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## **When love hurts. A systematic review on the effects of endometriosis surgical and pharmacological treatments on female sexual functioning**

*Running headline:* Endometriosis and sexual functioning

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## **Abstract**

*Introduction:* Endometriosis is associated with an increased risk of dyspareunia, therefore this chronic gynaecologic disease should be considered as a major cause of sexual dysfunctions.

The aims of this study were to review the literature on the effects of endometriosis surgical and pharmacological treatments on female sexual functioning, and to provide suggestions for future treatment strategies. *Material and methods:* We followed the PRISMA guidelines to conduct this systematic review, which involved an electronic database search of studies on the association between endometriosis and sexuality published between 2000 and 2016.

*Results:* As a result of the screening process, 22 studies were included in this systematic review. The 22 studies included were divided in 2 categories: 1) surgical intervention studies ( $n = 17$ ), examining postoperative sexual outcomes of surgery for endometriosis; 2) pharmacological intervention studies ( $n = 5$ ), evaluating the effects of pharmacological endometriosis treatments on sexual functioning. The studies considered showed that overall surgical and pharmacological interventions for endometriosis can lead to medium-/long-term improvement, but not necessarily to a definitive resolution of female sexual dysfunctions due to endometriosis. *Conclusions:* Sexual functioning is a multidimensional phenomenon and the ideal treatment for endometriosis related sexual dysfunctions should be conducted by a multidisciplinary team that involves not only gynaecologists, but also sexologists and psychologists/psychotherapists. Improving global sexual functioning, and not just reducing pain at intercourse, should be considered as a major clinical goal of endometriosis treatment.

## **Key-words**

endometriosis, sexual functioning, sexual dysfunction, dyspareunia, female sexuality, sexual health.

## Abbreviations

DIE: deep infiltrating endometriosis

FSFI: Female Sexual Function Index

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

RCT: randomized controlled trial

## Key message

Endometriosis surgical and pharmacological treatments can lead to medium-/long-term improvement, but not necessarily to a definitive resolution of female sexual dysfunction. . Thus, the ideal treatment should be conducted by a multidisciplinary team, with the aim of improving global sexual functioning, and not just reducing pain at intercourse.

## Introduction

Sexual functioning is an important dimension that impacts on women's physical and psychological health, and quality of life (1). Female sexual functioning can be negatively affected by a variety of factors, such as operative vaginal delivery (2) and life stressors related to medical illness, including infertility (1, 3). Among these stressors, endometriosis—a chronic gynaecological disease characterized by the presence of endometrial glands and stroma outside the uterine cavity—is associated with a ninefold increased risk of dyspareunia relative to the general female population (4, 5). Deep dyspareunia (i.e., pain experienced inside the vaginal canal, at the level of the cervix, or in the pelvic/uterine/abdominal region, associated with sexual intercourse) caused by endometriosis has been frequently linked to specific types of lesions, such as those infiltrating the uterosacral ligaments, the pouch of Douglas, the posterior vaginal fornix and the anterior rectal wall (1). Pain during intercourse can be triggered by traction of scarred and anelastic endometriotic tissue or by mechanical pressure on lesions occurring during coitus (1). Dyspareunia is also associated with other forms of sexual dysfunctions, such as hypoactive sexual desire, decreased lubrication, arousal difficulties, and orgasm disorders due for instance to fear and anticipation of pain, which represents one of the most powerful inhibitor of the sexual response cycle (6-8). Several

studies have demonstrated the association between pain at intercourse and anxiety, lower frequency or even avoidance of intercourse, lower levels of desire and arousal, and poorer orgasm (9-11), with negative effects on women's physical and psychological wellbeing, as well as on the couple relationship.

Research investigating the association between endometriosis and global female sexual functioning has outlined an even more complex clinical scenario, suggesting that dyspareunia is not the unique sexual problem associated with the disease. It was estimated that around two thirds of women with endometriosis suffer from some type of sexual dysfunction, such as pain at intercourse, low satisfaction, lack of desire, low arousal, orgasm difficulties, with a negative impact on women's psychological health and intimate relationships (8, 12-14). Because endometriosis affects from 5% to 10% of women of reproductive age (15), it is imaginable that a large proportion of young women in their most sexually active period of life present sexual dysfunction caused by the disease, which may interfere with conception (5). For this reason, dyspareunia and sexual dysfunctions associated with endometriosis represent a major clinical problem as well as an important outcome of endometriosis treatments. However, to our knowledge, there are no published review articles on the effects of surgical and pharmacological treatments for endometriosis on female sexual functioning.

The aims of the current systematic review are: 1) to describe and compare the effectiveness of surgical and pharmacological endometriosis treatments in relation to female sexual functioning; 2) to provide suggestions for treatment strategies based on research evidence.

## **Material and methods**

The present review was conducted according to the PRISMA guidelines for systematic reviews (16) and we ensured compliance by completing the PRISMA checklist. We further assessed the quality of evidence of the selected studies using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria (17). Since only published data were used, the present study was exempt from Institutional Review Board approval.

## *Sources*

An electronic database search (PubMed, Medline) was conducted to identify all English-language journal articles published between January 2000 and January 2016 on the impact of endometriosis treatments on female sexual functioning. Appropriate search terms were constructed by reviewing titles, abstracts, and key-words of a sample of articles investigating sexual dysfunctions in patients with endometriosis. Combinations of subject heading terms including 'endometriosis', 'rectovaginal endometriosis', 'deep infiltrating endometriosis', 'sexuality', 'sexual function', 'sexual dysfunction', 'dyspareunia', and 'sexual life' were used. All pertinent papers were retrieved and their reference lists were systematically examined to identify additional articles. No attempt was made to identify unpublished studies.

