

Approach to Pain in Endometriosis Patients: Systematic Literature Review

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Abstract

Background: Endometriosis is a gynecological, multifactorial condition that affects women's life quality, especially due to the pain inherent to it. Pain is caused by physical and psychological aspects; therefore, several factors must be analyzed, aiming to treat the whole. Conventional, drug or surgical treatments are the most used; however, the search for alternative therapeutic methods is growing. **Objective:** To analyze the approach to pain in women with endometriosis, seeking a better understanding of the pathophysiological mechanisms of this disease, its impact on life quality, as well as the means of treatments in use and innovations in this field. **Methods:** Systematic literature review, conducted in the Virtual Health Library databases between 2010 and 2021, restricted to articles in English and Portuguese with the descriptors: Endometriosis, Pain, and Treatment. After reading the abstracts, 197 articles were found, and, after reading them, 59 articles were selected. **Results:** This review analyzed 59 scientific studies that rigorously met the previously established characteristics in the sample selection. The synthesis included the following aspects: author/year of publication, article title, objective, type of study and database. Related factors such as acute or chronic pain, late diagnosis, discrediting symptomatic complaints and trivialization by health professionals have a profound impact on the physical and mental health of women with endometriosis. On the other hand, there are several classes of drugs, surgical procedures, and alternative therapies available for pain management. **Conclusion:** Given the context addressed, a certain need is suggested for health professionals to better understand the disease and adopt new behaviors or improve existing ones, such as reception, active listening, early diagnosis and comprehensive and individualized treatment. In addition, further studies are needed regarding alternative therapies, seeking to expand the scientific evidence of their benefits.

Keywords

Endometriosis, Pain, Treatment

1. Introduction

Endometriosis is a multifactorial, chronic gynecological condition characterized by the presence of endometrial tissue outside the uterine cavity. Endometriotic foci can develop in several regions, from the ovaries to the intestines, rectum and even the lungs [1]. Basically, the main symptoms associated with the condition include dysmenorrhea, dyspareunia, chronic pelvic pain, dysuria, dyschezia and infertility. These effects, especially when considered in chronic conditions, generate a great negative influence on the life quality of women with endometriosis, especially due to the associated pain [1].

It is often observed that these patients are known to have problems in their relationships, usually during sexual activity, in their working life, as the presence of activity problems can be associated with profit problems as well as isolation and isolation. All these factors imply necessary psychological changes [2]. It is estimated that about 10% of women of reproductive age are affected by this disease, and because it is a common and benign process, it is often not given relevance. However, studies have shown a strong relationship between endometriosis and epithelial ovarian cancer [1], which makes a better understanding of its origin, development, diagnosis, pathogenesis and treatment essential.

In pelvic endometriosis, activated macrophages promote increased synthesis of reactive oxygen and nitrogen species, a process that leads to oxidative damage to red blood cells, endometrial and peritoneal cells, which, in turn, stimulates the recruitment and activation of more mononuclear cells, perpetuating oxidative damage in the pelvic cavity [1] [3]. Oxidative stress also damages mesothelial cells, which may induce the appearance of adhesion sites for endometrial cells and favor the progression of endometriosis foci [3].

Given the circumstances, women tend to present variable clinical conditions, and may be asymptomatic and report only infertility or present more common symptoms (dysmenorrhea, cyclical pelvic pain) or other symptoms (dyspareunia, ovulatory pain, chronic fatigue, urinary and intestinal changes). Some symptoms associated with atypical locations of foci include pleuritic pain, hemoptysis, headache and pain in surgical scars [1] [4].

There are currently several treatments available to treat endometriosis pain. However, most of the methods used cause unwanted effects. Hormone treatment is usually associated with the appearance of hot flashes, loss of libido, vaginal dryness and amenorrhea. Surgical treatment is a relatively invasive method and has been accompanied by recurrence. There is, however, the possibility of alternative treatments, which, for the most part, bring good results without causing undesirable side effects; however, they are not widely used due to lack of scien-

tific investigations [5] [6].

In this context, this study is justified, as seeks information regarding the management of pain in women with endometriosis, aiming at better care for this population, since a good portion of these women are susceptible to experiencing pain in its acute or chronic forms.

2. Objective

To analyze the approach to pain in women with endometriosis, seeking a better understanding of the pathophysiological mechanisms of this disease, its impact on life quality, as well as the means of treatments in use and innovations in this field.

3. Material and Methods

3.1. Data Sources and Search Strategy

This systematic literature review adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) recommendations and addresses pain management in women with endometriosis. A broad electronic search was performed using the Virtual Health Library (VHL), which included Lilacs, SciELO, Medline, PubMed, and Cochrane, using the descriptors: Endometriosis, Pain and Treatment. These search terms were used individually and in varying combinations, such as treatment of endometriosis, endometriosis associated pain, treatment of endometriosis-related pain and treatment of chronic pain. To ensure the contemporary relevance of the data, the search was limited to articles written in English and Portuguese, published in peer-reviewed journals, between the years 2010 and 2021.

3.2. Eligibility Criteria

Initially, 239 articles were found, which underwent a relevance test consisting of the inclusion criteria: 1) reference to the term endometriosis and pain; 2) analysis of pain-related events in women with endometriosis; 3) description of results associated with pain management in endometriosis; and 4) publication in selected languages and periods.

