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## Abdominal-pelvic pain in female patients with endometriosis - a review of the literature

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## **Cover Page Footnote**

All authors have equally contributed to this paper.

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## Review

# Abdominal-pelvic pain in female patients with endometriosis - a review of the literature

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### Abstract

Abdominal-pelvic pain is the dominant symptom in endometriosis, one of the most common pathologies that affect women, being also a multifactorial disorder. Exploratory laparoscopy allows the correct assessment of the location as well as severity and extent of the lesions, thus representing the current gold standard in diagnosis. The correlation of pain intensity with the evolutionary stage of endometriosis is inconstant. Surgical treatment, preferably performed laparoscopically, includes the excision of the ectopic endometrium, having as a primary objective the control of persistent pain and the removal of all endometriotic foci. This procedure helps to improve the life quality of the patient, to reduce relapses, to control postoperative pain, and to eliminate the disease. Pre- and post-operative adjuvant medical treatment is used due to its effects on the symptomatology, prolonging the asymptomatic period of the disease. Despite the use of the above procedures, there are cases in which the abdominal-pelvic pain persists even after surgery, which makes endometriosis a significant challenge for both the specialist and the patient, as well as for the medical system itself, as the study of the pathogenic mechanisms is yet the subject of numerous studies. Nutritional education in these patients is essential, given the recommendation to restrict the range of foods and to increase other foods that have an important role in reducing the risk or even leading to regression of the endometrial pathology.

### Keywords

: endometriosis, pain, postoperative, estrogens, treatment, nutrition.

### Highlights

- ✓ Pain is the main symptom in endometriosis and its control/ monitoring by physician and patients is essential.
- ✓ The standard surgical treatment consists in laparoscopic excision of the ectopic endometrium, plus adjuvant pre/ postoperative medical therapy.

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## Introduction

Endometriosis is one of the most common gynecological and surgical pathologies that affect women during the fertile period, being a condition maintained by the presence of estrogen hormones (1, 2). It is the leading cause of chronic pelvic pain in women of reproductive age (3). The condition is defined by “the presence of endometrial glands and stroma outside the endometrium.” Thus, it can frequently affect the pelvic organs (the ovaries, Douglas’ cul-de-sac, the fallopian tubes and the uterine ligaments) and, more rarely, the structures in the peritoneal cavity, the periumbilical tissues, and even structures located far from the internal genitalia (the lymph nodes, the lungs, the heart, the bones) (4).

## Discussions

### Etiopathogenesis

Endometriosis is a multifactorial disorder. Data in the literature show an increased frequency of this pathology in women aged 20-50 years, this being based on the estrogen involvement in the pathogenesis of the disease (5). Genetic factors play an important role in the occurrence of endometriosis, patients with a 1st degree affected relative having a risk of developing endometriosis of approximately 7 to 10 times higher than other women, with multiple identified loci: WNT4, CDKN2B-AS1 and GREB1 [5].

Endometriosis presents a significant challenge to the medical system since its actual prevalence is difficult to estimate due to several factors: the diagnosis of certainty is made laparoscopically, many women being asymptomatic, and many of those who experience symptoms do not consult a doctor for a correct diagnosis (6). However, studies published in specialized journals reveal a prevalence of endometriosis of approximately 50% among women with chronic pelvic pain at a fertile age (7).

Among the risk factors are nulliparity, early menarche, and frequent or prolonged menstruation (3). Lifestyle, but especially dietary habits, appear to play an essential role in the establishment of endometriosis and frequently consumed foods such as red meat, coffee, and trans fats are also considered risk factors. As for protective factors, we note pregnancy, menopause, breastfeeding, and consumption of fresh vegetables, fruits, and omega -3 polyunsaturated fatty acids (3, 8).

### *Pain in Endometriosis*

The clinical manifestations of endometriosis depend on the location of the lesions, the most common being abdominal-pelvic pain, dyspareunia, and

dysmenorrhea (9). Women who experience symptoms of endometriosis have a low quality of life, as reported in medical studies (10). Moreover, the data in the literature reveal that the partners of the women affected by endometriosis are also affected, this being a disorder that compromises other aspects of the couple’s life (intimacy, pregnancy planning, active life, household income, etc.) (11).