## *Study selection and data extraction*

The present review was designed to provide an overview on the effects of endometriosis surgical and pharmacological treatments on female sexual functioning; thus, all published studies evaluating the impact of endometriosis treatments on sexual outcomes were included, without any specific restriction regarding the type of endometriotic lesion and medical intervention. Two authors (G.B. and F.F) conducted an independent screening of all titles and abstracts retrieved from peer-reviewed journals to exclude irrelevant or duplicate citations. Because of the paucity of randomized controlled trials (RCTs) on the sexual effects of medical interventions in patients with endometriosis, we decided to include all selected observational and retrospective studies based on adequacy of description of participants, setting, surgical or pharmacological intervention conducted, and sexual outcomes. In order to investigate all aspects of female sexual functioning, we included only studies in which sexual outcomes were evaluated with a comprehensive sexual questionnaire, focusing not only on dyspareunia, but also on other aspects, such as frequency of intercourses, desire, arousal, lubrication, sexual satisfaction, orgasm. Exclusion criteria were: qualitative research, case-report, commentaries or review articles that did not include original data, measurement of dyspareunia as unique sexual outcome.

Two authors (G.B. and F.F.) designed a data extraction form that was applied to each paper to independently extract data in relation to author, year of publication, location, setting, study design, number of participants, type of endometriosis, sexual functioning questionnaire, type of surgical or pharmacological intervention, time to follow-up, principal aims, and

outcomes. The quality of evidence of the included studies for the outcome of interest was assessed following the criteria described by the GRADE method (17). According to the GRADE criteria, the quality of evidence is divided into four categories: high, moderate, low, and very low.

## Results

A total of 615 articles were identified by database search as potentially relevant. Of these 615 articles, 60 had titles or abstracts reporting findings related to the association between endometriosis and sexuality, as well as to the assessment of sexual functioning after pharmacological or surgical treatment of endometriosis. Overall, 38 articles were not included in the current review: 3 studies because the language used was not English (18-20); 11 because they were review articles or commentaries (5, 11, 21-29); 2 because they were qualitative studies (30-31); 14 because dyspareunia was the only sexual outcome evaluated, no comprehensive sexual questionnaires were used, or no specific information from the questionnaires used was reported (1, 32-44); 8 because they were studies on the impact of having endometriosis on sexual functioning, without considering the effect of any medical intervention (7, 8, 12-14, 45-47). Complete author agreement (G.B. and F.F.) regarding included and excluded studies was achieved. Figure 1 shows the flow diagram of the literature search results. Because almost all studies included in this review are observational studies, the final assessment—according to the GRADE criteria (17)—was low level of quality.

### *Characteristics of studies*

Substantial differences were found in methodology, population, and outcome measures of the studies included. The characteristics of the selected studies are extensively reported in Table 1 in relation to the following variables: author, year, country, study aims, study design, sample, type of endometriosis, sexual functioning measures, time to follow-up. Overall, there were 16 prospective observational cohort studies (48-63), 2 retrospective cohort studies (64, 65), 2 RCT (66, 67), one patients' preference parallel cohort study (68), and one before and after study (69). The number of subjects with endometriosis enrolled in the studies ranged from 7 (50) to 250 (60). The most used questionnaire evaluating sexual functioning was the Female Sexual Function Index (FSFI).

Seventeen studies examined the effects of surgery for endometriosis on female sexual functioning (48-58, 60, 61, 63-65, 68), whereas the impact of pharmacological therapy on sexual functioning was assessed in only 5 studies (59, 62, 66, 67, 69). Four studies analysed the effects of combined surgical and post-operative pharmacological treatment on sexual functioning (52, 55, 60, 68).

The main sexual outcomes of the studies included in the review are reported in Table 2. The heterogeneity of the studies in relation to research methods, types of endometriosis, types of treatment, questionnaires used, and sexual outcomes considered did not allow to adopt a meta-analytic approach to summarize the results. Thus, we decided to classify the studies on the basis of the type of therapeutic intervention performed, so that two categories were identified: 1) surgical intervention and 2) pharmacological intervention studies.

#### *Surgical intervention studies*

We found 17 articles evaluating postoperative sexual outcomes of surgery for endometriosis (48-58, 60, 61, 63-65, 68), which was performed at laparoscopy in most of these studies (48-55, 57, 60, 63, 64, 65). Time to follow-up ranged from 4 (48) to 60 (49) months after surgery and participants were mainly patients with deep infiltrating endometriosis (DIE), rectovaginal or bowel endometriosis; sexual outcomes were often part of post-operative quality of life indicators. Indications for surgery were more frequently persistent pelvic pain or infertility rather than sexual complaints. Overall, postoperative global sexual functioning was assessed in 1505 women who underwent different types of surgery for endometriosis symptoms.

Specifically, Garry *et al.* (48) explored the effects of endometriosis radical laparoscopic excision on quality of life indicators, including sexual outcomes. Primary indication for surgery was pelvic pain (75.4% of women), whereas dyspareunia was an indication for surgery in only 10.5% of cases. The sexual questionnaire used was the Sexual Activity Questionnaire that provides separate scores for pleasure, frequency, and discomfort with sex. Four months after surgery there was significant improvement on all domains of the sexual questionnaire.

Abbott *et al.* (49) conducted a prospective observational cohort study on 176 women with surgical diagnosis of endometriosis. Laparoscopic excision was performed on all endometriosis patients with no hormonal pre-treatment and sexual outcomes were evaluated

up to 5 years after surgery. The majority of patients (74%) suffered from non-menstrual pelvic pain and only 3.5% from dyspareunia; 70% of patients had had one previous surgery. Data on revised American Fertility Society (rAFS) stage of endometriosis were recorded during surgery (see Table 1); 6% of patients had a full thickness vaginal lesion and 88% of women had an involvement of the uterosacral ligaments. Women showed improved sexual functioning (pleasure and habit) and decreased discomfort with intercourse at 60 months after surgery, although the probability of requiring further surgery was 36%.

Ferrero *et al.* (51) evaluated deep dyspareunia and quality of sexual life in 68 women with endometriosis who underwent laparoscopic full excision of endometriotic lesions. A sexual questionnaire based on the DSFI was administered before surgery, and at 6- and 12-month follow-up. Patients were also asked to rate their overall level of sexual satisfaction on a 9-point scale (the Global Sexual Satisfaction Index (GSSI)). At 6- and 12-month follow-up, 75% of women (either with or without endometriosis of the uterosacral ligaments) reported decreased deep dyspareunia. Women with endometriosis of the uterosacral ligaments exhibited increased variety in sexual life, higher frequency of intercourse, more satisfying orgasms, and were more relaxed and fulfilled after sex. A similar tendency was identified in women without endometriotic lesions of the uterosacral ligaments, but statistical significance was not always reached.