After a detailed analysis, 42 articles were excluded due to duplication and failure to present the proposed criteria. After reading the abstracts, 53 articles were excluded for not presenting the full text and the proposed theme; and finally, after reading the articles in full, 85 articles were excluded for not presenting the proposed criteria. Thus, this review is based on the remaining 59 articles that met the pre-established eligibility criteria for the analysis, as shown in (**Figure 1**).

3.3. Data Extraction and Statistical Analysis

Studies that met the inclusion criteria were divided among the authors and data were independently extracted into a standardized spreadsheet. The articles were

evaluated by the researchers and any discrepancies were resolved by consensus. The following information was collected: author/year of publication, article title, objective, type of study and data base.

In summary, a narrative synthesis was applied to approach the collected data, and a descriptive statistical analysis was performed using the Office 2021 Excel program for Mac.

4. Results

After eliminating duplicates and selecting publications, the articles were read in full, from which the parameters proposed in the analytical matrix of the present study were analyzed. This systematic literature review analyzed 59 scientific studies that rigorously met the previously established characteristics in the sample selection.

Of this total of articles, 18 were quantitative/qualitative studies, 10 was a quantitative study and 31 were qualitative. The synthesis of these selected scientific articles is presented below, covering the following aspects: Author/Year of publication, Article title, Objective, Type of study and Data base (**Table 1**).

Though the reading and study of these articles, it was possible to understand the pathophysiological mechanism of endometriosis, the cause of pain and its associated symptoms and the various viable approaches for these patients, highlighting the adverse effects that may be present.

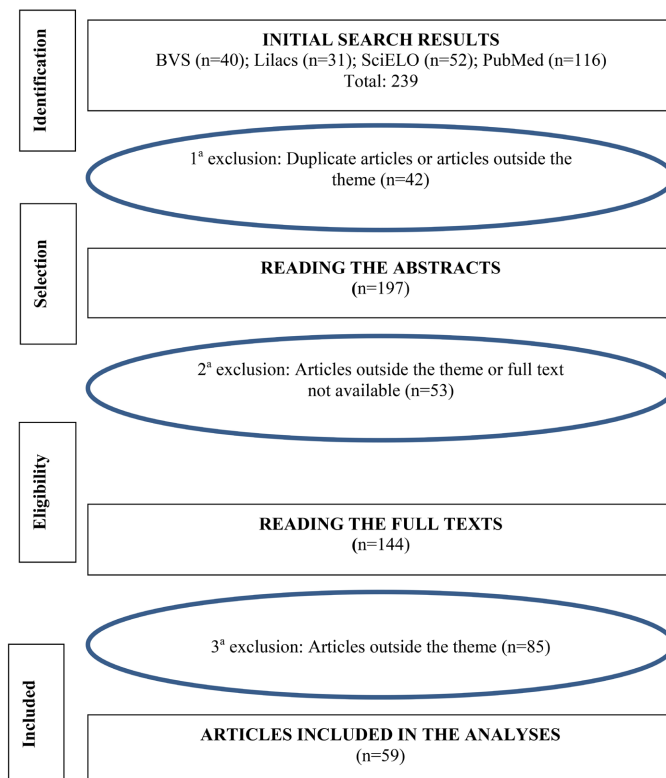


Figure 1. PRISMA flow diagram: representation of eligibility and inclusion of articles.

Table 1. Description of the articles selected for analysis.

