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Management of pelvic pain caused by endometriosis

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Management of pelvic pain caused by endometriosis

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ABSTRACT



Endometriosis is a disorder of the epithelium and/or endometrial-like stroma outside the endometrium and myometrium, usually with an associated inflammatory process. It mainly affects young women of reproductive age, the prevalence being estimated at approximately 10%. Due to the varied clinical symptoms marked by chronic pelvic pain, dysmenorrhea, infertility, dyspareunia, dysuria, endometriosis requires a complex treatment. Endometriosis is a major health problem with socioeconomic impact, which is why many gynecological societies have published different guidelines to assist clinicians in the diagnosis and treatment of endometriosis. The variety of available treatments combined with the complexity of this disease leads to significant discrepancies between recommendations. The most used is the ESHRE guidelines published in 2022, which represents an update of the ESHRE guidelines on endometriosis published in 2013 and 2005 regarding the diagnosis and treatment of endometriosis. The purpose of this review is to provide an overview of endometriosis treatment methods after comparing several widely used guidelines in endometriosis management.

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Introduction

Pain caused by endometriosis is one of the most common chronic pelvic pains in women. It has a debilitating potential and a significant impact on the quality of life. Endometriosis is a benign gynecological affection, difficult to diagnose and treat. It presents multiple localizations (uterine or outside the uterus) and it is involved in more than 25% of infertility cases and in more than 75% of episodic pelvic pain (depending on the phase of the menstrual cycle) or permanent pelvic pain cases. Secondary dysmenorrhea is sometimes associated with external endometriosis. Dyspareunia also occurs as part of the painful picture of endometriosis [1]. Surgical treatment of endometriosis in combination with drug treatment is the standard therapy, although a high relapse of symptoms is observed [2]. The etiology of endometriosis is not fully understood, but there are several theories.

Transplantation theory: fragments of the endometrium during menstruation may reflux through the fallopian tubes into the abdominal cavity, with subsequent insemination [3].

The theory of epithelium metaplasia: mesothelial cells covering the internal genitalia, peritoneal cavity and viscera undergoing a process of endometrioid metaplasia [4].

The induction theory is based on the association of the two previous theories. Endometriosis originates from the coelomic mesothelial stem cells, under the influence of certain induction factors released by menstrual blood and endometrial cells destroyed by macrophages [5].

Other factors responsible for the development of endometriosis: vascular and lymphatic propagation (explaining endometriotic lesions at a distance), genetic and immunological factors, obstructive congenital anomalies, grafting of ectopic endometrium during surgery [6].

This paper represents a review of the existing literature on treatment of pelvic pain caused by endometriosis. Eligible studies were found on PubMed, Cochrane Library and Medline databases performing a research based on keywords such as “endometriosis” and “pain” or “allodynia” or “hyperalgesia” and “treatment” or “management”. The study aims to discuss the options for

treatment regarding pain associated with endometriosis, discussing benefits and disadvantages while trying to identify the most successful therapeutic approach of pain caused by endometriosis.

Discussions

Mechanisms of endometriosis induced pain

During the effort of explaining the mechanisms of endometriosis induced pain, the focus has mainly been on the endometrial lesions and adhesions, although lesion removal does not succeed to produce pain relief in all patients, approximately 30% of patients still presenting pain after surgery as proven in a 2004 study on 39 women, suggesting that that other additional mechanisms are taking part in pain generated by endometriosis [7,8]. Other mechanisms involved in pain generation include inflammation as a result of cyclical bleeding from lesions, and the consequences of the created inflammatory environment which determine a change in sensory nerve activation and altered activation of nociceptive pathways [9-11]. As the mechanisms behind chronic pain associated to endometriosis are complex so is the management approach.

Treatment considerations

The therapeutic plan should be individualized for each patient. Consideration should be given to: patient's age, desire to preserve fertility, lesion's anatomical location, lesion extension, symptoms, risks and adverse reactions of treatment methods, and of course the cost of each method [12-14].

Endometriotic lesions involved in the development of pelvic pain may be located at uterine level, ovarian, vesical, ureteral, rectal or even parietal. Depending on the lesion's extension, they can generate different degrees of pelvic pain, accentuated or diminished by certain positions or movements, or even intra-abdominal adhesions.