The impact of laparoscopic radical resection for endometriosis on different sexual outcomes (i.e., dyspareunia, sexual function, quality of sex life, and interpersonal relationships) was also investigated by Fritzer *et al.* (63) in a multicentre study on 96 women who underwent surgery for endometriosis and concomitant dyspareunia. At 12-month follow-up women reported decreased pain and improved quality of sex life. No postoperative hormonal treatment was administered and the authors concluded that radical laparoscopic excision of endometriosis is effective as it leads to improved dyspareunia and quality of women's sexual experience.

Setälä *et al.* (56) examined sexual functioning in women with deep endometriosis nodules of the vagina after surgery, including vaginal resection. Before surgery and at 12-month follow-up, women's sexual functioning was evaluated using the McCoy Female Sexuality Questionnaire (MFSQ), which assesses sexual satisfaction (sexual enjoyment, satisfaction with frequency of intercourse, frequency of sexual thoughts, arousal during sex,



frequency of orgasm), sexual problems (poor lubrication, painful sexual intercourse), and satisfaction with the partner as a lover and friend. A significant increase in sexual satisfaction and decrease in sexual problems was detected at follow-up. No significant differences were observed in relation to the satisfaction with the partner. Three patients (14%) reported new-onset sexual dysfunctions (i.e., decreased libido, decreased vaginal lubrication, dyspareunia).

Che *et al.* (58) evaluated the sexual functioning of 108 women with DIE by comparing 63 participants who underwent conventional surgery (i.e., complete resection of all detectable endometriotic lesions with a standard surgical procedure at laparoscopy or laparotomy) with 45 patients who underwent nerve-sparing surgery. The Female Sexual Function Index (FSFI) was administered at 6-, 12-, and 24-month follow-up, with significant improvement in all the FSFI domains and the FSFI total score at the 24-month follow-up (except for satisfaction in the conventional surgery group). However, in both groups the total FSFI scores at 24-month follow-up were below the cut-off score indicating sexual dysfunction. Severe postoperative complications such as bladder dysfunction (self-catheterization or alteration in voiding symptoms) were also observed in 15.9% of women who underwent conventional surgery.

Six studies evaluated the impact of laparoscopic bowel resection for severe endometriosis on sexual functioning (50, 53, 54, 57, 64, 65). Meuleman *et al.* (64) retrospectively evaluated sexual function following multidisciplinary CO<sub>2</sub> laser radical laparoscopic excision of deep infiltrating colorectal endometriosis, with a median 29-month follow-up. All 56 procedures were carried out by laparoscopy, and no protective ileostomy was needed in this group of patients. When post-operative hormonal contraception was desired, a low dose oral contraception or a levonorgestrel-releasing intrauterine device was prescribed. No data were provided about the proportion of patients requiring post-surgery hormonal treatment. Sexual functioning improved significantly after surgery with respect to pleasure, discomfort, and frequency of sexual intercourse. In a similar retrospective study published in 2011 (65), the authors confirmed that a radical CO<sub>2</sub> laparoscopic excision of endometriosis with colorectal wall invasion combined with laparoscopic segmental bowel resection and reanastomosis is effective in ameliorating sexual life, in relation to sexual pleasure, frequency of sexual activity and discomfort during sexual intercourse.

Kössi *et al.* (54) prospectively evaluated sexual functioning in 26 patients who underwent rectal or sigmoid resection for endometriosis. At 12 months after surgery, there was a statistically significant improvement in the sexual satisfaction subscale of the McCoy Female Sexuality Questionnaire. A numerical decrease, although not statistically significant, was detected on the Sexual problems subscale, in particular with regard to “painful sexual intercourse”. No differences were found in the partner satisfaction subscale. Two patients reported new-onset deep dyspareunia.

Only one study (53) compared the effects of two different surgical techniques (i.e., the laparoscopic nerve-sparing approach and the classical laparoscopic approach) on sexual functioning in patients with severe deep endometriosis. A total of 126 women were included in the research, 61 treated with nerve-sparing radical excision of pelvic endometriosis with segmental bowel resection and 65 treated with the classical technique. At 12-month follow-up, women’s sexual functioning was evaluated in terms of change in frequency of sexual intercourse, presence of dyspareunia, vaginal dryness, vaginal blood loss after intercourse, use of lubricants, sexual desire, orgasm frequency, and patient’s assessment of comprehensive sexual satisfaction, without using any validated sexual questionnaire. No group differences were found on frequency of sexual intercourses after surgery and number of patients claiming dyspareunia, psychological distress, and vaginal dryness. Patients who underwent traditional surgery reported more frequent vaginal bleeding and lowered sexual desire. Surprisingly, reduced sexual pleasure/frequency of orgasm was more often exhibited by patients treated with the nerve sparing approach relative to those treated with traditional surgery.

Van den Broeck *et al.* (57) compared two surgical procedures (i.e., laparoscopic surgery with bowel resection and laparoscopic surgery without bowel resection) performed on 203 patients with moderate or severe endometriosis on sexual functioning. Both procedures led to improved postoperative sexual functioning relative to preoperative sexual functioning. Specifically, women in the bowel resection group showed significantly better sexual arousal. No significant differences between the two groups were found in relation to sexual desire, orgasm problems, and pain during intercourse. In another study (50), fertility-sparing laparoscopic surgery with bowel resection for severe endometriosis was associated with increased sexual functioning at 12-month follow-up, although full statistical significance was not reached due to the small sample size ( $n = 7$ ).

A recent study by Morelli *et al.* (61) reported preliminary results of a single-institution experience that involved robotic radical treatment (i.e., the DaVinci system) of 10 patients suffering from DIE with colorectal involvement. All women (with the exception of patients who were trying to conceive) were treated with either a continuous low-dose of oral contraceptives or oral progestin for 6 months after surgery. Findings revealed worsened sexual functioning at one-month follow-up as compared with preoperative sexual functioning, which returned comparable with preoperative sexual functioning at 12-month follow-up. A statistically significant improvement one year after surgery was observed only as regards dyspareunia.