Author Date	Article Title	Objective Purpose	Type of Study	Data Base
[1] Vercellini, P. <i>et al.</i> , 2014	Endometriosis: pathogenesis and treatment	Address the pathogenesis and possible treatments for endometriosis	Qualitative	PubMed
[2] Silva, C.M. <i>et al.</i> , 2021	Experiences of women regarding their pathways to the diagnosis of endometriosis	To describe womens experiences of their trajectories from the onset of symptoms to the diagnosis of endometriosis	Qualitative	SciElo
[3] de Andrade, Z.A. <i>et al.</i> , 2010	Serum markers of oxidative stress in infertile women with endometriosis	To compare serum markers of oxidative stress between infertile patients with and without endometriosis, associating it with disease staging	Quantitative	SciElo
[4] de Oliveira, J.G.A. <i>et al.</i> , 2019	Transvaginal ultrasound in deep endometriosis: pictorial essay	Recognize the importance of transvaginal ultrasound in the diagnosis and follow-up of endometriosis	Qualitative	SciElo
[5] Andres, M.P. <i>et al.</i> , 2015	Dienogest in the treatment of endometriosis: systematic review	Point out the effects of dienogest in the treatment of endometriosis	Quantitative and Qualitative	PubMed
[6] Falcone, T. <i>et al.</i> , 2018	Clinical Management of Endometriosis	Point out the main measures for the control of endometriosis	Qualitative	PubMed
[7] de Marqui, A.B.T. <i>et al.</i> , 2015	Evaluation os endometriosis-associated pain and influence of conventional treatment: a systematic review	Address the outcomes and evolution of pain associated with endometriosis after the adoption of conventional treatment	Quantitative and Qualitative	SciElo
[8] Caraça, D.B. <i>et al.</i> , 2011	Pathophysiological mechanisms of pelvic pain in deep endometriosis	Expose the pathophysiological mechanisms involved in the pain of deep endometriosis	Qualitative	BVS
[9] Cozzolino, M. <i>et al.</i> , 2019	Variables Associated with Endometriosis-related Pain: A Pilot Study using a Visual Analogue Scale	Expose the pathophysiological mechanisms involved in the pain of deep endometriosis	Quantitative and Qualitative	SciElo
[10] Hernandez, C. <i>et al.</i> , 2020	Regulatory T cells isolated from endometriotic peritoneal fluid express a different number of Toll-like receptors	Address the changes that occur in Toll-like receptors in peritoneal endometriotic fluid	Quantitative and Qualitative	SciElo
[11] Silva, J.B.D. <i>et al.</i> , 2020	Analysis of Body Composition and Pain Intensity in Women with Chronic Pelvic Pain Secondary to Endometriosis	Address the relationship between body composition and the intensity of chronic pelvic pain in women with endometriosis	Quantitative	PubMed
[12] Andres, M.P. <i>et al.</i> , 2014	Endometriosis is an important cause of pelvic pain in adolescence	To report the clinical characteristics of adolescent patients with endometriosis monitored in a tertiary hospital	Quantitative	SciElo
[13] Donatti, L. <i>et al.</i> , 2017	Patients with endometriosis using positive coping strategies have less depression, stress and pelvic pain	To observe the correlation between coping strategies, depression, stress levels and pain perception in patients with endometriosis	Quantitative and Qualitative	SciElo
[14] São Bento, P.A.S. <i>et al.</i> , 2018	When the eyes do not see what women feel: pain in the narratives of women with endometriosis	Discuss the meanings attributed by women to the pain caused by endometriosis	Qualitative	SciElo

Continued

[15] Spigolon, D.N. <i>et al.</i> , 2012	Endometriosis: economic impact and its prospects	Analyze the economic impacts due to expenses corresponding to late diagnosis, consultations, exams, surgical procedures and treatment of endometriosis	Qualitative	BVS
[16] Minson, F.P. <i>et al.</i> , 2012	Importance of quality of life assessment in patients with endometriosis	To examine the relationship between clinical aspects and quality of life in a group of patients with endometriosis	Quantitative and Qualitative	SciElo
[17] Yela, D.A. <i>et al.</i> , 2020	Quality of Life in Women with Deep Endometriosis: A Cross-Sectional Study	To describe the clinical and sociodemographic characteristics of women with deep endometriosis, associating them with their quality of life	Quantitative and Qualitative	SciElo
[18] Mattos, L.A. <i>et al.</i> , 2019	Structured Ultrasound and Magnetic Resonance Imaging Reports for Patients with Suspected Endometriosis: Guide for Imagers and Clinicians	Point out the use of ultrasound and magnetic resonance imaging in patients with suspected endometriosis	Quantitative and Qualitative	PubMed
[19] Nacul, A.P. <i>et al.</i> , 2010	Current aspects of the diagnosis and treatment of endometriosis	To analyze the main aspects involved in the diagnosis and treatment of endometriosis	Qualitative	SciElo
[20] Craig, E.V. <i>et al.</i> , 2020	The Complementary Role of Ultrasound and Magnetic Resonance Imaging in the Evaluation of Endometriosis: A Review	Address the importance of ultrasound and magnetic resonance imaging in monitoring the evolution of endometriosis	Qualitative	PubMed
[21] Dunselman, G.A.J. <i>et al.</i> , 2014	ESHRE guideline: management of women with endometriosis	Expose the best approach to women with endometriosis, according to the European Society of Human Reproduction and Embryology	Qualitative	PubMed
[22] Bazot, M. <i>et al.</i> , 2017	European society of urogenital radiology (ESUR) guidelines: MR imaging of pelvic endometriosis	To analyze the use of magnetic resonance imaging in the diagnosis of pelvic endometriosis	Quantitative and Qualitative	PubMed
[23] Reis, F.M. <i>et al.</i> , 2017	Biomarkers of Pelvic Endometriosis	Identify biomarkers associated with pelvic endometriosis	Qualitative	SciElo
[24] Bray-Beraldo, F. 2018	Surgical Treatment of Intestinal Endometriosis: Outcomes of Three Different Techniques	Addressing different surgical approaches to intestinal endometriosis	Quantitative	SciElo
[25] Niu, X. <i>et al.</i> , 2021	Effects of Etonogestrel implants on pelvic pain and menstrual flow in women suffering from adenomyosis or endometriosis: Results from a prospective, observational study	To evaluate the effects of etonogestrel implants on pelvic pain and menstrual flow in patients with adenomyosis or endometriosis	Quantitative	PubMed
[26] Vercellini, P. <i>et al.</i> , 2019	Elagolix for endometriosis: all that glitters is not gold	Address the use of Elagolix for the treatment of endometriosis, presenting positive and negative points	Quantitative and Qualitative	PubMed
[27] Taylor, H.S. <i>et al.</i> , 2017	Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist	Addressing the efficacy of Elagolix on pain in endometriosis patients	Quantitative	PubMed

