

# Sexual function in endometriosis patients and their partners: effect of the disease and consequences of treatment

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**BACKGROUND:** Sexual function is an important aspect of health and quality of life and is influenced by both medical conditions and health-care interventions, especially when gynecologic disorders are involved. Coital pain is among the main factors that affect sexual functioning, and this symptom is reported by almost half of women suffering from endometriosis. However, sexuality is a complex phenomenon driven by social, psychological and biological/hormonal factors and the presence of endometriosis might further affect domains of sexual function and the quality of a sexual relationship.

**OBJECTIVE AND RATIONALE:** The objective of this report is to review the current state of knowledge on the impact that endometriosis and its treatments have on the sexual function of women and their sexual partners.

**SEARCH METHODS:** A systematic literature search was performed to identify studies evaluating sexual function in endometriosis patients, and a narrative analysis of results is presented. The review discusses relevant quantitative and qualitative studies analyzing the effect of endometriosis and its hormonal and surgical treatments on measures of sexual function and quality of sexual relationship.

**OUTCOMES:** Endometriosis negatively affects different domains of sexual function, and the presence of dyspareunia is not the only determinant of sexual health in these women. Chronic pelvic pain, advanced stages of disease and the presence of physical and mental comorbidities affect sexual function, as well as personality traits and women's expectations. Although a number of studies have evaluated

the effect of surgery and hormonal treatment on deep dyspareunia, overall sexual function and quality of the relationship with the partner are often under-investigated.

**WIDER IMPLICATIONS:** Multiple clinical and personal determinants affect sexual function in women with endometriosis, with potentially negative consequences on the sexual function of partners and quality of the relationship. Additional prospective and longitudinal investigations are warranted using specific instruments to analyze biopsychosocial variables of sexual pain in endometriosis patients and the effects that actual treatments have on measures of quality of sexual function and relationship.

**Key words:** endometriosis / sexual function / surgery / hormonal treatment

## Introduction

Human sexuality is a complex phenomenon driven by social, psychological and biological/hormonal factors. Sexual health is a critical aspect of quality of life and is also influenced by medical conditions and health-care interventions, particularly when gynecological disorders are involved, such as gynecological cancer, breast cancer or infertility (Langer *et al.*, 2015; Lindau *et al.*, 2015; Candy *et al.*, 2016). Although there has been great progress in understanding human sexuality and improving sexual health in recent years, health-care providers should accelerate and promote this progress to be more inclusive and comprehensive. Sexual and reproductive health are mentioned in the United Nations Sustainable Development Goals, and they represent a target in the post-2015 agenda (United Nations General Assembly, 2015), a sign of increasing global awareness and initiative in moving forward on global sexual health issues, including education, care and rights (Hawkes, 2014; Temmerman *et al.*, 2014; Khosla *et al.*, 2015).

Endometriosis is a global disease affecting 5–15% of women during their reproductive years. According to main international guidelines, endometriosis should be viewed as a chronic disease that requires a life-long individualized management plan with the aim of avoiding repeated surgical procedures. General principles that should guide medical management of endometriosis are not different from those applicable to other chronic inflammatory disorders (Vercellini *et al.*, 2011a; ASRM Practice Committee, 2014; Dunselman *et al.*, 2014). However, endometriosis is also a disease that affects young, sexually active women during different phases of their sexual life and during development of their sexual behavior. Consequently, sexual health is a major concern for endometriosis patients and should also be a primary concern in endometriosis care and research. Because endometriosis is viewed as a chronic disease that affects young women during their reproductive years, it is absolutely necessary to bridge the artificial divide between reproductive and sexual health in endometriosis patients and their partners.

However, the international consensus on future research priorities following the 10th World Congress on Endometriosis did not consider sexual health among symptoms and treatment outcomes (Rogers *et al.*, 2009). Three years later, recommendations for future directions for endometriosis research following the 11th World Congress on Endometriosis underlined the need to better identify clinical features of pain and quality of life, although the notion of sexual functioning did not clearly emerge (Rogers *et al.*, 2013). The importance of analyzing overall sexual function in endometriosis patients gained direct attention only recently in an article published in

2014 by members of the World Endometriosis Society, although the importance of sexual health has been argued since 2011 (Vercellini *et al.*, 2011b; Hummelshoj *et al.*, 2014).

Physical, mental and social dimensions characterize sexual health. The inability to engage in sexual activity in a fulfilling way may affect self-esteem, self-worth and relationships with partners (Basson, 2008). This issue deserves particular attention in the case of endometriosis, in which the decision-making process for treatment is mainly based on patients' symptoms and priorities.

The objective of this review is to analyze the current state of knowledge on the impact that endometriosis and its treatments (medical and surgical) have on sexual function and to provide insights into women's perspectives of sexual pain and consequences for the sexual partner.

## Determinants of female sexual function and dysfunction, with special reference to genital pain

The sexual response is a psychophysiological experience. It is a sequence of physiological events, including sexual desire, arousal and genital responses (Bianchi-Demicheli and Ortigue, 2007; Ortigue *et al.*, 2009). Basson conceptualized sexual response as a motivation-/incentive-based cycle comprising phases of physiological response and subjective experience (Basson, 2015). Phases of this cycle may overlap, and their order may vary. Psychological and biological factors influence the processing of sexual stimuli to allow or preclude subsequent arousal, and the type of outcome (sexual or non-sexual) influences future sexual motivation. Multiple factors, including stage of life cycle, age, relationship duration, mental health and relationship happiness, influence the sexual response between individuals and within a person's own sexual life (Basson, 2015).

Female sexual dysfunction includes a range of disorders, namely, hypoactive sexual desire, reduced subjective and/or physical genital arousal (poor sensation, vasocongestion, lubrication), sexual pain and inability to achieve orgasm/satisfaction, which are multidimensional by nature and often coexisting (Basson *et al.*, 2004; van Lankveld *et al.*, 2010). Therefore, a global approach has been proposed in the DSM-5 diagnostic criteria, which combine desire and arousal disorders into one disorder, namely female sexual interest/arousal disorder. Similarly, diagnosis of vaginismus, vulvodynia and dyspareunia were merged into a new genito-pelvic pain/penetration disorder (GPPPD) (<http://www.dsm5.org>). GPPPD is characterized by persistent or recurrent difficulties for 6 months or more with at least

one of the following symptoms: (1) inability to have vaginal intercourse/penetration, (2) marked genito-pelvic pain during vaginal intercourse/penetration attempts, (3) fear of pain as a result of vaginal penetration or (4) marked tensing or tightening of the pelvic floor muscles during attempted vaginal penetration (<http://www.dsm5.org>).