Several authors have investigated the impact of surgical treatments for endometriosis and subsequent pharmacological therapies on sexual functioning (52, 55, 60). Ferrero *et al.* (52) examined the effects of laparoscopic excision of endometriosis combined with a postoperative 6-month treatment with triptorelin. Main sexual outcome measures were deep dyspareunia and quality of sex life. At 12 months after completing the postoperative treatment, 45.9% of women did not have deep dyspareunia, 34.7% showed decreased dyspareunia, and 62.2% reported increased frequency of sexual intercourse, as well as improvements in several aspects of sexual life, such as orgasm and satisfaction.

Mabrouk *et al.* (55) investigated the impact of laparoscopic full excision of endometriosis and subsequent combined oral contraceptive therapy on sexual functioning among 106 women with DIE. At 6 months after surgery and subsequent postoperative pharmacological treatment, there were improvements in sexual desire, satisfaction with sex, and pelvic problem interference with intercourse. No significant pre-postoperative differences were found in relation to orgasm between women who underwent intestinal resection and those who had intestinal nodule excision.

Di Donato *et al.* (60) evaluated the impact of laparoscopic surgery for endometriosis (with postoperative hormonal treatment) on sexual functioning by comparing 250 patients affected by DIE with 250 healthy controls. The DIE group showed improved desire, satisfaction, and pelvic problem interference at 6 months after surgery, to the point that these scores were comparable to those reported by healthy women (with the exception of orgasm).

Vercellini *et al.* (68) examined the effects of surgical versus low-dose progestin treatment on sexual functioning in women with endometriosis and associated severe deep dyspareunia. Treatments (laparoscopic surgery or norethisterone acetate 2.5 mg/day per os) were not randomly allocated, as the design of the study was a patient preference, parallel cohort study with a 12-month follow-up. Findings showed improved sexual function immediately after surgery, but the effect declined over time. A more gradual, but progressive increase was observed during progestin use and no significant between-group differences emerged at 12-month follow-up. The authors concluded that both surgery and low dose norethisterone acetate treatment can be considered as valuable strategies for reducing the negative effects of deep dyspareunia related to endometriosis on women's sexual functioning.

Taken together, the above mentioned studies showed that surgery for endometriosis may lead to improved sexual functioning, although the extent and the length of these positive effects were often poorly defined. Most articles had an exclusive focus on DIE and radical laparoscopic surgery (including bowel resection). Although several studies considered of a post-operative pharmacological adjuvant therapy, a comparison between surgery and hormonal treatment was systematically addressed only in one study (68).

#### *Pharmacological intervention studies*

We found only 5 studies (59, 62, 66, 67, 69) investigating the effects of pharmacological treatments for endometriosis on global female sexual functioning. Overall, 396 women were examined. This paucity of data may seem surprising if one considers the huge amount of research evidence for the efficacy of medical treatment for symptomatic endometriosis. However, almost all of these studies focused exclusively on the effects of treatments on deep dyspareunia, without considering global female sexual functioning. Moreover, most studies evaluated the effects of hormonal therapy after surgical treatment for endometriosis, and for this reason were included in the "Surgical intervention studies" section of this review.

Two of the studies investigating the sexual impact of pharmacological treatment for endometriosis are RCTs. The RCT conducted by Vercellini *et al.* (68) compared the effects of cyproterone acetate with continuous monophasic oral contraceptive. Sexual outcomes were examined after 6 months of treatment and improved sexual functioning was identified in both groups, with no statistically significant differences. The RCT conducted by Guzick *et al.* (67)

compared the efficacy of leuprolide and continuous oral contraceptives with regard to sexual satisfaction, with no between-group differences.

Three studies have recently evaluated the efficacy of dienogest, a new progestin specifically proposed for the treatment of endometriosis, on sexual functioning. Morotti *et al.* (59) assessed sexual function after 6-months of dienogest treatment in women with symptomatic rectovaginal endometriosis, who had pain persistence and were unsatisfied after 6 months of treatment with norethisterone acetate therapy. Patients treated with dienogest exhibited increased lubrication, decreased pain, and overall improved sexual functioning. Dienogest was generally well tolerated, with no reported serious adverse effects.

Vercellini *et al.* (69) assessed sexual functioning in 90 patients with symptomatic endometriosis who were treated with norethindrone acetate and 90 who were treated with dienogest. After 6 months of therapy, all participants reported increased sexual functioning, although with no significant group differences, and the average total FSFI score remained below the threshold for sexual dysfunction in both groups.

Caruso *et al.* (62) investigated quality of life and sexual functioning in 54 women affected by endometriosis-associated pelvic pain during a 6-month treatment with 2 mg/daily of dienogest. The control group was composed of women with pelvic pain due to endometriosis who refused to assume hormonal treatments for different reasons and were treated only with non-steroidal anti-inflammatory drugs. Women in the dienogest group showed reduced pain symptoms and increased sexual functioning, whereas no significant changes were observed in the control condition.

## **Discussion**

The aims of the current review were to describe and compare the effectiveness of different treatments of endometriosis in relation to sexual functioning and to suggest useful treatment strategies based on research evidence, as well as new avenues for future studies. In our systematic review, we adopted a comprehensive approach as we considered multiple dimensions of female sexuality, and not just pain at intercourse. Such a wide-ranging perspective is consistent with the evidence provided by the research literature, which has shown that: a) reduction of pain at intercourse, though important, does not necessarily lead to

improved overall sexual functioning (6); b) female sexual function is a multifactorial process that involves different psychological dimensions (e.g., personality traits, body image, self-esteem, relational adjustment) and sexual mechanisms (e.g., interest in sex, desire, arousal, pleasure, satisfaction with sex and with partner), which are pivotal for good sexuality.

Overall, the studies examined in this review highlighted that endometriosis, especially when associated with deep dyspareunia and/or chronic pelvic pain, has strong negative effects on several domains of female sexual functioning, such as desire, orgasm, satisfaction with sex, and frequency of sexual intercourses. Particular types of endometriotic lesions, such as DIE and rectovaginal endometriosis, are associated with the poorest sexual functioning, perhaps because the women affected suffer from deep dyspareunia more frequently than those who have other forms of endometriosis or healthy women (7, 12, 14).