Continued

[28] Abu Hashim, H.A., 2014	Potential role of aromatase inhibitors in the treatment of endometriosis	Discuss the effects of aromatase inhibitors in the treatment of endometriosis	Qualitative	PubMed
[29] Rafique, S.R.A.H., 2017	Medical Management of Endometriosis	Point out the main conducts for women with endometriosis	Qualitative	PubMed
[30] Ferrero, S. <i>et al.</i> , 2011	Use of aromatase inhibitors to treat endometriosis-related pain symptoms: a systematic review	Point out the effectiveness of aromatase inhibitors in controlling symptoms associated with endometriosis	Qualitative	PubMed
[31] Guo, S-W. <i>et al.</i> , 2011	Use of mifepristone to treat endometriosis: a review of clinical trials and trial-like studies conducted in China	To evaluate the use of mifepristone in the treatment of endometriosis	Quantitative	PubMed
[32] Bateman, J. <i>et al.</i> , 2017	Histomorphological changes in endometriosis in a patient treated with ulipristal: A case report	Point out the histomorphological changes of a patient with endometriosis treated with ulipristal	Qualitative	PubMed
[33] Fu, J. <i>et al.</i> , 2017	Progesterone receptor modulators for endometriosis	To evaluate the efficacy and safety of using progesterone receptor modulators in the management of pain in women with endometriosis	Quantitative and Qualitative	PubMed
[34] Bressler, <i>et al.</i> , 2017	Treatment of endometriosis-related chronic pelvic pain with Ulipristal Acetate and associated endometrial changes	To report the results of the treatment of a patient with endometriosis after the use of ulipristal acetate	Qualitative	PubMed
[35] Singh, S.S. <i>et al.</i> , 2020	Ulipristal Acetate Prior to Surgery for Endometriosis	Address the effects of ulipristal acetate on endometriosis symptoms and lesions before surgery	Quantitative and Qualitative	PubMed
[36] Andres, M.A. <i>et al.</i> , 2019	Hormone treatment as first line therapy is safe and relieves pelvic pain in women with bowel endometriosis	To report the clinical changes and complications of patients with intestinal endometriosis undergoing hormone therapy	Quantitative	SciElo
[37] Jensen, J. T. <i>et al.</i> , 2018	Use of combined hormonal contraceptives for the treatment of endometriosis-related pain: a systematic review of the evidence	To assess clinical evidence for the use of combined hormonal contraceptives in the treatment of endometriosis pain	Qualitative	PubMed
[38] Oladosu, F.A. 2018	Nonsteroidal antiinflammatory drug resistance in dysmenorrhea: epidemiology, causes, and treatment	Addressing other forms of treatment when first-line options don't work	Qualitative	PubMed
[39] Antônio, L.G.L. <i>et al.</i> , 2019	Thalidomide Reduces Cell Proliferation in Endometriosis Experimentally Induced in Rats	To analyze the effects of thalidomide on endometriomas in rats	Qualitative	PubMed
[40] Afors, K. <i>et al.</i> , 2014	Employing laparoscopic surgery for endometriosis	Document the importance of laparoscopic surgery in cases of endometriosis	Qualitative	PubMed
[41] Togni, R. 2016	The role of diagnostic laparoscopy in gynecology	Point out the indications for the diagnosis of endometriosis through videolaparoscopy	Qualitative	PubMed
[42] Rolla, E. 2019	Endometriosis: advances and controversies in classification, pathogenesis, diagnosis, and treatment	Addressing key endometriosis innovations and controversies	Qualitative	PubMed

Continued

[43] Seracchioli, R. 2010	Long-term cyclic and continuous oral contraceptive therapy and endometrioma recurrence: a randomized controlled trial	To compare the administration of cyclic and continuous contraceptive pills in preventing endometrioma recurrence after laparoscopy	Quantitative	PubMed
[44] Restaino, S. <i>et al.</i> , 2020	Robotic surgery vs laparoscopic surgery in patients with diagnosis of endometriosis: a systematic review and meta-analysis	Comparing the effectiveness of robotic and conventional laparoscopy in the treatment of endometriosis	Quantitative and Qualitative	PubMed
[45] Xu, Y. <i>et al.</i> , 2017	Effects of acupuncture for the treatment of endometriosis-related pain: A systematic review and meta-analysis	To determine the effectiveness of acupuncture in treating endometriosis pain	Quantitative and Qualitative	PubMed
[46] Zhu, X. <i>et al.</i> , 2013	Acupuncture for pain in endometriosis	To determine the efficacy and safety of acupuncture for endometriosis pain	Quantitative and Qualitative	SciElo
[47] Payne, J.A. 2019	Acupuncture for Endometriosis: A Case Study	To report possible problems in the application of Traditional Chinese Medicine in the treatment of pelvic pain associated with endometriosis	Qualitative	PubMed
[48] Liang, R. <i>et al.</i> , 2018	Efficacy of acupuncture on pelvic pain in patients with endometriosis: study protocol for randomized, single-blind, multi-center, placebo-controlled trial	To verify the efficacy and safety of acupuncture in the treatment of endometriosis	Quantitative	PubMed
[49] Lund & Lundeberg, T. 2016	Is acupuncture effective in the treatment of pain in endometriosis?	Document the clinical effects of acupuncture on visceral pelvic endometriosis pain	Quantitative and Qualitative	PubMed
[50] Mira, T.A.A. <i>et al.</i> , 2018	Systematic review and meta-analysis of complementary treatments for women with symptomatic endometriosis	Point out complementary treatments for endometriosis symptoms	Quantitative and Qualitative	PubMed
[51] Poli-Neto, O.B. <i>et al.</i> , 2020	Strength Exercise Has Different Effects on Pressure Pain Thresholds in Women with Endometriosis-Related Symptoms and Healthy Controls: A Quasi-experimental Study	Point out the relationship between intense exercise and pain sensitivity in patients with endometriosis	Qualitative	PubMed
[52] Evans, S., <i>et al.</i> , 2019	Psychological and mind-body interventions for endometriosis: A systematic review	Point out psychological approaches to the control of endometriosis symptoms	Qualitative	PubMed
[53] Halpern, G. <i>et al.</i> , 2015	Nutritional aspects related to endometriosis	Address nutritional aspects related to endometriosis	Qualitative	PubMed
[54] García-Ibañez, P. <i>et al.</i> , 2020	Brassica Bioactives Could Ameliorate the Chronic Inflammatory Condition of Endometriosis	Evidencing the benefits of consumption of brassica for the chronic inflammation caused by endometriosis	Qualitative	PubMed
[55] Arablou, T. <i>et al.</i> , 2018	Curcumin and endometriosis: Review on potential roles and molecular mechanisms	Addressing the benefits of turmeric consumption for patients with endometriosis	Qualitative	PubMed