The association between coital pain and sexual dysfunction is the result of repeated experiences of sex associated with pain and fear of pain. The fearful reaction in turn negatively affects desire, arousal, reward, lubrication, loss of genital congestion and heightened pelvic floor tone in a circular model (Payne et al., 2005; Thomten et al., 2011; Thomten and Linton, 2013). Furthermore, emotional elaboration (anxiety, bitterness or frustration during or after sexual engagement, feelings of guilt, distress) and cognitive elaboration of pain (hypervigilance, catastrophizing) negatively affect sexual motivation and desire/arousal. Finally, central sensitization leads to hyperalgesia and allodynia and secondary hyperalgesia, worsening pain perception (Basson, 2012; Thomten and Linton, 2013; Thomten et al., 2014).

However, while endometriosis-associated sexual pain is classically deep dyspareunia, the majority of studies investigating sexual pain in women have assessed patients affected by superficial dyspareunia/provoked dyspareunia (Basson, 2012; Thomten et al., 2014). Therefore, their conclusions cannot be directly translated into the clinical setting of endometriosis patients, despite the occurrence of symptoms and emotional/cognitive elaboration shared with other causes of sexual pain. Specific features of endometriosis, namely the evolution of disease/symptoms over time, the presence of chronic pelvic pain, long-term hormonal treatment, fertility concerns, extensive pelvic surgery at a young age and risk of recurrence, might affect sexual response and exacerbate the emotional/cognitive elaboration of pain.

## Methods

A systematic literature search was performed to identify studies evaluating sexual function in endometriosis patients. Articles were identified through the following electronic databases: MEDLINE, EMBASE, Google Scholar and The Cochrane Library (until December 2015) databases for all the prospective and retrospective studies with no date limits. We used the following combination of Medical Subject Headings (MeSH): endometriosis, dyspareunia, sexual function, sexuality, libido, arousal, desire, orgasm, satisfaction, pleasure, pain, quality of life, marital status and relationship. All relevant articles were examined, and their reference lists were systematically reviewed to identify other studies for potential inclusion in this review. Selection criteria included retrospective and prospective studies and the analysis of qualitative and quantitative variables. Only studies investigating sexual function in endometriosis patients were included. Studies investigating pelvic pain and dyspareunia without the concomitant analysis of sexual, psychological and social variables were arbitrarily excluded. Additional cross-references were identified during the review search.

## Dyspareunia as a major reported sexual symptom in endometriosis patients

Pain during sexual intercourse is one of the main symptoms among endometriosis patients, and women with endometriosis are at an increased risk of experiencing sexual pain compared with the normal population. In a large case-control study evaluating more than 5000 women with

endometriosis, symptoms associated with sexual intercourse occurred in 11.5% of cases, with an OR of 7.4 (CI 6.5–8.5) compared with controls (Ballard et al., 2006). Specifically, the presence of dyspareunia is an independent risk considered to be affected by endometriosis, with an adjusted OR of 6.8 (CI 5.7–8.2). Interestingly, this risk estimate was in the same range as that of the occurrence of dysmenorrhea and subinfertility/infertility (Ballard et al., 2008). More recently, the WERF EndoCost study showed that 47% of endometriosis patients suffer from dyspareunia (dysmenorrhea was reported by 57% and chronic pelvic pain by 60% of the women; De Graaff et al., 2013). In the same study, multivariate regression analysis showed that sexual pain and chronic pelvic pain (but not dysmenorrhea) negatively affected both the physical health and mental health domains in the SF36 questionnaire (De Graaff et al., 2013). Patients enrolled in that study experienced multiple medical treatments, including hormonal and fertility treatments and in most cases, at least one surgical intervention (De Graaff et al., 2013).

A retrospective qualitative study evaluating the long-term consequences of endometriosis over 15 years showed that 48.5% of patients reported that endometriosis had caused problems with their sex life, but one-third of those patients experienced pain only during certain parts of their menstrual cycle. A significant correlation between dyspareunia and a negative influence on relationships was clearly evidenced (Fagervold et al., 2009). In another cross-sectional study among patients, sexual pain occurred 'most of the time' and 'some of the time' in 27.2% and 35.2% of women, respectively (Lemaire, 2004). A similar prevalence of sexual pain was reported in two additional studies (Jones et al., 2004; Denny and Mann, 2007).

The presence of deep dyspareunia caused by endometriosis is mostly associated with deep lesions infiltrating the utero-sacral ligaments, the pouch of Douglas, the posterior vaginal wall, and the rectum and is less frequently associated with ovarian and bladder lesions (Fauconnier et al., 2002). The association of dyspareunia with adenomyosis is more controversial, although the co-existence of adenomyosis and deep endometriosis (50% of patients) may further worsen sexual pain (Lazzeri et al., 2014).

Reviewing the anatomical and biological causes of dyspareunia in endometriosis is beyond the scope of this review, and many other articles have extensively examined pain symptoms (Fauconnier and Chapron, 2005; Brawn et al., 2014; Morotti et al., 2014b). However, some considerations are critical for the analysis of the effects of chronic sexual pain on overall sexual function, specifically in endometriosis: (1) Dyspareunia may be particularly harmful because it usually occurs whenever intercourse is attempted, whereas dysmenorrhea typically afflicts women during menstruation (Vercellini et al., 2011b). (2) Endometriosis is a risk factor (OR 4.30; CI 1.16–15.90) for the concurrent presence of deep dyspareunia and superficial dyspareunia/provoked vestibulodynia. The presence of these symptoms is also associated with a higher prevalence of depression symptoms (OR 1.07; CI 1.02–1.12) (Yong et al., 2015). Furthermore, the prevalence of pelvic floor tenderness was 40% in a cohort of patients with pelvic pain (OR 4.61; CI 1.55–13.7). In this cohort, dyspareunia was independently associated with pelvic floor tenderness in a multiple logistic regression analysis (OR 4.45; 95% CI 1.86–10.7) (Yong et al., 2014). (3) Other conditions may overlap (10–50% of cases) with endometriosis contributing to painful sex, mostly interstitial cystitis/bladder pain syndrome (Cervigni and Natale, 2014; Yong et al., 2014). (4) Endometriosis lesions are associated with central and peripheral hyperalgesia caused likely by local neuroinflammation, neuroangiogenesis and dysregulation of sensory and autonomic fibers. (5) Dyspareunia in endometriosis is often associated with chronic pelvic pain. The latter is correlated with modifications in the behavioral and functional brain response to noxious stimuli, changes in brain structure, activity of hypothalamic–pituitary–adrenal axis and autonomic nervous system and consequently personal distress (Morotti et al., 2014b).

## Female sexual function in endometriosis patients: not only deep dyspareunia

Although the prevalence of deep dyspareunia and chronic pelvic pain have been widely investigated in endometriosis, female sexual function and the relationship with the sexual partner have been scantily examined in the last decades. Indeed, deep dyspareunia occurrence and intensity has been considered for long time the only instrument to assess sexual functioning in endometriosis.