However, several authors (30, 70) have recently suggested that the assessment of dyspareunia itself does not allow for a comprehensive and precise evaluation of female sexual functioning. Although dyspareunia is perceived as very distressing by many women, there may be variability in the way it is experienced, as women may display different coping strategies. For example, some women may decide to avoid pain by limiting, or even avoiding, sexual intercourses; other women may try to find their own way to deal with the pain during sex (for instance, by changing position) for several reasons, such as the importance given to sexual intimacy, or the wish for a pregnancy (30). Different coping strategies may lead to differences in the psychological impact of dyspareunia, for example as regards mental health, self-esteem, feelings of femininity, and sense of guilt toward the partner. These issues have been poorly investigated so far and future studies should examine the role of individual differences, especially in terms of personality traits and coping strategies, to reach broader understanding of sexual dysfunction associated with endometriosis. In this light, interdisciplinary research conducted by different cooperating professionals (such as gynaecologists, psychologists, and sexologists) may lead to increased knowledge, as well as to the development of effective treatment programmes.

Overall, research has shown that surgical and pharmacological interventions are both valuable options to ameliorate sexual outcomes in a medium-/long-term period in women with endometriosis, although the extent and the duration of the observed positive effects have been poorly defined. The reviewed articles focused more on surgical rather than

pharmacological treatment, thus limited evidence is available on the efficacy of hormonal therapy on endometriosis-related sexual dysfunction. This paucity of data may be due to the fact that the types of endometriosis more frequently associated with sexual impairment (i.e., DIE and rectovaginal endometriosis) have been historically treated with surgery, although some authors have underlined that medical treatments other than surgery may lead to substantial relief of pain in women with these forms of endometriosis (23, 33, 70-73).

Overall, heterogeneity of population, instruments, and sexual outcomes considered did not allow to pool data and estimate the sexual effects of the interventions evaluated by the studies included in this review. However, some conclusions can be drawn from our analysis. Surgical treatment may improve sexual functioning in women with endometriosis, irrespective of the type of surgery (standard surgical procedure at laparoscopy or laparotomy; radical, conservative, or nerve sparing surgery). Postoperative improvement in sexual functioning is presumably linked to cessation of pain, especially dyspareunia, due to the excision of endometriotic foci. Several studies (11, 14) have shown that this sexual benefit appears more evident when the endometriotic lesions are localized in the posterior pelvic compartment (i.e., pouch of Douglas, uterosacral ligaments, posterior vaginal fornix, recto sigmoid portion of the bowel), thus confirming the hypothesis that pain at intercourse may have an organic, mechanistic origin. Future studies with longer follow-up times should investigate whether the positive sexual effects of surgery are long-lasting or tend to fade over time, which represents an important clinical issue.

It should also be reminded that complete radical excision of DIE frequently involves concomitant bowel or parametrial resections and/or vaginal opening; these procedures are often associated with a high risk of intra- and postoperative major complications, such as ureteral, bladder, or bowel injuries or potential risk of pelvic denervation (1, 14, 63). Therefore, this surgery requires high level technical competence and should be performed in specialized referred centres for surgical treatment of endometriosis; patients should be exhaustively informed about types and incidence of possible complications, and gynaecological surgeons should be able to adequately manage bowel or urinary damages or, alternatively, they should work in a multidisciplinary team that includes a general and/or urological surgeon.



Risks and benefits of any surgical procedure must always be considered and clearly explained to women in order to obtain a full informed consent. This is important if one considers that the expected advantages of surgery may influence women's choices. For example, expectations of pain relief, infertility resolution, or amelioration of sexual health may affect patients' decisions to undergo high risk elective surgery. Moreover, women should be informed that, unfortunately, the global effectiveness of surgical treatment of DIE is operator-dependent. Overall, in the absence of absolute medical indications, surgery can be considered as a good option to improve dyspareunia and global sexual functioning when hormonal treatment is not feasible (such as for women who are attempting spontaneous conception), or when estrogen-progestin or progestin treatment is ineffective, contraindicated or not tolerated because of side effects.

The evidences (although limited) provided by the studies on the efficacy of different hormonal treatments with respect to female sexual functioning suggest that pharmacological intervention could be a good option for women who are not seeking conception, or underwent multiple surgeries for endometriosis without long-lasting benefit, or refuse surgery due to potential complications. Further research is needed in order to investigate the role of hormonal therapy, as well as the effects of the various available compounds.

Overall, the generalizability of the results provided by the studies examined in this review is limited. In most studies evaluating surgical treatments, the presence of sexual dysfunction was not the reason for surgical intervention and sexual functioning was not the primary study outcome, which involves limitation in the external validity of the reported benefits. The population examined represents another limitation, since several studies included only women with deep dyspareunia, while other articles did not provide clear information about pain severity or types of endometriotic lesions. In several studies (52, 55, 60) women underwent a combined surgical and postoperative hormonal treatment, such that it was not possible to clearly identify the proportion of variance explained by surgery versus hormonal therapy. Furthermore, many studies did not report whether patients underwent a pre- or postoperative hormonal treatment, which entails partial understanding of the results. More research is necessary to explore in-depth sexual functioning in women with endometriosis. Future studies should consider the impact of other dimensions, such as infertility, which significantly affects intimate relationships, as well as the role of the partner.



## Conclusions

Sexual functioning is negatively affected by endometriosis, which means that a large proportion of women of reproductive age present sexual dysfunction. The research literature on endometriosis, as well as our own clinical practice, undoubtedly indicate that these young women very often do not have the chance to experience pleasure associated with sexual activity. Furthermore, the extant literature on the effects of surgical and pharmacological interventions for endometriosis suggests that medical treatment is indeed useful, but may not necessarily lead to long-term, definitive resolution of women's sexual problems.

Since sexual functioning is a multidimensional phenomenon deriving from the interaction of multiple physical/anatomical, psychosocial, and emotional factors (74), and considering that endometriosis affects multiple physical and psychological dimensions (75), we think that the best treatment programme can be provided by multidisciplinary teams composed of gynaecologists, sexologists, and psychologists/psychotherapists.