### *Mechanism of pain in endometriosis*

Pain in endometriosis occurs due to the long-term stimulation of nociceptive receptors, but, despite this, the precise mechanisms which lead to the occurrence of pain are incompletely elucidated, with several theories postulated (12). One posits that endometriosis occurs due to the direct and indirect effect of active bleeding of the endometrial tissue with abnormal localization (9). Another theory posits an inflammatory cause in which cytokines and growth factors which activate the macrophages and other cells associated with the functional endometrial tissue are suspected (9, 13). A third postulation which has gained increasing numbers of followers assumes that pain in endometriosis occurs through the irritation or direct invasion of the nerves by the ectopic endometrial tissue (especially those within Douglas’ cul-de-sac) (9). However, all three theories may play some role in understanding the etiopathogenesis of pain in endometriosis (9).

### *Measurement of pain*

Since pain is the primary symptom in endometriosis, its quantification in time has been attempted by the introduction of different systems such as a Visual Analogue Scale (VAS), the McGill Pain Questionnaire, or a unique, simple categorical scale. Despite these efforts, studies have generally shown that the intensity of pain is not correlated with the severity of the disease (9, 14).

### *The psychological impact of pain in endometriosis*

A study conducted on 81 women with chronic pelvic pain has shown that women with endometriosis have a psychological profile different from those with pelvic pain due to other causes. Also, pain intensity is not always correlated with standardized psychometric scores, thus concluding that there are various psychological aspects which predispose confident women with endometriosis to more intense suffering (15).

### Diagnosis

#### *Clinical diagnosis*

The specialist can diagnose endometriosis after a case history and clinical examination in approximately 80% of the cases. Being an estrogen-dependent

affliction, endometriosis is most commonly suspected in women at a reproductive age who suffer from chronic abdominal-pelvic pain. The clinical examination must include a speculum and a bimanual examination for more accurate diagnosis (16).

#### *Invasive paraclinical diagnosis*

The gold standard in the diagnosis of endometriosis remains (exploratory and perhaps therapeutic) laparoscopy followed by the withdrawal of bioptic samples for making the diagnosis of certainty; the open path approach is reserved for cases in which laparoscopy is contraindicated (1, 16, 17).

Data that permit the determination of the stage of endometriosis can also be obtained laparoscopically. Several stage scales have been used in time, one of the most important being American Fertility Society classification of endometriosis (18, 19). A retrospective study conducted at Tohoku University Hospital on 618 patients diagnosed with endometriosis following laparoscopic exploration revealed that in 40% of the cases, the stage of endometriosis was not correlated with the severity of the pelvic pain experienced by those patients. At laparoscopic exploration, there have been women with advanced stages of the disease who did not experience severe abdominal-pelvic pain and women with mild stages of the disease whose quality of life was low due to severe pelvic pain (20).

#### *Non-invasive paraclinical diagnosis*

Although laparoscopy is the gold standard for the diagnosis of endometriosis, its disadvantages (invasiveness, delay in diagnosis and treatment, major limitation in the diagnosis of retroperitoneal lesions) have led, in recent years, to intensive research to find more efficient and less invasive methods for diagnosing this extremely unpleasant and persistent-pain causing malady (20).

Despite such efforts, imaging explorations (abdominal-pelvic ultrasound, MRI, CT with contrast medium) and the identification of serum markers for endometriosis (CA-125, CA 19-9, CA-125+NLR, CA-125+MCP-1+leptin, CA-125+MCP-1+leptin+MIF) have limited utility in medical practice, the role of laparoscopy continuing to be of a crucial importance (16, 21).

#### Treatment

The treatment of endometriosis can be surgical, medical, or combined (22). The objectives of the treatment are the control of the symptoms and the decrease in the relapse rate, as there is no curative treatment. The choice of optimal treatment for the

patients should consider the particularities of each case since currently no evidence support one therapeutic method over another regarding the control of the symptoms (3). However, irrespective of the method of treatment chosen, the effect of treatment in endometriosis is generally accepted as being useful regarding rates of recurrence and control of the symptoms (3).