One of the first assessments of sexual function in endometriosis was done in 1995, where the analysis of 17 patients with minimal or mild symptomatic endometriosis showed an increased rate of sexual avoidance using the Golombok Rust Inventory of Sexual Satisfaction questionnaire, in comparison to controls (Waller and Shaw, 1995). Avoidance was also confirmed in other qualitative studies where the majority of women who suffered dyspareunia avoided or reduced sexual intercourse (Jones et al., 2004; Denny and Mann, 2007).

In 2005, sexual health was evaluated among a cohort of patients suffering from deep dyspareunia caused by different genital diseases. Patient with deep endometriosis infiltrating the utero-sacral ligaments showed more pain based on visual analog scale (VAS) and lower scores in the Global Sexual Satisfaction Index (GSSI) than patients with peritoneal endometriosis and non-endometriosis patients (Ferrero et al., 2005). In addition, sexual pain of patients with deep implants affected the intensity of the orgasm and satisfaction, causing a less relaxed and fulfilled state compared with controls. The presence of endometriosis (any type) was also associated with a reduction of the quality of communication with the partner about sex (Ferrero et al., 2005).

Vercellini et al. confirmed the complexity of the relationship between endometriosis, pain and sexual function (Vercellini et al., 2012). Although patients with deep rectovaginal lesions had poorer sexual function compared to non-endometriosis controls, differences in sexual function domains between women with different types of endometriosis (deep versus peritoneal/ovarian) were only marginal, suggesting that the diagnosis/presence of endometriosis, has a role in determining overall sexual health. Indeed, no significant correlation was observed between deep dyspareunia VAS scores and sexual rating scale. Specifically, rectovaginal endometriosis negatively affects current sexual interest and activity, and previous sexual satisfaction, sexual pleasure, and ability to reach orgasm, with ORs ranging from 2.32 (previous sexual activity) to 5.58 (current sexual interest) on the Sabbatsberg Sexual Self-Rating Scale. This is a 12-item questionnaire suitable for self-assessment of sexual functioning that evaluates six subdomains separately, including sexual interest, sexual activity, satisfaction of sexual life, experience of sexual pleasure, orgasm capacity and sexual relevancy (Garratt et al., 1995). In the rectovaginal endometriosis group, the risk of being sexually unsatisfied or feeling little or no sexual pleasure was three times higher, and the risk of engaging in limited or no sexual activity and of reduced capacity to reach orgasm was approximately two times higher, compared with subjects in the non-endometriosis group (Vercellini et al., 2012). Interestingly, the retrospective assessment of sexual functioning in the years immediately following coitarche did not show any differences, suggesting that sexual impairment in women with rectovaginal endometriosis arose and increased over time, most likely as a result of the development of lesions/symptoms.

A recent multicenter cohort study conducted in Austria and Germany assessed sexual function using two common and validated instruments, the Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale revised (FSDS) (Fritzer et al., 2013). The FSFI is a 19-item questionnaire that has been developed as a brief, multidimensional self-report instrument for assessing the key dimensions (desire, arousal, lubrication, orgasm, satisfaction and pain) of sexual function in women. This test has the advance to investigate pain symptoms and provide a cut score for

differentiating women with and without sexual dysfunction (Wiegel et al., 2005). The FSFI has been widely tested and validated in different cultural environments and medical conditions and it has been also proposed as valid instrument to assess sexual function in endometriosis in a recent consensus paper (Vercellini et al., 2012; Vanhie et al., 2016). The FSDS was developed to provide a standardized, quantitative measure of sexually related personal distress in women with sexual dysfunction (Derogatis et al., 2008).

The cumulative prevalence of sexual dysfunction using the FSFI and FSDS were 32% and 78%, respectively, with a significant correlation between stage of disease, dyspareunia and score on both questionnaires (56% of patients had sexual dysfunction at AFS stage 4). In this cohort, more than half of women (66%) were afraid of pain before or during sexual intercourse. When sexual dysfunction was diagnosed, patients also had a significantly fewer episodes of sexual intercourse per month and greater fear of separation because of coital pain than patients without sexual dysfunction (Fritzer et al., 2013). These results are consistent with those reported in two other studies using the FSFI (Jia et al., 2013; Evangelista et al., 2014) that showed a crude prevalence 70–75% of sexual dysfunction among endometriosis patients. Specifically, compared with the patients with no to mild pelvic pain, those with moderate-to-severe pelvic pain had a 3.4-fold (CI 1.3–8.8) higher risk of sexual dysfunction. Patients with stage III or IV had a 4.4-fold (CI 1.3–15.5) higher risk than those with stage I or II (Jia et al., 2013). The presence of advanced states of disease also affected the desire domain, in addition to sexual satisfaction, orgasm and pain, when analyzed separately using the Sexual Health Outcomes in Women Questionnaire (SHOW-Q) (Montanari et al., 2013; Di Donato et al., 2014). The SHOW-Q is a recently developed 12-item scale for the assessment of four domains of sexual function: satisfaction, orgasm, desire and pelvic problem interference (Learman et al., 2008).

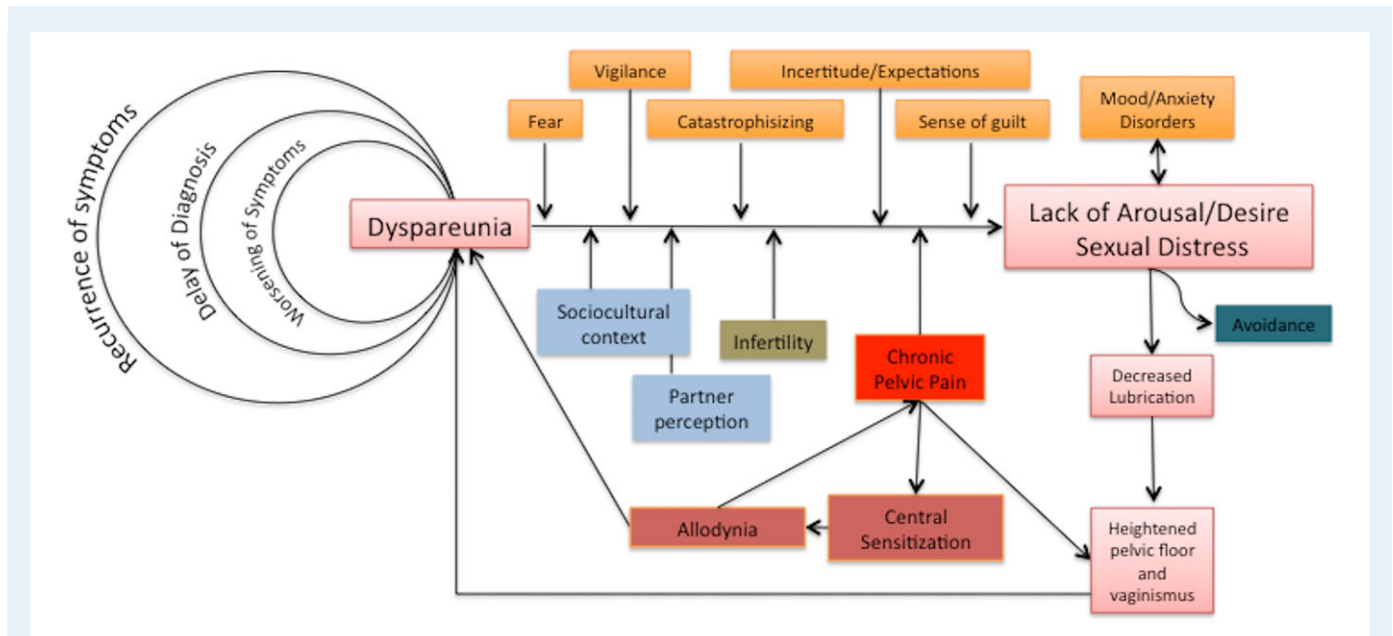
In conclusion, based on available, although limited evidence, endometriosis appears to impact all domains of sexual function, desire/arousal, orgasm, satisfaction, and pain, leading to sexual dysfunction and distress in 70–75% of patients, at least in advanced/chronic cases. According to the motivation/incentive-based cycle of sexual response, repetitive painful experiences and the absence of reward (negative outcome) likely shift sexual response from motivation/arousal to hypervigilance and from desire to fear and avoidance, leading to sexual distress in symptomatic endometriosis patients (Fig. 1).