A more comprehensive perspective not exclusively focused on pain may help rule out sexual dysfunction in a more complete and precise manner, with subsequent identification of the most appropriate approach to treatment. As demonstrated by several studies (6), different types of sexual dysfunction (such as pain during intercourse, hypoactive sexual desire disorder, lack of arousal, or lack of orgasm) require different treatment programmes. Therefore, comprehensive sexual health assessment should be routinely conducted with all women referring to dedicated endometriosis centres and the improvement of sexual functioning should be considered as a major therapeutic goal. Sexual questionnaires may be effectively used by all gynaecologists during preliminary assessment to outline women's sexual profile, as well as to facilitate patient expression of thoughts, feelings, complaints or questions regarding sexual life. This is particularly important if one considers that patients may feel embarrassed and therefore reluctant to express any type of feeling or concern regarding sexuality to their gynaecologists. At the same time, gynaecologists may be more likely to prioritise addressing other endometriosis-related issues, such as pelvic pain and its medical treatment, with a general lack of knowledge about sexual medicine that may not allow formulating appropriate questions to rule out sexual dysfunction and indicate adequate therapeutic options.

We believe that gynaecological practice with endometriosis patients may be improved by providing gynaecologists with training in sexual medicine . If sexual dysfunction is ruled out during preliminary assessment, further investigation should be conducted by professionals specialized in sexual counselling and therapy focusing not only on the symptoms presented by the patient, but also on the association between sexual problems and other important psychological, relational, and cultural dimensions, such as for instance self-esteem, body image, quality of intimate relationship and dyadic coping strategies, and cultural beliefs about femininity and sexuality.

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## Legends

Figure 1. Study selection flow chart.

Table 1. Characteristics of studies included in systematic review of evaluation of sexual function after treatments for endometriosis.

Table 2. Interventions and main results of individual studies included in systematic review of evaluation of sexual function after treatments for endometriosis.

Table 1. Characteristics of studies included in systematic review of evaluation of sexual function after treatments for endometriosis.

Author, year	Country	Study aims (only regarding sexual function)	Study design	Sample	Type of endometriosis	Sexual functioning measures	Time to follow-up (months)
Garry <i>et al.</i> , 2000 (48)	United Kingdom	To evaluate sexual outcomes after radical laparoscopic excision of endometriosis	Prospective study	57 women with endometriosis	63.2% of women with rAFS stage III-IV 44 women with DIE of uterosacral ligaments; 23 women with ovarian endometriosis 19 women with complete obliteration of the pouch of Douglas 34 women with rectovaginal endometriosis	Sexual Activity Questionnaire	4
Vercellini <i>et al.</i> , 2002 (66)	Italy	To evaluate the degree of satisfaction with medical therapy	RCT	90 women with endometriosis	Women with rAFS stage I-IV	SRS Scale	6
Abbott <i>et al.</i> , 2003 (49)	United Kingdom	To evaluate sexual outcomes after laparoscopic excision of endometriosis	Prospective observational cohort study	176 women with endometriosis	14% of women with rAFS stage I 28% of women with rAFS stage II 17% of women with rAFS stage III 41% of women with rAFS stage IV	Sexual Activity Questionnaire	60

Author, year	Country	Study aims (only regarding sexual function)	Study design	Sample	Type of endometriosis	Sexual functioning measures	Time to follow-up (months)
Lyons <i>et al.</i> , 2006 (50)	Australia	To describe the effect of fertility-sparing laparoscopic excision of endometriosis and bowel resection on sexual outcomes	Prospective observational cohort study	7 women with endometriosis	Severe endometriosis involving the bowel	Sexual Activity Questionnaire	12
Ferrero <i>et al.</i> , 2007 (51)	Italy	To examine the quality of sex life and deep dyspareunia in women who underwent complete laparoscopic excision of endometriosis and did not receive any post-operative medical treatment.	Observational cohort prospective study	68 women with endometriosis	59 women with rAFS stage I-II 9 women with rAFS stage III-IV 44 women with endometriosis of the uterosacral ligaments	Sexual Satisfaction Subscale of the DSFI; GSSI	12
Ferrero <i>et al.</i> , 2007 (52)	Italy	To evaluate the quality of sex life and deep dyspareunia after laparoscopic full excision of endometriosis combined with postoperative triptorelin treatment for 6 months	Observational cohort study	98 women with endometriosis and 64 women with inclusion of the uterosacral ligaments	Not specified	Sexual Satisfaction Subscale of the DSFI; GSSI	12
Meulemann <i>et al.</i> , 2009 (43)	Belgium	To evaluate sexual outcomes after CO <sub>2</sub> laparoscopic excision of colorectal endometriosis	Retrospective cohort study	56 women with endometriosis	Deep infiltrating colorectal endometriosis 95% of women with rAFS stage IV	Sexual Activity Questionnaire	29 (median follow-up period)
Guzick <i>et al.</i> , 2011 (67)	U.S.A	To evaluate sexual satisfaction in patients underwent leuprolide versus OC treatment for endometriosis associated pain	RCT	47 women with endometriosis	Not specified	Index of Sexual Satisfaction (ISS)	12

Author, year	Country	Study aims (only regarding sexual function)	Study design	Sample	Type of endometriosis	Sexual functioning measures	Time to follow-up (months)
Meulemann <i>et al.</i> , 2011 (65)	Belgium	To evaluate sexual functioning after CO <sub>2</sub> LPS excision of colorectal endometriosis combined with laparoscopic segmental bowel resection and reanastomosis	Retrospective cohort study	45 women with endometriosis	DIE with colorectal involvement	Sexual Activity Questionnaire	27 (median follow-up period)
Ceccaroni <i>et al.</i> , 2012 (53)	Italy	To compare laparoscopic nerve-sparing approach versus classical laparoscopic procedure in relation to different clinical outcomes including sexuality	Prospective cohort study	126 women with endometriosis	DIE	Self-report questionnaire (frequency of intercourse, dyspareunia, vaginal dryness, sexual desire, orgasm, sexual satisfaction)	12
Kössi <i>et al.</i> , 2012 (54)	Finland	Evaluation of sexual functioning after rectosigmoid resection for endometriosis	Prospective study	26 women with endometriosis	Colorectal endometriosis	MFSQ	12
Mabrouk <i>et al.</i> , 2012 (55)	Italy	To evaluate the impact of the laparoscopic full excision of DIE (intestinal resection or nodule excision) and postoperative combined oral contraceptives administration on sexual functioning	Prospective cohort study	106 women with endometriosis	DIE	SHOW-Q	6
Setälä <i>et al.</i> , 2012 (56)	Finland	To evaluate sexual functioning after surgery for endometriosis, including vaginal resection	Prospective observational study	22 women with endometriosis	Rectovaginal endometriosis	MFSQ	12