Continued

[56] Golabek, A. <i>et al.</i> , 2021	Polyphenols as a Diet Therapy Concept for Endometriosis-Current Opinion and Future Perspectives	Present a possible treatment for endometriosis from a diet rich in polyphenols	Qualitative	PubMed
[57] Ilhan, M. <i>et al.</i> , 2019	Novel Drug Targets with Traditional Herbal Medicines for Overcoming Endometriosis	To describe the pharmacological activity of medicinal plants and their active ingredients in patients with endometriosis	Qualitative	PubMed
[58] Sinclair, J. <i>et al.</i> , 2021	Effects of cannabis ingestion on endometriosis-associated pelvic pain and related symptoms	Evidencing the effects of the administration of medical cannabis in patients with pelvic pain associated with endometriosis	Quantitative and Qualitative	PubMed
[59] Bouaziz, J. <i>et al.</i> , 2017	The Clinical Significance of Endocannabinoids in Endometriosis Pain Management	Point out the relationship between the mechanisms of endocannabinoids and endometriosis pain	Qualitative	PubMed

5. Discussion**5.1. Endometriosis and Pain**

Endometriosis is multifactorial and usually affects regions such as the ovaries, posterior and anterior cul-de-sac, posterior leaflet of the broad ligament, uterosacral ligaments, fallopian tubes, sigmoid colon, appendix and round ligaments and, more rarely, diaphragm and pleural cavity [1]. Commonly affects women of reproductive age, and the association of one or more biological factors can increase susceptibility to the disease [3]. Furthermore, it is associated with the development of epithelial ovarian cancer [1]. In pelvic endometriosis, activated macrophages induce increased synthesis of reactive oxygen and nitrogen species and consequent oxidative stress, which affects endometrial, mesothelial and peritoneal cells [3].

Women with endometriosis may be asymptomatic or present (dysmenorrhea, dyspareunia, cyclic pelvic pain, dysuria, dyschesia, dyspareunia, ovulatory pain, chronic fatigue, infertility, and urinary and bowel changes) as well as other symptoms (pleuritic pain, hemoptysis, headache, and pain in surgical scars) [1] [4]. In addition, the presence of endometriotic foci can generate systemic effects in the body [3].

When it comes to pain, this is a very common symptom experienced by women with endometriosis. The chronic pelvic pain experienced by these women is characterized by non-menstrual, non-cyclical pain, lasting at least one semester, of intensity strong enough to affect daily activities [7]. Several studies seek to better understand the pathophysiological mechanisms that generate this pain. It has been reported that the most evident mechanism is related to the deposition of ectopic endometrial fragments, which induce the release of pro-inflammatory cytokines, prostaglandins, chemokines and other substances from endometriotic foci during the chronic inflammatory process. In addition, the very deep infiltration with tissue damage, adhesion formation, fibrotic thickening, and accumulation of menstrual bloodshed in endometriotic implants result in painful traction

[8].

These changes can also stimulate the release of growth factors that induce the growth of nerve fibers in endometriotic foci, accentuating pain [8]. It has also been reported that women with chronic pelvic pain have neurological changes in the dorsal horn of the spinal cord, which results in neurogenic inflammation in the pelvic region, hyperalgesia, dysreflexia, decreased sensory threshold and, consequently, increased pain sensation [9]. Another factor is the mechanisms that modulate the inflammatory response through Toll-Like receptors (TLR) located on the membrane of regulatory T lymphocytes. TLRs, present in greater quantity and variety in women with endometriosis, can identify microorganisms in retrograde menstrual blood and respond with exacerbation of the inflammatory response and consequent worsening of pain [10].