### *Specific biological and psychosocial variables associated with sexual dysfunction in endometriosis*

Although dyspareunia can be considered the first step in the development of sexual dysfunction, additional factors characterize the evolution towards an impairment of sexual health. According to the fear-avoidance model, multiple biopsychosocial variables influence sexual distress (Fenton, 2007; Desrochers et al., 2009; Basson, 2012; Crombez et al., 2012; Thomten and Linton, 2013).

Some of them may be related to the evolution of disease toward advanced stages and worsening of pain intensity or duration and the development of chronic pelvic pain (Tripoli et al., 2011); others may be related to the hallmarks of endometriosis, namely fertility concerns (up to 30–50% of cases), diagnostic delay and recurrence of symptoms after treatment. Infertility can affect an intimate relationship in a range of ways (Glover et al., 2009): sexual self-esteem may be deflated, paired with a perceived failure to fulfill traditional gender roles and/or external pressures to conceive (Monga et al., 2004; Bayley et al., 2009). Evidence also indicates that infertility status, length of infertility and IVF are associated with worse scores in all domains of the FSFI (Ashraf et al., 2015; Smith et al., 2015). How do fertility concerns and infertility treatment affect





**Figure 1** Adaptation of the fear-avoidance model in endometriosis patients. Sexual pain in endometriosis patients induces a fear-avoidance reaction, leading to arousal/desire disorder and sexual distress in the majority of patients. Biopsychosocial variables of sexual pain play a critical role in the fear-avoidance model. Senses of incertitude, fear, expectations and guilt are often reported in qualitative studies. Similarly, personality traits, coping strategies (catastrophizing) and the occurrence of mood/anxiety disorders are crucial in the evolution from coital pain to sexual dysfunction and distress. The partner's perception of sexual pain and the sociocultural context in which sexual pain and fertility concerns are experienced may exacerbate sexual distress, lack of arousal/desire and avoidance. As result, decreased lubrication and loss of genital congestion (also worsened by pharmacological hypogonadism) heighten pelvic floor tone, risk of vaginismus and pain. Central sensitization caused by chronic pelvic pain leads to hyperalgesia and allodynia, worsening dyspareunia in a circular model. Hallmarks of endometriosis, such as delay of diagnosis and worsening and recurrence of pain, exacerbate dyspareunia and dysfunctional behavior, prolonging the distress.

sexual health in endometriosis patients and their partners? Does the length of infertility (and sexual pain) play a role in predicting the worsening of sexual functioning? What is the effect of getting pregnant on sexual functioning? The available evidence, unfortunately, does not address these questions.

Endometriosis patients suffering from dyspareunia experience a sense of guilt towards their partner, lower feelings of femininity, alteration of body image and alexithymia, which, in turn, exacerbate sexual dysfunction (Fritzer et al., 2013; Melis et al., 2014, 2015) in endometriosis (Fig. 1). In a cohort of patients with chronic pelvic pain due to endometriosis, catastrophizing, a well-known pain-coping mechanism, played a pivotal role in pain experience, severity and recurrence (Martin et al., 2011). Although dyspareunia and sexual health was not assessed in this cohort, catastrophizing was a significant predictor of pain at 1 year of follow-up, and women who showed severe catastrophizing at baseline had higher pain at follow-up (Martin et al., 2011). Interestingly, across control subjects and the chronic pain population, patients with high levels of catastrophizing show augmented musculoskeletal tenderness and intensified pain sensitivity. This population has a higher risk of developing post-surgical and persistent pain syndromes (Turner et al., 2002; Granot and Ferber, 2005).

The long delay between the first onset of symptoms of the disease and diagnosis may also play a role in sexual functioning. Painful sex is rarely brought up to medical attention, and physician awareness/education/sympathy is often inadequate in evaluating the symptom (Jones et al., 2004). Coupled with the delay in endometriosis diagnosis, the perpetuation of painful sexual episodes in young women may exacerbate fear, catastrophizing and avoidance (Fig. 1). Symptomatic patients have frequently reported that they felt a sense of relief, legitimation, liberation

and empowerment, when the nature of disease is identified, replacing incertitude and frustration (Cox et al., 2003a; Ballard et al., 2006; Culley et al., 2013).

An association between endometriosis and psychiatric disturbances such as depression, anxiety and increased stress has also been identified and widely described (Cheong et al., 2008; Lagana et al., 2015; Pope et al., 2015; Chen et al., 2016). Younger patients have an elevated likelihood of developing major depression, any depression disorders and anxiety disorders (Chen et al., 2016). Depression is often associated with chronic illness and independently leads to a higher prevalence of sexual dysfunction (Piazza et al., 1997; Basson et al., 2010). However, whether mood disorders predict sexual dysfunction in endometriosis patients is unknown, and no study has specifically addressed this issue. Thus, the presence of a causal effect, although likely, can only be hypothesized.

### Effect of endometriosis on sexual function of partner and relationship quality

The effects of endometriosis on relationships have not been featured prominently in the available literature. Dyspareunia, female sexual dysfunction and associated infertility (or concerns about possible infertility) may disrupt the relationship with the partner and his/her sexual functioning, especially in young couples. Moreover, the social (and relationship) dimension of pain constantly influences the changing dynamic of pain.