Author, year	Country	Study aims (only regarding sexual function)	Study design	Sample	Type of endometriosis	Sexual functioning measures	Time to follow-up (months)
Van den Broeck <i>et al.</i> , 2013 (57)	Belgium	To rule out differences in sexual functioning in women with endometriosis who underwent laparoscopic surgery with versus without bowel resection	Prospective cohort study	203 women with endometriosis	Women with rAFS stage III-IV	SSFS	18
Vercellini <i>et al.</i> , 2013 (68)	Italy	To estimate the effect of surgical versus low-dose progestin treatment on sexual functioning	Patients preference, parallel cohort study	154 women with endometriosis	Women with rAFS stage III-IV 55 women with ovarian endometriosis and 59 with rectovaginal endometriosis	FSFI	12

Che <i>et al.</i> , 2014 (58)	China	To investigate the efficacy of nerve-sparing surgery for DIE on sexual functioning	Prospective study	108 women with endometriosis	DIE	FSFI	24
Morotti <i>et al.</i> , 2014 (59)	Italy	To evaluate changes in sexual functioning at 6-months dienogest treatment in women who were unsatisfied after 6-months of norethisterone acetate therapy.	Prospective study	25 women with endometriosis	Rectovaginal endometriosis	FSFI	6
Di Donato <i>et al.</i> , 2015 (60)	Italy	To evaluate the impact of laparoscopic excision on sexual functioning in women with DIE compared with healthy women	Prospective study	250 women with endometriosis and 250 healthy controls	DIE	SHOW-Q	6
Caruso <i>et al.</i> , 2015 (62)	Italy	To evaluate sexual functioning and quality of life in women with symptomatic endometriosis	Prospective study	54 women with endometriosis and 48 women with endometriosis who	Symptomatic endometriosis	FSFI, FSDS	6

		and treated with dienogest		refused to take use of dienogest			
Morelli <i>et al.</i> , 2016 (61)	Italy	To evaluate sexual functioning after robot-assisted surgery for radical treatment of DIE with colorectal involvement	Prospective study	10 women with endometriosis	DIE with recto-sigmoid colon involvement	FSFI	12
Vercellini <i>et al.</i> , 2016 (69)	Italy	To evaluate sexual functioning after six months of dienogest therapy versus sexual functioning observed during previous noretisterone acetate therapy	Before and after study	90 women with endometriosis	Symptomatic endometriosis	FSFI	6
Fritzer <i>et al.</i> , 2016 (63)	Austria and Germany	To evaluate the effect of LPS radical resection of endometriosis on quality of sex life and dyspareunia	Prospective study	96 women with endometriosis	Patients with histological proven endometriosis and dyspareunia lasting for at least 6 months	FSFI, FSDS	12

Abbreviations: rAFS, revised American Fertility Society; DIE, deep infiltrating endometriosis; RCT, randomized controlled trial; SRS Scale, revised Sabbatsberg Sexual Self-Rating Scale; GSSI, Global Sexual Satisfaction Index; MFSQ, McCoy Female Sexuality Questionnaire; SHOW-Q, Sexual health Outcomes in Women Questionnaire; FSDS, Female Sexual Distress Scale; SSFS, Short Sexual Functioning Scale; FSFI, Female Sexual Function Index.

Table 2. Interventions and main results of individual studies included in systematic review of evaluation of sexual function after treatments for endometriosis.

Author, year	Type of surgical intervention	Type of pharmacological intervention	Results (Only sexual outcomes)
Garry <i>et al.</i> , 2000 (48)	Radical laparoscopic excision of all detected endometriosis	//	Four months after surgery all domains of the questionnaire (habit, pleasure, and discomfort with sex) significantly improved.
Vercellini <i>et al.</i> , 2002 (66)	//	Low-dose cyproterone acetate versus continuous monophasic oral contraceptive	A significant improvement in sexual function was observed in both the cyproterone acetate arm and the oral contraceptive arm; there were no significant differences between the two groups.
Abbott <i>et al.</i> , 2003 (49)	Laparoscopic excision of endometriosis	//	There is a significant improvement in pleasure and habit, and a decrease in discomfort with intercourse that is maintained up to 5 years..
Lyons <i>et al.</i> , 2006 (50)	Fertility-sparing laparoscopic surgery with bowel resection	//	Sexual outcomes improved 12 months after surgery, although measurements did not reach statistical significance
Ferrero <i>et al.</i> , 2007 (51)	Complete laparoscopic excision of all visible endometriotic lesions	//	12 months after surgery patients with endometriosis of the uterosacral ligaments reported increased variety in sex life, increased frequency of intercourse, more satisfying orgasms and being more relaxed and fulfilled after sex. Similar improvements were observed among women with endometriosis but no involvement of uterosacral ligaments; however for some variables statistical significance was not reached.
Ferrero <i>et al.</i> , 2007 (52)	Complete laparoscopic excision of endometriosis	Postoperative triptorelin treatment for 6 months	12 months after surgery, 45.9% of patients had no deep dyspareunia, and 34.7% reported a decrease in deep dyspareunia intensity. 62.2% of women reported an increase in the frequency of sexual intercourse. Improvements in achieving orgasm and global sexual satisfaction were reported.
Meulemann <i>et al.</i> , 2009	Radical laser CO <sub>2</sub>	//	Sexual function improved significantly following surgery with respect to pleasure, discomfort

Author, year	Type of surgical intervention	Type of pharmacological intervention	Results (Only sexual outcomes)
(64)	laparoscopic excision of deep infiltrating colorectal endometriosis, with active involvement of a colorectal surgeon and/or urologist		and frequency of sexual intercourse.
Guzick <i>et al.</i> , 2011 (67)	//	12 months of either depot leuprolide, 11.25 mg every 12 weeks with hormonal add-back using norethindrone acetate 5 mg orally daily, or a generic monophasic oral contraceptive daily	There were no significant differences between the two groups as regard to sexual satisfaction
Meuleman <i>et al.</i> , 2011 (65)	Radical laser CO <sub>2</sub> laparoscopic excision of deep infiltrating colorectal endometriosis, combined with laparoscopic segmental bowel resection and reanastomosis	//	The sexual activity questionnaire showed a significant improvement after surgery in sexual pleasure, frequency of sexual activity and a significant reduction in discomfort during sexual intercourse
Ceccaroni <i>et al.</i> , 2012 (53)	Nerve-sparing radical excision of pelvic endometriosis with segmental bowel resection (group B) versus laparoscopic non nerve-sparing excision of pelvic endometriosis with bowel resection (group A)	//	No difference were found between the two groups in frequency of sexual intercourses after interventions and the rates of patients claiming dyspareunia, psychological distress and vaginal dryness. Patients in group A claimed more frequent vaginal bleeding, lowered sexual desire. Contrarily, a reduced sexual pleasure/frequency of orgasm was claimed by more patients in group B.