In addition, the amount/density of C and A-delta sensory nerve fibers, cholinergic and adrenergic, closely related to nociceptive mechanisms, is also related to a relevant factor in the assessment of pain in women with endometriosis [8]. Multiple small unmyelinated nerve fibers were observed in the functional layer of the endometrium, in addition to a large concentration of myelinated and unmyelinated nerve fibers in the deepest part of the basal endometrium, compared to the endometrium of healthy women [8]. Finally, it is worth noting that overweight and/or obesity were also reported as influencing factors for pain attenuation in women with endometriosis. This is due to the greater presence of M1 pro-inflammatory macrophages in these individuals [11].

5.2. Impacts on Women's Life Quality

There are several difficulties faced by women with endometriosis and the factors that impact their life quality. According to the analyzed literature, it often starts with the difficulty of early diagnosis and treatment, since the vast majority of these women already presented the first symptoms in adolescence [2]. Over time, physical and emotional factors related to personal, affective, family, professional, social, economic and psychological life are associated with the worsening of the condition, concomitantly with the worsening of chronic pain and infertility [2].

With regard to these factors, some relevant aspects are reported that impact the life of women with endometriosis, affecting their physical and consequently psychological and/or mental health. These aspects need to be addressed with greater care: 1) Frequency/duration of pain: Commonly, due to late diagnosis, the woman spends long periods of her life looking for ways to solve the pain and is often discredited by family members, companions, friends and even health professionals, which further affects their mental health [12]. There are reports of women who initially receive support from those closest to them, however, due to the persistence of pain, these begin to discredit them, which causes them to "live with and despite the pain", including as a strategy to avoid isolation [2]. In addition, it is also reported that most women with endometriosis have some degree

of depression [13], with a higher incidence among those who complain of severe pelvic pain [2]. 2) Incorporation of the disease: The disease becomes something central in the life of the woman, who then starts to live and carry out her activities “according to the disease and when the disease allows”, situations that can lead to family, affective and emotional isolation social [14]. 3) Report of absenteeism: It has been reported that women with endometriosis miss about 1 day of work per week, in addition to having compromised income, due to interference of symptoms [15]. 4) Attention of health professionals: This can be a point of great relevance for the improvement of these women. Banalization and negligence were reported by health professionals in relation to pain complaints, as quoted below [2].

“A large cross-sectional study, considered the largest prospective multicenter research on the effects of endometriosis carried out to date, showed that the trivialization of women’s complaints by professionals is a worldwide problem. [...] Many times, professionals were not interested in identifying the important aspects of pain, such as quantity, intensity, duration, nature or impact. Classifying endometriosis pain as normal reveals a lack of training or updating on the part of some professionals, a lack of active listening, treatment of their symptoms and proper referrals. [...] Therefore, a large part of the delays in diagnosis is attributed to professional negligence”.

Furthermore, it is worth remembering that even after treatment, a portion of these women continue to experience chronic pain with consequent changes in life quality life [16]. There are reports of the persistence of psychological aspects (difficulty in socialization and depression), as well as in contrast, there are reports of improvement of physical pain even though it does not disappear after treatment [17].

For a better understanding of the impact that endometriosis brings to women’s lives, especially in the psychological/mental sense, the use of questionnaires (SF-36, WHOQOL and EHP-30) was reported, which allow the assessment of psychological and social functions and the measurement of life quality [16]. Thus, it is obvious that the life quality of these women is potentially impaired due to the effects of the disease. Therefore, it is important to carry out a complete/detailed clinical examination so that these women, especially those with greater susceptibility and probability, receive early and adequate diagnosis/treatment.

5.3. Parameters for Diagnosis of Endometriosis

According to the literature, there is no report of the existence of a specific ideal scale regarding the clinical assessment of pain complaints in women with endometriosis. In one study, the Visual Analog Scale (VAS) was reported to have the best balance between strengths/weaknesses of disease-associated pain [9]. Regarding the definitive diagnosis, laparoscopy was reported as the gold standard, being commonly indicated for completion of the diagnosis in cases of high probability, however, it is an invasive method that also presents risks [4].

Other non-invasive methods such as imaging tests, including transvaginal ultrasound (TVUS) and pelvic magnetic resonance imaging (MRI) have been commonly addressed [18]. The association of TVUS and pelvic MRI has been relevant in the accuracy of the diagnosis, as reduces the need for videolaparoscopy [19]. TVUS, as is a more accessible method, is the first to be suggested for evaluation in case of clinical suspicion. However, findings of deep endometriosis are not easily located by TVUS and the accuracy of the examination may still largely depend on professional skill/experience [20]. Pelvic MRI is usually requested for symptomatic patients, in whom the lesions were not identified by TVUS, in cases of endometriotic foci in the upper abdominal region and/or in cases of complex surgeries [21]. However, it is a more expensive method and sometimes limits the diagnosis, making it impossible to dynamically assess indirect signs of pelvic involvement, such as adhesions for example [21]. Furthermore, the existence of a standardization protocol for the indication and interpretation of MRI in endometriosis is reported, which focuses on optimizing time and resources in reaching the diagnosis [22]. More recently, a systematic ultrasound evaluation of the female pelvis has also been proposed, aiming at tracking the sites of greatest incidence and adequately describing the location and characteristics of the lesions, which allows for a more comprehensive and effective investigation [20].