A reduction in the quality of communication about sex with the partner has been assessed in different studies on endometriosis. (Ferrero et al., 2005; Vercellini et al., 2012; Fritzer et al., 2013). In the WERF

Endocost study, among women with affected relationships, 67% declared significant problems with their partner caused by endometriosis (34% of women) and 19% of women considered endometriosis as a cause of their divorce (of 10% of women) (De Graaff *et al.*, 2013). In the retrospective qualitative study by Fagervold *et al.*, 15% of women with endometriosis reported that, over a period of 15 years, they had serious problems in their relationships and 7.7% suffered from a broken relationship due to the symptoms of endometriosis (Fagervold *et al.*, 2009). Previous qualitative studies have documented a strain on social relationships, including reduced social support and several relational difficulties (Cox *et al.*, 2003a,b; Strzempko Butt and Chesla, 2007; Denny, 2009). Decreased socialization due to disease/illness and the incapacity of partners to tolerate chronic symptoms has been attributed to relational breakups or divorce. However, in most cases, the overlap of sexual symptoms with chronic pelvic pain does not allow for any conclusions to be made specifically on sexual complaints. Similarly, the consequences of chronic dyspareunia with or without associated sexual dysfunction for the sexual partner are largely unknown in endometriosis couples. Male partners of women with provoked vestibulodynia also suffer from the consequences of the partner's pain, showing increased rates of psychological distress, increased prevalence of sexual difficulties (e.g. erectile dysfunction), and decreased sexual satisfaction (Jodoin *et al.*, 2008; Smith and Pukall, 2014; Boerner and Rosen, 2015). In the same setting, the quality of the couple relationship, male psychosocial functioning and male self-reported response to pain have all been linked to pain, sexual functioning and emotional/cognitive elaboration of pain among women (Boerner and Rosen, 2015).

## Effects of endometriosis surgery on sexual function

Given the multifaceted aspects of sexual health in endometriosis patients, the question regarding whether surgery might affect sexual function is highly pertinent. Extensive surgery for endometriosis is feasible and effective, but it may be associated with significant complication rates (Dunselman *et al.*, 2014; Pluchino *et al.*, 2015). The potential beneficial effect of extensive surgery on deep dyspareunia has been extensively described in retrospective and prospective studies (Koninckx *et al.*, 1991, 2012; Vercellini *et al.*, 2006, 2009; Meuleman *et al.*, 2009 2011 2014; Dunselman *et al.*, 2014). However, three RCTs comparing diagnostic versus operative laparoscopy on dyspareunia changes did not note any significant outcome difference when the two procedures were compared in case of mild or moderate endometriosis (although the evidence was low quality) (Jacobson *et al.*, 2014).

The assessment of sexual health in the surgical management of endometriosis has not received the same attention as dyspareunia (Fritzer *et al.*, 2014). The paucity of data, methodological limits and inconsistencies of studies compromise the analysis of sexual health in women who have undergone endometriosis surgery.

Conservative surgery was shown to improve dyspareunia and sexual symptoms using the Revised Sabbatsberg Sexual Rating Scale at 1-year follow-up in an RCT comparing the effect of resection with that of non-resection of utero-sacral ligaments on symptom recurrence (Vercellini *et al.*, 2003). Although the presence of deep lesions was not assessed in this trial, the resection of utero-sacral ligaments did not provide any additional advantage in improving sexual health (Vercellini *et al.*, 2003). Similarly, a significant improvement in pleasure and habit and a decrease in discomfort with intercourse was reported 4 months after surgery (Garry *et al.*, 2000), and was maintained for up to 5 years (median follow-up 3.2 years) (Abbott *et al.*, 2003). Interestingly, in the latter study, dyspareunia was the main indication for surgery in only 3.5% of cases and

the second indication in less than 1% of cases (Abbott *et al.*, 2003). A more detailed analysis showed that, 1 year following surgery, patients had an increased variety in sexual life, an increased frequency of intercourse, a relaxed disposition during sex, and more satisfying orgasms and were more relaxed and fulfilled after sex (Ferrero *et al.*, 2007; Dubuisson *et al.*, 2013). Vaginal resection in the case of deep lesions did not impair the recovery of sexual activity and was associated with an improvement in some domains of sexual function in the McCoy Female Sexuality Questionnaire (sexual satisfaction and sexual problems but not satisfaction with partner) (Setala *et al.*, 2012).

Extensive surgical procedures, including bowel resection and/or deep parametrial excision are associated with higher morbidity (rectal, ureteral and bladder fistula, atonic bladder and anal incontinence) and may require additional procedures such as ileostomy and colostomy (Ret Davalos *et al.*, 2007; Vercellini *et al.*, 2009; Ceccaroni *et al.*, 2012). Short- and long-term consequences for personal and couple distress, body image and sexual functioning are therefore expected. Nerve-sparing surgery may provide some advantages over conventional surgery (Ceccaroni *et al.*, 2012; Che *et al.*, 2014). The latter is associated with an increased post-operative sexual impairment (72.3% of patients had neither sexual sensations nor orgasmic pleasure at all), although altered sexual pleasure or reduced sexual pleasure and orgasm frequency have been observed in 47.5% and 11.8% of cases, respectively, also after nerve-sparing surgery (Ceccaroni *et al.*, 2012). Additional studies investigated the effect of bowel resection on sexual function in endometriosis patients. The results were consistent to a certain extent with a reduction in sexual pain but inconsistent among all other domains of sexual function investigated (Kossi *et al.*, 2013; Che *et al.*, 2014; Morelli *et al.*, 2015). A multidisciplinary approach in case of extensive surgery appears to improve functional results in terms of personal distress and sexual health, without significant differences between conservative management and bowel resection (Van den Broeck *et al.*, 2013). Specifically, surgery improved all assessed domains (arousal, sexual desire, orgasm problems and pain during intercourse) and these remained stable over the 18-month follow-up period. Interestingly, relationship satisfaction was not affected by surgery or by the type of surgery (bowel resection versus no bowel resection) (Van den Broeck *et al.*, 2013). Similarly, two studies conducted in the same institution involving 103 and 250 patients with mixed lesions and mixed types of surgical procedures (including bowel resection), respectively, showed an improvement in SHOW-Q scores in all sexual domains at 6 months follow-up without a marked effect of post-operative administration of an oral contraceptive (Mabrouk *et al.*, 2012; Di Donato *et al.*, 2015). However, if not adequately analyzed, the use of post-operative hormonal treatment may represent a limit for the correct interpretation of surgical outcomes. As shown in Table 1, surgical findings of five studies are not properly controlled for the use of post-operative hormones, limiting the interpretation of the real contribution of surgery in improving symptoms (Setala *et al.*, 2012; Dubuisson *et al.*, 2013; Kossi *et al.*, 2013; Di Donato *et al.*, 2015; Morelli *et al.*, 2015). In a recent multicentre study, sexual function (FSFI total score) did not improve after surgery and FSD improved only in patients with symptomatic deep lesions (Fritzer *et al.*, 2016). However, the emotional elaboration of pain (fear, feeling of guilt and physical tension) and the frequencies of interrupted sexual intercourse improved independently of the severity of disease and type of the associated surgical procedure (Fritzer *et al.*, 2016).

