometriosis-associated pain are crucial to preventing the development of CPP and sensitization and hopefully likewise preventing the development of depression, anxiety, and sexual dysfunction. Once these psychological problems have developed, treatment can be challenging, expensive, and often tedious, possibly also because of the underlying neurologic alterations induced by chronic pain (23). Currently, there are no specific recommendations regarding the timing of screening and subgroups at particular risk for depression and anxiety in international guidelines. Nevertheless, given the results of the present review, we recommend the use of short screening questionnaires for depression and anxiety, especially in symptomatic patients with endometriosis.

Recent literature attempts to tease out which women with endometriosis are at the highest risk of mental health problems, as it appears that not all women with endometriosis are at equal risk. Two recent studies aimed to define different phenotypes of endometriosis, probably linked to different, currently unknown pathogenic pathways. Urteaga et al. (71) used patient-generated health data (mostly signs and symptoms) and data-driven phenotyping and characterized four subtypes of endometriosis patients. One subtype with especially severe symptoms was linked to anxiety, depression, chronic fatigue syndrome, and other comorbidities. Similarly, a study on the basis of electronic health records by Sarria-Santamera et al. (7) distinguished six different clusters of women with endometriosis on the basis of their comorbidities. One of the clusters, which was the largest in terms of patient numbers, showed a higher prevalence of anxiety and musculoskeletal disorders. These studies support the hypothesis that different endometriosis phenotypes are associated with different risks of psychological comorbidities, but thus far, clinically useful criteria for distinguishing these subgroups are lacking. Further studies are needed to confirm these results and develop clear and easily applicable tools that allow clinicians to identify patients at risk. Such an approach would allow targeted screening for psychological problems in subgroups with a higher probability of mental health disorders, e.g., using specific questionnaires, and facilitate an earlier diagnosis and initiation of appropriate treatment (72). Another important research field is the influence of treatment for symptomatic endometriosis on coexisting anxiety and depression.

Given the multifactorial pathogenesis and reciprocal influence of physical and psychological factors, the approach to treatment of depression, anxiety, and sexual disorders in patients with endometriosis should be multimodal and multidisciplinary, involving gynecologists, mental health professionals, pain management specialists, and sexual therapists.

Surgical intervention does appear to improve mental health, measured as mental component scores, as reported by most studies included in a meta-analysis by Arcoverde et al. (24). An individualized approach on the basis of endometriosis-related symptoms, life circumstances, and patient priorities (e.g., need for contraception, wish to conceive, and pain management) is necessary to improve the patient's overall QoL. According to recent studies, clinical interventions aimed at enhancing self-compassion and self-care seem to be beneficial (23, 73). Their positive effect on mental health and QoL might be mediated by an increased feeling of self-efficacy and a reduction of the feelings of helplessness and loss of control described by many patients (46, 60). In this respect, the use of mobile applications developed specifically for endometriosis patients could also be helpful. In fact, there is increasing evidence that app-based interventions are an effective cotreatment for chronic pain (74, 75). Recently, some applications have been designed specifically for patients with endometriosis (e.g., Phendo App in the US, Endo-App in Germany), and preliminary data on their effectiveness on pain and QoL are promising (71, 76, 77). When these results are confirmed by larger studies, the assumption of costs by health insurance should be considered, as is already the case for Endo-App in Germany. Moreover, these applications allow the obtaining of longitudinal, patient-generated data via self-monitoring, which can be used to better characterize different endometriosis phenotypes and contribute to a more targeted approach (71).

Another important resource that should be taken into account is intimate relationships. Studies have shown that supportive partners of women with endometriosis can positively influence pain perception, decrease psychological distress, and improve sexual satisfaction (63, 65). Therefore, it is important to involve the partner when counseling and treating women with endometriosis.

CONCLUSIONS

Clinicians should be aware of the high prevalence of anxiety, depression, and sexual dysfunction in patients with endometriosis. Although a subgroup with a particularly high risk of mental health problems among affected women has yet to be defined, those with chronic pain appear to be most affected. The use of short screening questionnaires for anxiety and depression can be used to identify women who should be referred to specialists for further care. Early diagnosis of endometriosis and appropriate management of this chronic disease are vital and will hopefully prove to be a preventive measure for the development of psychological comorbidities. For patients suffering from mental health problems, an individualized, multidisciplinary approach is recommended.

CRedit AUTHORSHIP CONTRIBUTION STATEMENT

Anna Lena Zippl: Writing – review & editing, Writing – original draft, Investigation. **Elisabeth Reiser:** Writing – review & editing, Writing – original draft, Methodology. **Beata Seeber:** Writing – review & editing, Writing – original draft, Project administration, Conceptualization.

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