Treatment methods

Treatment ranges from a medical approach based on hormonal medications to laparoscopy for removing endometriotic implants includes NSAIDs, hormonal contraceptives, GnRH analogues, and aromatase inhibitors, depending on the severity of symptoms and the patient's treatment response [15-17].

Both treatment methods, medical or surgical, are effective in reducing pelvic pain, but have different risk profiles. In most cases, single treatment modality has been proven not to be effective, better results being achieved using both surgical and drug treatment [18].

The American Society of Reproductive Medicine Practice Committee states that "endometriosis should be viewed as a chronic condition requiring a long-term therapeutic management plan, with the predominant use of drug treatment, avoiding repeated surgery as much as

possible". Also, another commonly accepted approach is that before starting treatment, the patient should have a thorough anamnestic, clinical and paraclinical documentation of the disease, excluding other causes of pelvic pain [19,20].

The choice of the therapeutic plan is based both on the efficacy of the method and on the patient's tolerance and goals.

Medical treatment

Patients with mild or moderate painful symptoms, which do not involve absence from daily activities, and without ultrasound evidence of endometrioma, benefit as first-line treatment from non-steroidal anti-inflammatory drugs (NSAIDs) or hormonal therapy with combined oral contraceptives (COCs), as these have few side effects, are effective in reducing symptoms in most women and have a systemic effect, acting on all likely sites. Women who wish to become pregnant can safely use non-steroidal anti-inflammatory drugs, with the caveat of avoiding COX-2 inhibitors (coxibs), as these can interfere with ovulation. Studies cannot prove a greater efficacy of non-steroidal anti-inflammatories over oral contraceptives or vice versa [18,21].

First-line treatment for patients without contraindications is a combination of NSAIDs and combined oral contraceptives (COCs). For patients with contraindications or who do not want estrogen treatment, a combination of NSAIDs and progestin-based oral contraceptives is indicated [18].

Patients with severe symptoms, involving regular absence from work, who do not respond to the above therapies, benefit from treatment with GnRH analogues, sometimes accompanied by hormone therapy or diagnostic or operative laparoscopy. Hormone therapy helps to combat hypoestrogenic effects such as vaginal dryness or hot flushes [18].

Treatment with aromatase inhibitors is a treatment of last resort, as its long-term effect is not sufficiently studied in endometriosis. It is intended for patients with symptoms refractory to other therapeutic methods [18].

A meta-analysis of 41 studies of GnRH agonists, made by Julie Brown and Roger J Hart, has shown that they are as effective in treating the pelvic pain symptoms of endometriosis as other drug therapies [19]. However, the study failed to establish a therapeutic course, optimal dosage or duration of treatment. Due to numerous adverse effects, including vasomotor symptoms and accelerated bone density reduction, treatment with GnRH agonists is limited to 6 months of treatment. This period can only be exceeded if add-back therapy is combined. The add-back therapy is a treatment that contains a small amount of estrogen and progestin or progestin-only that is taken every day. Since hormones are important to keep our bones healthy, low levels of hormones can lower our bone density, putting us at risk for osteoporosis [18,20].

The advantages of drug therapy include concomitant treatment of all sites of the disease, good tolerance and compliance with treatment, low number of side effects, and ancillary benefits such as contraception [21,22].

Disadvantages of the drug method are represented by the time needed for the medication to produce a response, not being effective in all patients and continuity until menopause, when lesions typically regress in the absence of hormonal stimulation. Also, discontinuation/non-compliance may lead to recurrence of symptoms. In addition, women who plan to become pregnant in the near future should discontinue drug treatment, as these drugs have been shown to have not only a contraceptive effect, but also a potential teratogenic effect.

Hormone treatment with GnRH

The mechanism of action of GnRH agonists involves induction of amenorrhea and endometrial atrophy [23,24].

Their benefit relates to the fact that they can be used in Extragenital Endometriosis, being the first line of treatment in this pathology, succeeding in inhibiting the production of pituitary hormones and thus inhibiting the growth of ectopic tissue [25].

Disadvantages of their administration are the variety of adverse reactions induced by the hypoestrogenic state: hot flushes, vaginal dryness, decreased libido, mood swings, headache and bone fragility.