The reported recurrence rate of endometriosis has been estimated to be between 5% and 21.5% at 2 years and between 5% and 40% at 5 years (Guo, 2009; Meuleman *et al.*, 2011). Severe deep dyspareunia associated with persistent or recurrent endometriosis after unsuccessful first-line conservative surgery is associated with low scores on FSFI, below the cut-off for normal sexual function (Vercellini *et al.*, 2013). The second-line surgery in this cohort improved all domains of sexual function relative

**Table 1** List of studies investigating the effect of surgical management of endometriosis on sexual function.

| Reference                    | Type of study                | Number of patients                                    | Type of lesion   | Follow-up                | Measuring instrument   | Result  | Note   |
|------------------------------|------------------------------|---|--|--------------------------|--|---|--|
| Garry et al. (2000)          | Prospective, Observational   | 57  | AFS I-IV   | 4 months                 | The sexual Activity Questionnaire  | Improved pleasure, habit, discomfort  |  |
| Vercellini et al. (2003)     | RCT                          | 37 without USL resection + 28 with USL resection      | AFS I-IV   | 1 year                   | Revised Sabbatsberg Sexual Rating Scale                                    | Index score improved in both groups   | No effect of USL resection   |
| Abbott et al. (2003)         | Prospective, Observational   | 125   | AFS I-IV and mixed deep lesions                        | 2–5 (3.2) years          | The Sexual Activity Questionnaire  | Improved pleasure, habit, discomfort  | Results are not controlled for type of procedure                                   |
| Ferrero et al. (2005)        | Prospective, Observational   | 34  | AFS I-IV and mixed deep lesions                        | 1 year                   | Sexual Satisfaction Subscale of the Derogatis Sexual Functioning Inventory | Improved variety in sexual life, frequency of intercourse, relaxed more easily during sex; more satisfying orgasms and more relaxed and fulfilled after sex |  |
| Setala et al. (2012)         | Prospective, Observational   | 22  | Deep Lesion involving the vagina                       | 1 year                   | McCoy Female Sexuality Questionnaire                                       | Improved sexual satisfaction and sexual problems; satisfaction with partner unchanged   | Results are not controlled for hormone use   |
| Mabrouk et al. (2012)        | Prospective Observational    | 103   | Mixed deep lesions                                     | 6 months                 | SHOW-Q   | Improved satisfaction, desire, pelvic pain. Orgasm unchanged  | All patients received post-operative COC.  |
| Meuleman et al. (2011)       | Retrospective, Observational | 30  | Deep lesions involving the bowel (bowel resection)     | 27 (range: 16–40) months | The Sexual Activity Questionnaire  | Improved pleasure, habit, discomfort  |  |
| Dubuisson et al. (2013)      | Prospective                  | 20  | Mixed deep lesions                                     | 23.3 months              | Brief Index of Sexual Functioning for Women                                | Improved desire, arousal, pleasure, orgasm, relational satisfaction   | Results are not controlled for hormone use and type of procedure (bowel resection) |
| Kossi et al. (2013)          | Prospective, Observational   | 26  | Deep lesions involving the bowel (bowel resection)     | 1 year                   | McCoy Female Sexuality Questionnaire                                       | Improved sexual satisfaction; sexual problems and satisfaction with partner unchanged   | Results are not controlled for hormone use   |
| Vercellini et al. (2013)     | Prospective                  | 51  | AFS I-IV and mixed deep lesions<br>Second-line surgery | 1 year                   | FSFI   | Improved all domains. Score remained below the threshold for sexual dysfunction   |  |
| Van den Broeck et al. (2013) | Prospective                  | 76 with bowel resection + 127 without bowel resection | AFS III-IV and deep lesions                            | 18 months                | Short sexual functioning Scale   | Improved arousal, sexual desire, orgasm problems and pain during intercourse. Relationship satisfaction unchanged   |  |
| Morelli et al. (2015)        | Retrospective                | 10  | Deep lesions involving the bowel                       | 1 year                   | FSFI   | Improved pain; other domains unchanged  | Results are not controlled for hormone use   |

Continued

Table I Continued

| Reference                      | Type of study            | Number of patients | Type of lesion                          | Follow-up        | Measuring instrument | Result  | Note                                       |
|--------------------------------|--------------------------|--------------------|---|------------------|----------------------|---|--|
| Di Donato <i>et al.</i> (2015) | Prospective              | 250                | (bowel resection)<br>Mixed deep lesions | 6 months         | SHOW-Q               | Improved all domains                                | Results are not controlled for hormone use |
| Fritzer <i>et al.</i> (2016)   | Prospective, multicenter | 96                 | AFS I-IV and mixed deep lesions         | 10 months (9–12) | FSFI and FSD         | FSFI unchanged<br>FSD improved only in deep lesions |  |

FAFS: American Fertility Society; USL: utero-sacral ligaments; COC: combined oral contraceptive; FSFI: Female Sexual Function Index; FSD: Female Sexual Distress; SHOW-Q: Sexual Health Outcomes in Women Questionnaire.

to the baseline, but the FSFI score remained below the threshold for normal sexual function over the entire study period (1 year). Interestingly, the score improved substantially in the short term after surgery; it then deteriorated after 6–9 months (Vercellini *et al.*, 2013) (Table I).

### Effects of hormonal treatment on sexual function

Currently, hormonal contraceptives, progestins, danazol, GnRH agonists and antagonists and aromatase inhibitors are used in clinical settings for the medical management of endometriosis-associated pain and for secondary prevention (Rocha *et al.*, 2012; Dunselman *et al.*, 2014; Brown and Farquhar, 2015; Pluchino *et al.*, 2016). Although they reduce or counteract the effects of estrogens on endometriosis growth and inflammation, endogenous and exogenous sex steroids interact with nociceptive processes at multiple levels of the peripheral and central nervous system (Martin, 2009; Pluchino *et al.*, 2013a; Morotti *et al.*, 2014b). Pharmacological hypogonadism and hormonal therapy affect brain areas involved in sexual response (desire, arousal, libido), in emotional and behavioral changes (mood, anxiety, fear) as well as in peripheral genital response to sexual stimuli (Fenton, 2007; Pluchino *et al.*, 2009; Pletzer *et al.*, 2015). Use of GnRH analogs in adults with endometriosis is associated with menopausal side effects including hot flashes, mood changes, and sleep disturbance (DiVasta and Laufer, 2013). Depression is also reported as an adverse event in 23% of adult women treated with GnRH analogs (DiVasta and Laufer, 2013). There are no available data on the effect of GnRH agonists on sexual function in endometriosis patients, although studies are consistent with a reduction in deep dyspareunia but also a significant decline in libido and vaginal lubrication. Follow-ups were no longer than 6 months (Henzl *et al.*, 1988; Mettler *et al.*, 1991; Cirkel *et al.*, 1995). Furthermore, there were no data indicating that add-back therapy (any type) would reverse adverse effects on libido in endometriosis patients treated by a GnRH agonist. In contrast, fewer women experienced a loss of libido when NETA, instead of triptorelin, was associated with letrozole (Ferrero *et al.*, 2011).