On the other hand, although there are no specific markers for optimizing the diagnosis, interleukin-6 (IL-6) [19], as well as cancer antigen 125 (CA-125) [19] [23], produced by endometrial cells during inflammatory processes, were cited for monitoring and/or suspected disease recurrence [19] [23].

According to the literature, regarding the therapeutic approach, it varies according to the classification revised by the American Society of Reproductive (rASRM), based on the definition of the staging of the disease and associated complaints (pelvic pain and infertility). This classification covers 4 stages and considers characteristics such as; size, depth, location of endometriotic foci and severity of adhesions [19]. Other less used methods, such as the ENZIAN-Score classification that analyzes deep endometriosis from the involvement of deep organs, determining the severity of the extension of the disease, and the Endometriosis Fertility Index (EFI) classification that analyzes infertility factors from a basic scoring system were also reported [24]. Ideally, the choice of therapy should be decided jointly by the doctor/patient, so that the best method is applied, respecting factors such as: age, reproductive plans, degree of pain and illness, patient preferences, costs, risks, duration of treatment and side effects, as well as aiming to reduce symptoms and/or relapses and the need for repeat surgeries.

5.4. Parameters for Treatment for Endometriosis

5.4.1. Hormonal Pharmacological Therapies

Progestins

Progestins inhibit the hypothalamic-pituitary-ovarian axis, reducing serum estrogen levels and leading to anovulation and atrophy of the eutopic endome-

trium and endometrial lesions. They modulate the immune response involved in the pathogenesis of endometriosis, decreasing peritoneal inflammatory mediators, inhibiting angiogenesis and suppressing matrix metalloproteinases, factors that facilitate the growth and implantation of the ectopic endometrium [5]. Of this class, the main drugs and/or methods reported were: dienogest [5], medroxyprogesterone acetate [7] and norethisterone acetate [6] [7], as well as the levonorgestrel-releasing system (LGN-IUS) and the etonogestrel-releasing implant [25].

It was found that dienogest, a 4th generation selective progesterone, composed of 19-nortestosterone and progesterone derivatives, has low androgenic, estrogenic, glucocorticoid and/or mineralocorticoid activities. In addition, it has anovulatory, antiproliferative effects and inhibits the secretion of cytokines in the stroma of endometrial cells [5]. Dienogest (2 mg/day) suppressed pain about 24 weeks after starting treatment, in addition to reducing bone mineral loss observed with the use of leuprolide acetate [7].

Norethisterone acetate, a low-cost drug, improves chronic pelvic pain, dyspareunia and dyschezia, as well as symptoms referred to the gastrointestinal tract [7]. However, recurrence of pain was reported when associated with letrozole, as well as more side effects when associated with triptorelin and, consequent abandonment of therapy [7]. As for medroxyprogesterone acetate, an improvement of about 68% of pain in one year has been reported [7].

The levonorgestrel-releasing system (LGN-IUS) has been reported as a comfortable use/maintenance intrauterine device, requiring replacement every 5 years; however, it can be displaced or expelled from the body in the condition of endometrial thickening, arising from endometriosis or adenomyosis. Subdermal etonogestrel-releasing implant (68 mg) lasting up to 3 years has been shown to reduce pelvic pain as well menstrual flow [25]. Furthermore, the most common side effects associated with these drugs were acne, bone mineral loss, weight gain, and mood change [5], seborrhea, oily hair, pimples, headache, breast tenderness, and vaginal irritation [25].

Gonadotropin-releasing hormone agonists (GnRH)

Regarding the class of GnRH agonists, the drugs (leuprolide, goserelin and nafarelin) were reported as the main ones, which demonstrate efficacy in improving symptoms, especially pelvic pain. Side effects (vaginal bleeding, headache, weight gain, breast tenderness and loss of bone mineral density) associated with prolonged treatment with these drugs have also been reported, situations that limit their use [5] [7].

Gonadotropin-releasing hormone antagonists (GnRH)

Regarding the class of GnRH antagonists, the drug (elagolix) was reported as a great innovation for the treatment of endometriosis, due to its mechanism of action. Elagolix acts on the binding site of an endogenous decapeptide in the anterior pituitary, but without activating. Unlike GnRH agonists, it does not induce the onset of gonadotropin release, a fact that leads to milder hypoestrogenism

with consequent reduction in pain and side effects [26].

The main side effects observed include hot flush, headache, nausea, loss of bone density and hyperlipidemia [27]. It is reported that this drug can be used in both low and high doses, the latter being more effective in the treatment of dysmenorrhea, pelvic pain and dyspareunia. There was also a reduction in the use of associated analgesics (non-steroidal anti-inflammatory drugs and opioids) after 3 months of elagolix use [27].

Aromatase inhibitors

Regarding the class of aromatase inhibitors, the 3rd generation drugs (letrozole and anastrozole) were reported as the most used. They have a potent selective but reversible action on the aromatase enzyme [28], which is responsible for converting cholesterol into estrogen, a hormone that exerts great activity on the growth and maintenance of endometriotic lesions and foci [29]. Excellent effects/results have been reported in the treatment of chronic pain, however, side effects such as, hot flashes, headache, arthralgia and significant bone mineral loss have been reported [28]. At dosages of 1 - 5 mg/day orally, these drugs were able to reduce estrogen levels by 97% - 99% [28].