Surgical treatment includes the ablation or the excision of the ectopic endometrium and can be performed laparoscopically (preferably) or classically. The goal of the surgical treatment is the removal of all foci of endometriosis identified in the pelvic genital structures and within the peritoneal cavity, a procedure which has been identified as significantly relieving the painful symptoms, improving the quality of the patients' life, and reducing the risk of relapse (17).

#### *Control of postoperative pain*

The rates of postoperative recurrence for pelvic pain, in the case of patients with endometriosis, are still significant (23). This significant rate of recurrence is associated with ovulation, and thus it has been found that the inhibition of ovulation after surgery greatly decreases the risk of postoperative relapse (24). Therefore, pre- and postoperative adjuvant medical treatment is used due to its effects on symptomatology, prolonging the asymptomatic or oligosymptomatic period of the patients (1). In the immediate postoperative period, the administration of painkillers and anti-inflammatory treatment is sufficient (25).

Subsequently, attention is directed to the prevention of postoperative recurrences. For this purpose, several classes of medication are used in different therapeutic regimens. The theory "the production of pseudo-pregnancy," considered to be the gold standard in the past, consists of inducing pseudo-pregnancy in patients with endometriosis by the administration of gestagenic agents followed by the administration of GnRH and Danazol analogues. Currently, this strategy has been replaced by simple (Dienogest) progesterone treatment or the treatment with GnRH analogues, these having the same efficacy as the old therapeutic strategy, as evidenced by numerous studies (9, 26).

Treatment with GnRH analogues (Nafarelin acetate, Goserelin acetate) has proven effective in the control of painful symptom recurrence in the postoperative period, but it also has adverse effects such as bone demineralisation, vasomotor symptoms, and mood swings. Therefore, it is recommended that the value of serum estradiol be maintained, as much as possible, around 60 pg/mL (26).

Danazol, a derivative of 17  $\alpha$ -ethinyltestosterone, has proven as efficient as GnRH analogues in the control of postoperative pain. On the other hand, GnRH analogues have been better tolerated, since Danazol has more frequent and important adverse reactions: hirsutism, acne, weight gain, and deepening of the voice (10).

As for the control of postoperative pain through the administration of oral contraceptives, results are mixed regarding the efficacy of continuous vs. cyclic regimens, leaving the preferred method to be confirmed by future studies (9).

Another approach worth consideration is the determination of nutrient deficiencies in patients, knowing that such deficiencies alter lipid metabolism, cause oxidative stress, and strongly promote epigenetic changes involved in the genesis and progression of this pathology. The nutritional recommendations in patients with endometrial pathology specifically target the consumption of fresh vegetables and fruits, of organic origin, of products rich in omega-3 fatty acids, and of whole grains that have proven their protective effect. Along with these recommendations, administering resveratrol supplements, dietary supplementation with vitamin D, and N-acetylcysteine seem to have an adjuvant effect (27-29).

## Conclusions

Pain is the main symptom in endometriosis and its control through different methods is a significant challenge for both the physician and the patient. Since no curative treatment is available due to the non-clarification of pathogenic mechanisms, the management of endometriosis is based on the control of the symptomatology and prevention of relapse, for such purposes being used both medical and surgical methods. The standard surgical treatment consists in excision or ablation of the ectopic endometrium through a laparoscopic approach, and the pre- and postoperative medical treatment is an adjuvant one (NSAIDs, oral contraceptives, GnRH analogue, Danazol).

Despite these therapeutic measures, there is a fairly high rate of relapse and implicitly of the quasi-constant pain that accompanies it. Nutritional education in these patients is important, given the recommendation to restrict certain foods and increase intake of foods that reduce the risk of or even lead to regression of the endometrial pathology. It is necessary to reconsider nutritional medical intervention as well as dietetic education in these patients, these two aspects being important tools in the prevention and treatment of endometriosis.

## Conflict of interest disclosure

The authors declare that there are no conflicts of interest to be disclosed for this article.

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