All combined oral contraceptives (COC) and progestins are effective in relieving pelvic pain and deep dyspareunia in endometriosis patients in several studies, although comparisons between different progestins or COC are lacking (Razzi *et al.*, 2007; Momoeda *et al.*, 2009; Brown *et al.*, 2012; Pluchino *et al.*, 2013b; Berlanda *et al.*, 2016). Nevertheless, only a few studies have investigated the effect of these agents on sexual function in endometriosis. The use of hormonal contraception in healthy women

may be associated with the experience of negative sexual side effects in different domains (sexual activity, arousal, pleasure and orgasm and more difficulty with lubrication) (Davis *et al.*, 2013; Smith *et al.*, 2014). Similarly, certain personality traits (somatic anxiety and stress susceptibility) in healthy women may predict the development of mood disorders during COC use, reducing long-term compliance (Borgstrom *et al.*, 2008). The occurrence of mood disorders and anxiety-like behavior has been also described during progestins treatment, although the bulk of this evidence is not consistent among different studies and can vary according to the class and chemical profile of progestins (Smith *et al.*, 1994; Panay and Studd, 1997; van Wingen *et al.*, 2008; Pluchino *et al.*, 2009; Pluchino *et al.*, 2013b).

At any rate, the occurrence of mood and anxiety changes during hormonal treatment may have far-reaching implications in endometriosis patients, in whom pain, personal distress and sexual function are strongly interrelated and it may also represent an important aspect for long-term treatment compliance.

Moreover, the use of psychotropic treatments can further worsen sexual function in young women, perpetuating negative consequences of endometriosis on sexual function. Indeed, antidepressants with serotonergic activity and antipsychotics that increase prolactin and block dopamine signaling, frequently cause mild to severe sexual dysfunction (Basson *et al.*, 2010; Montejo *et al.*, 2015).

The investigation of sexual functioning in endometriosis following estrogen/progestin treatments commenced only after the year 2000. Table II summarizes the available evidence. A group of 90 patients with pain recurrence/persistence after surgery were randomized to receive cyproterone acetate (CA) or ethinyl estradiol (EE) (0.02 mg) and desogestrel (0.15 mg). The total score on the Sabbatsberg Sexual Rating Scale increased in both groups, without any inter-group difference after 6 months, although 16% of patients receiving CA reported lower libido (Vercellini *et al.*, 2002). Patients with pain recurrence or persistence after surgery were also randomized to receive 1 mg norethisterone acetate (NETA) + 35 µg EE or Leuprolide acetate (LA) + 5 mg NETA daily (Guzick *et al.*, 2011). The index of sexual satisfaction increased only in the LA group (10 patients) after 1-year follow-up despite the improvement in sexual pain in both groups (Guzick *et al.*, 2011). In the case of persistence or recurrence of deep dyspareunia after previous surgery, daily administration of 2.5 mg NETA improved sexual functioning based on the FSFI total score, although the score remained below the cut-off of normal sexual function over the entire study period (1 year). In the same study, patients who opted for surgery instead of administration of NETA showed a better total FSFI score, desire, arousal and lubrication and a



**Table II** List of studies investigating the effect of hormonal management of endometriosis on sexual function.

| Reference                | Type of study                   | Number of patients (Intervention) | Type of lesion/ inclusion criteria                                    | Follow-up            | Measuring instrument            | Result   | Note   |
|--------------------------|---------------------------------|-----------------------------------|---|----------------------|---------------------------------|--|--|
| Vercellini et al. (2002) | RCT                             | 45 (CA) + 45 (EE + DSG)           | Pain recurrence/persistence after surgery (<1 year)                   | 6 months             | Sabbatsberg Sexual Rating Scale | Improved in both groups. Libido decreased in 13% of CA group.  |  |
| Guzick et al. (2011)     | RCT                             | 26 (EE +NETA) + 21 (LA + NETA)    | Pain recurrence/persistence after surgery                             | 1 year (19 patients) | Index of Sexual Satisfaction    | Improved only in LA+NETA group after 1 year.   |  |
| Vercellini et al. (2013) | Prospective                     | 103 (NETA)                        | Deep dyspareunia recurrence/persistence after surgery (mixed lesions) | 1 year               | FSFI                            | Improved all domains. Score remained below the threshold for sexual dysfunction.                               |  |
| Morotti et al. (2014a)   | Prospective                     | 25 (DNG)                          | Rectovaginal lesions in patients not responsive to NETA               | 6 months             | FSFI                            | Improved total score. Mean score remained below the threshold for sexual dysfunction.                          | Two doses of NETA had been used.             |
| Vercellini et al. (2016) | Retrospective, before and after | 90 (NETA) + 90 (DNG)              | Mixed lesions   | 6 months             | FSFI                            | Improved total score in both groups. Score remained below the threshold for sexual dysfunction in both groups. | Results are not adjusted for type of lesion. |

CA: cyproterone acetate; LA: leuprolide acetate; NETA: norethindrone acetate; DNG: dienogest.

similar score for pain and satisfaction at 12 months follow-up. Interestingly, stratified analyses showed that the difference in lubrication, in favor of surgery, was limited to nulliparous women, whereas a benefit of NETA over surgery with respect to orgasm was observed in parous participants (Vercellini et al., 2013). Dienogest (DNG) and NETA showed similar effects in controlling pain symptoms, including deep dyspareunia (Vercellini et al., 2015). The total FSFI score increased in both groups after six months of treatment but was still lower than the threshold value for normal sexual function (Vercellini et al., 2015). Similarly, the FSFI total score improved after switching from NETA to DNG in patients who were unsatisfied by the use of NETA, but it remained below the cut-off for normal sexual function (Morotti et al., 2014a). Although switching to another progestin slightly improved chronic pain, the mean dyspareunia value on the 10 cm VAS scale still measured between 5.5 and 6 cm after 6 months of treatment with DNG in patients with deep rectovaginal lesions (Morotti et al., 2014a) (Table II).