Therefore, to reduce the severity of hypoestrogenic side effects associated with GnRH agonist treatment, combination therapy with a progestogen or a combination of estrogen and progestogen has been advocated. Studies have shown that combination therapy does not decrease the efficacy of GnRH agonists, but only ameliorates side effects [26,27].

Analysis of 15 studies comparing different GnRH agonist treatment regimens with Danazol, involving a total of 1,821 women, found no significant differences between the two drugs in terms of pain relief, regardless of the dose administered [28]. The difference, however, lies in the adverse reactions induced, Danazol being associated with anabolic and androgenic side effects: weight gain, hirsutism, acne, oedema and myalgia. But of all 15 studies, only one found that the GnRH agonist was more effective than Danazol in reducing endometriosis symptoms (58.7% vs. 43.9%) [23].

A long-term follow-up study conducted by Tandoi I and Candiani M at the Obstetrics and Gynecology Unit, Scientific Institute San Raffaele, Milano, Italy on young women undergoing first-line conservative surgery for endometriosis treated with only a GnRH agonist for six months found a 53% recurrence of disease/symptoms two years after treatment, but recurrence rates after GnRH agonist treatment, similar to recurrence rates after Danazol therapy [29].

Surgical treatment

Medical therapy is typically the first line of treatment for endometriosis due to the risks associated with surgery, including recovery time and upfront cost. However, if medical therapy fails to alleviate symptoms or if a woman experiences recurrent pain, surgical options such as resection of endometriosis or nerve transection procedures may be recommended. Surgery can provide a histologic diagnosis, assess pelvic cysts or masses with features that suggest malignancy, and reduce pain by eliminating endometriotic implants [30].

Surgery is considered for women who have persistent pain despite medical therapy, are unable or unwilling to undergo medical therapy, require a tissue diagnosis of endometriosis, need to exclude malignancy in an adnexal mass, or have bowel or urinary tract obstruction.

Conservative versus definitive surgery

Conservative surgery is the first-line surgical option for most patients. Its advantages are that it preserves fertility and hormone production, is less invasive, has less morbidity than definitive surgery and has documented short-term efficacy. When conservative surgery is performed, excision of the lesions is recommended rather than ablation in most cases [19].

Definitive surgery includes hysterectomy, with or without oophorectomy. Hysterectomy is reserved for women with persistent bothersome symptoms of endometriosis, who are not planning a future childbirth and in whom both medical therapy and at least one conservative treatment procedure have failed. Definitive surgery is also reasonable for women who have additional indications for hysterectomy (e.g., symptomatic fibroids or prolapse). Hysterectomy is an effective treatment for the painful symptoms of endometriosis, with a reoperation rate of 19% in one study compared to a reoperation rate of 58% for women undergoing conservative surgery [31-34].

Women receiving oophorectomy include those with extensive adnexal disease and those for whom the risks of reoperation outweigh the risks of premature menopause. Oophorectomy likely increases the effectiveness of definitive surgery but is also accompanied by quality-of-life issues and potential adverse effects of premature menopause [35-37].

The main disadvantages of definitive surgery are loss of fertility, higher rates of surgical complications, negative impact on body image and surgical menopausal symptoms. The advantages are a lower reoperation rate than for conservative surgery [38,39].

Prospective studies of over 37,000 hysterectomies reported an overall complication rate of 3.5%, compared with a laparoscopic complication rate of 0.2%, as reported in a recent retrospective series of 1894 laparoscopic procedures [40-43].

Conclusions

Endometriosis should be viewed as a chronic disease that requires a lifelong management plan in order to maximize the use of medical treatment and avoid repeated surgical procedures [44].

Both drug and surgical treatment are effective in treating endometriosis-associated pain. First-line treatment for patients without contraindications is the combination of NSAIDs and combined oral contraceptives (COCs) [45].

GnRH agonists should be used in women who have not responded to first-line treatment, preferably in combination with add-back therapy or for up to 6 months without add-back therapy. Treatment with aromatase inhibitors is a drug treatment of last resort, as its long-term effect is not sufficiently studied in endometriosis [46,47].

Conservative surgery, consisting of laparoscopic excision and/or ablation, is the first-line surgical option for most patients who do not respond to drug treatment. Definitive surgical treatment of endometriosis should be reserved for women with debilitating symptoms who no longer wish to conceive and who have failed both medical therapy and at least one conservative treatment procedure [48-50].

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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