Author, year	Type of surgical intervention	Type of pharmacological intervention	Results (Only sexual outcomes)
Kössi <i>et al.</i> , 2012 (54)	Laparoscopic complete excision of all pelvic endometriotic lesions and bowel resection for colorectal endometriosis	//	12 months after surgery a significant increase in the sexual satisfaction subscale ( $P=0.01$ ) was observed. A statistically significant decrease was detected in “painful sexual intercourse”. Sexual problems and partner satisfaction scores had not changed significantly.
Mabrouk <i>et al.</i> , 2012 (55)	Laparoscopic surgery for deep endometriosis: complete, nerve sparing excision of endometriotic lesions (intestinal resection or nodulectomy).	Postoperative administration of OC	At 6 months follow-up sexual desire, satisfaction with sex and pelvic problem interference with intercourse are significantly improved ( $P<0.05$ ). Laparoscopic management of DIE did not change significantly the orgasm area of the sexual function ( $P=0.7$ ) No difference in sexual outcomes was observed between patients submitted to intestinal resection or nodule excision.
Setälä <i>et al.</i> , 2012 (56)	Complete excision of endometriotic nodules in the posterior fornix of the vagina, including vaginal resection, by a laparoscopic or combined laparoscopic-vaginal approach.	//	12 months after surgery, the sexual satisfaction score was higher ( $P =0.03$ ) and the sexual problems score lower ( $P=0.04$ ) compared with baseline values.
Van den Broeck <i>et al.</i> , 2013 (57)	Laparoscopic radical surgery for endometriosis, with or without bowel resection	//	Overall women in the bowel resection group had better outcomes in the SSFS arousal domain For sexual desire, orgasm problems and pain during intercourse no significant differences between the two groups were found ( $P<0.05$ ).
Vercellini <i>et al.</i> , 2013 (68)	51 patients in surgery group: attempt to remove all endometriosis lesions. Two patient with rectovaginal lesions underwent colorectal resection	103 patient in progestin group: Norethisterone acetate 2.5 mg per day	Global sexual function improved immediately in the surgery group, but worsened with time, whereas sexual function improved more gradually, but progressive, in the progestin therapy group. No significant differences were observed between the two study group at 12 months follow-up. A tendency was observed towards a slightly better sexual function after surgery at the end of the study period.

Author, year	Type of surgical intervention	Type of pharmacological intervention	Results (Only sexual outcomes)
Che <i>et al.</i> , 2014 (58)	A total of 108 women underwent conventional laparoscopic or laparotomic surgery (n=63) or nerve-sparing surgery (n=45) for the treatment of DIE	//	The total postoperative FSFI score 24 months after surgery increased significantly in both groups, with no between-group difference. When analyzed separately for each FSFI domains, both groups showed similar results for desire, arousal, and orgasm and had an elevated score immediately after surgery, which almost remained unchanged over time. Differently, pain score significantly increase after surgery and dropped over time. For satisfaction FSFI domain, the results showed no significant difference at the 24-month follow-up compared with the pre-operative assessment. However, the total post-operative FSFI score and the 6 subdomain scores of the questionnaire were below the cut-off of dysfunction before and after surgery.
Morotti <i>et al.</i> , 2014 (59)	//	Treatment with dienogest in patients who were unsatisfied with previous 6 months noretisterone acetate treatment	Women after 6 months of dienogest treatment showed increased FSFI values compared to women at the end of 6 months of noretisterone acetate treatment. Regarding each domain of the FSFI questionnaire, a statistical increase was found on lubrication and pain scores
Di Donato <i>et al.</i> , 2015 (60)	Complete laparoscopic excision of all visible endometriotic lesions	//	A significant improvement was found between pre- and post- laparoscopic surgery in the desire, satisfaction, and pelvic problem interference with sex scales of the sexual questionnaire. At 6 months follow-up the distribution of the SHOW-Q scores was comparable to healthy women's scores, apart for the orgasm score.
Caruso <i>et al.</i> , 2015 (62)	//	6-months Dienogest therapy	All aspects of the FSFI and FSDS questionnaire significantly improved after 6 months of 2 mg/daily dienogest therapy, as compared to the control group
Morelli <i>et al.</i> , 2016 (61)	Robot-assisted surgery for the radical treatment of DIE with colorectal involvement	Post-operative OC in all cases except for women who were trying to conceive	All aspects of the FSFI questionnaire worsened significantly 1 month after surgery, but showed a subsequent progressive increase and 12 months post surgery the scores were comparable to those assessed pre-operatively. Dyspareunia was significantly improved 12 months after surgery with respect to the baseline assessment.
Vercellini <i>et al.</i> , 2016 (69)	//	6-months Dienogest therapy	A statistically significant increase in total FSFI score was observed in women treated with dienogest, with no statistically differences compared with women treated with noretisterone acetate. The increase in sexual function was homogenous on the six different subdomain of the FSFI. Although, the 6 month total FSFI score remained below the threshold for sexual dysfunction
Fritzer <i>et al.</i> , 2016 (63)	Laparoscopical radical resection of endometriosis	//	Pain scores as well as feelings of guilt toward the partner, being afraid of pain and feeling of being a burden for the relationship significantly decreased after surgery.

Abbreviations: OC, oral contraceptives; FSFI: Female Sexual Function Index; DIE: deep infiltrating endometriosis; SSFS: Short sexual functioning scale; FSDS: Female Sexual Distress Scale; SHOW-Q: Sexual health Outcomes in Women Questionnaire.

Figure 1. Study selection flow chart.