## Discussion

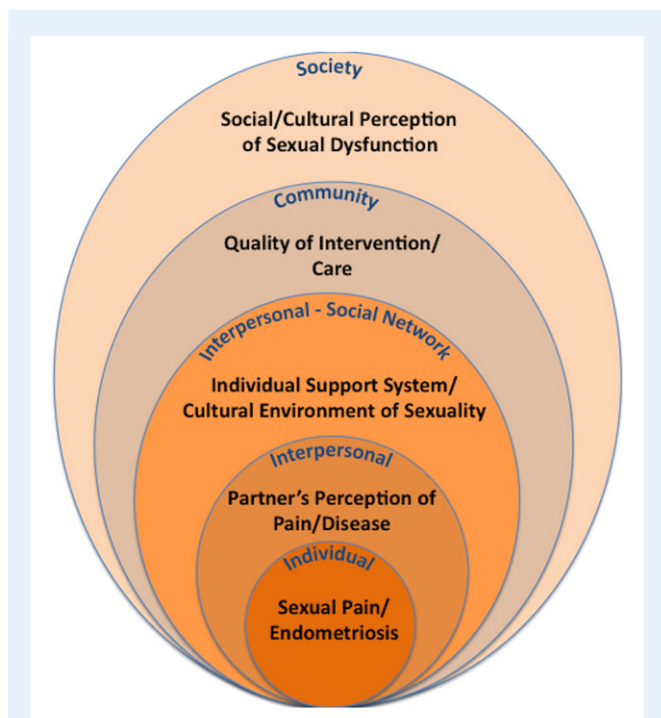
Substantial evidence from qualitative and quantitative studies shows that symptomatic endometriosis negatively affects all domains of female sexual function causing distress. The presence and the assessment of deep dyspareunia provide only a partial clinical picture of the sexual health of the patient, her partner and the couple.

When sexual function is investigated, it does not represent the primary study end-point in most cases, limiting a comprehensive evaluation of sexual functioning. Therefore, evidence lacks quality in terms of research design, diagnostic instruments, study power or adjustment for confounding factors. Follow-ups are rarely longer than 1 year. Moreover, studies have often reported only the total score on questionnaires, hampering the analysis of specific domains of sexual response, such as arousal/desire, satisfaction or orgasm. In addition,

the modality of coital pain assessment limits the interpretation of results. Indeed, the analysis of pain through questionnaires completed by patients does not differentiate between deep dyspareunia, superficial dyspareunia/provoked vestibulodynia, vaginismus and pelvic floor tenderness or their co-existence. Furthermore, as recently described, recruitment strategy (tertiary referral center, community hospitals or patient associations) may also represent a bias in the analysis of outcomes of quality of life (De Graaff et al., 2015).

Nevertheless, in any form of its manifestation, sexual pain in endometriosis patients induces a fear-avoidance reaction, leading to arousal/desire disorder in the majority of patients. Biopsychosocial variables of sexual pain are under-investigated in endometriosis, although they play a critical role in the fear-avoidance model. A sense of incertitude, fear, expectations and a changing self-image are often reported in qualitative studies, but they are neglected in quantitative studies. Similarly, personality traits, coping capacity (i.e. catastrophizing), and the occurrence of mood/anxiety disorders are crucial in the evolution from coital pain to sexual dysfunction and distress, although their risk estimation and predictive values are largely unknown. The social dimension of pain and long-term implications, crucial in the case of sexual pain, have been under-investigated, particularly from an ecological model perspective (Fig. 2). At the intimate level, the partner's perception of sexual pain and the sociocultural context in which pain (and sex) is experienced may exacerbate behavior associated with sexual pressure or withdrawal, perpetuating the distress (Jodoin et al., 2008). At the health-care providers level, the quality of interventions, such as a prompt diagnosis or a physicians' awareness of sexual pain severity, affect fear, incertitude and expectations (Fig. 2).

Although certain speculations emerge from clinical scenarios of other causes of painful sex, the role played by hallmarks of endometriosis (delay of diagnosis, extensive or repetitive surgeries, fertility



**Figure 2** Ecological framework model describing multiple (and interacting) determinants of sexual function in endometriosis patients and their sexual partners, from an individual to a societal perspective. The social dimension of pain constantly influences the changing dynamic of pain, especially in case of sexual pain. At the intimate level, the partner's perception of sexual pain, relational difficulties and cultural environment exacerbate distress for the couple. At the health-care providers level, the quality of interventions, such as a timely diagnosis or a physicians' perceptions of sexual pain severity, affect fear and uncertainty. In a larger perspective, the social/cultural perception of sexual dysfunction influence expectations, attitudes and response to treatment. Long-term implications of sexual pain, from an ecological model perspective, have been largely under-investigated.

concerns) has been neglected. This lack of knowledge (and proper investigation) might explain the inconsistent findings obtained following treatment when the reduction of sexual pain does not necessarily aid the recovery of normal sexual function.

Surgical results are consistent with respect to the reduced sexual pain, but the effects on other domains of sexual function are less consistent. However, radical techniques involving the resection of pelvic nerves may worsen peripheral sexual functioning, and the evaluation of the long-term impacts of surgery may also be affected by other technical factors, mainly the absence of standardization of surgical procedures and quality of care (Pluchino *et al.*, 2015). The persistence or recurrence of pain following surgery has harmful effects on sexual function. Indeed, the identification of psychosocial and biological variables contributing to pain is critical to predicting results and meeting the expectation of patients. Similarly, the effect of hormonal treatment on sexual functioning is less clear. Patients have reported reduced sexual pain, but other sexual function domains are only slightly affected or not affected, especially in case of rectovaginal lesions.

Sexual function in adolescents with endometriosis has also been under-investigated. Two-thirds of adolescent girls with severe dysmenorrhea show laparoscopic evidence of endometriosis, and the consequences of sexual pain in the development of sexual behavior and self-image in this specific population, are largely unknown (Janssen *et al.*, 2013).

## Conclusion

Sexual pain associated with endometriosis has the potential to affect sexual function in young women, leading to fear, a sense of uncertainty and relationship difficulties. Over a longer period of time, this pain may lead to a lack of desire, arousal difficulties and withdrawal. Social, cultural, psychological and biological factors may further exacerbate this clinical picture, particularly in the case of chronic painful disease. Surgical and hormonal treatments do not consistently allow for the recovery of normal sexual function, although they improve pain. However, obtaining consistent findings is hampered by several research limitations. A more inclusive and comprehensive analysis of sexual health in endometriosis is therefore required, including the use of proper instruments and quantitative assessments of pain symptoms, sexual function and distress, taking biological, psychological and socio-ecological variables into account.

Moreover, the value of early treatment (surgical or hormonal) of symptomatic patient requires more attention. At the same time, there is a need for better long-term measures of treatment, which incorporate social, physical and psychological outcomes. These improvements are essential for counseling, treating and meeting the expectations of young, sexually active women affected by endometriosis and their partners.

## Authors' roles

N.P. and M.B. had roles in the study design, acquisition, analysis and interpretation of data and drafting of the article; J.-M.W., P.P., R.T., H.S.T. and F.B.-D. contributed to the analysis and interpretation of data, revision of the article and final approval of the version to be published.

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## Conflict of interest

N.P., J.-M.W., P.P., R.T., M.B., and F.B.-D. have nothing to disclose. H.S.T. is a consultant for Pfizer and has received grants from Pfizer and OvaScience to support research.

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