When analyzing the association of letrozole with some drugs from other classes, the reported results are interesting, for example: letrozole/norethisterone acetate increased the degree of relief of pelvic pain and deep dyspareunia compared to the use of progestin alone; as well as letrozole/GnRH agonist decreased the risk of lesion recurrence [30].

Selective progesterone receptor modulators

Traditional progesterone-based drugs, widely used, can cause many side effects due to nonspecific binding to androgen and glucocorticoid receptors. Thus, new drugs with greater specificity to progesterone receptors have been developed, seeking to attenuate these undesirable results [5]. Regarding the class of selective progesterone receptor modulators, the drugs, mifepristone [31] and ulipristal acetate [32] have been addressed in the treatment of pain and endometriotic foci.

Women under mifepristone treatment [31] [33] obtained improvements in symptoms of chronic pelvic pain and dyspareunia, as well as reduction of endometriotic lesions [31], however, side effects such as amenorrhea, hot flush and fatigue were observed [33]. On the other hand, use of mifepristone for abortion has been reported, mainly associated with misoprostol. Due to this abortifacient characteristic, there is strict control over its commercialization in much of the world; in addition, there is also a scarcity of studies proving its effectiveness [31].

Ulipristal acetate attenuates pain and reduces endometriotic foci through regulation of prostaglandin and COX-2 synthesis and consequent pro-apoptotic, anti-proliferative and anti-inflammatory effects [32]. In contrast, studies have reported its relationship with pathological endometrial changes, which led physicians to discontinue its administration [34] [35]. Considering these effects, the fact that it is a more recent drug with abortifacient properties, the use of this

drug needs further studies.

Combined contraceptives

Combined estrogen and progesterone contraceptives have been reported as first-line therapy for endometriosis-related pain because of their high tolerance and efficacy, few adverse effects, and low cost [6] [36]. These drugs block endogenous estradiol synthesis and ovulation, generating a hormonal environment with a predominance of progesterone; which deregulates the local estrogen receptors responsible for fueling the proliferation of lesions. In addition, this environment reduces the density of nerve fibers and inhibits angiogenesis in endometriotic foci. In this way, it is possible to delay the progression of the disease [37].

The use of these drugs has been reported in a cyclical or continuous way; however, the continuous use has a better result in the attenuation of pain, due to the promotion of amenorrhea and extinction of dysmenorrhea [6]. However, mainly because they constitute long-term therapies, they have disadvantages such as risks of thromboembolism, impairment of fertility during use and high recurrence rate after discontinuation [29]. Regarding the risk of venous thromboembolism, low-dose hormonal contraceptives are more widely recommended and have lower risks [29].

Improvement of chronic pelvic pain, dysmenorrhea and pain on defecation has been reported, mainly 12 months after starting treatment. However, side effects such as uterine bleeding, moderate weight gain, headache and decreased libido have been observed [7]. Furthermore, when comparing the use of combined contraceptives and other hormonal drugs, the progestogen dienogest alone showed a greater decrease in pain scores [37]. In addition, women commonly opt for progesterone-only methods because of the side effects and their impact on life quality [6].

5.4.2. Therapies with Non-Steroidal Anti-Inflammatory Drugs

Regarding the recommendation of anti-inflammatory drugs, non-steroidal anti-inflammatory drugs (NSAIDs) have been reported as first-line therapy for the control of pain and dysmenorrhea associated with endometriosis. NSAIDs can nonspecifically bind to the two isoforms of cyclooxygenase (COX-1 and COX-2) promoting its inhibition and/or blockade [38].

Although both COX-1 and COX-2 receptors are present in the endometrium, a higher concentration of COX-2 receptors has been reported in ectopic endometrial tissue [29]. Both selective and non-selective COX-2 inhibitor NSAIDs have been reported, which should be administered a few days before the start of the menstrual cycle, aiming to reduce inflammatory mediators and consequently dysmenorrhea [38].

Selective COX-2 inhibitors, in addition to blocking the inflammatory process, also inhibit the growth of endometrial tissue [29]. These drugs should be used with caution, due to their side effects on the gastric system and the risk of kidney damage when in chronic use [38]. Factors such as genetic polymorphisms, bio-

availability, and changes in cytochrome P450 have been reported to interfere with cyclooxygenase inhibition, which explains why some women experience significant symptom improvement and others do not [38]. However, further studies are needed to fully understand the molecular mechanisms that justify resistance to these drugs. Furthermore, thalidomide, a drug that acts on cell proliferation without interfering with ovarian function, has been shown to reduce the size of cysts in the retrocervical and ovarian regions, as well as decrease pelvic pain, in women with endometriosis [39].

5.4.3. Surgical Interventions

On the other hand, laparoscopy has been the gold standard surgical method performed in patients with endometriosis. It allows the definitive diagnosis, through evaluation of the lesions at a macro and microscopic level [40], classifying them according to their severity [41], in addition to being a quick, efficient and minimally invasive procedure, which generally does not involve major complications [40]. Its indication has been reported mainly for women with chronic pelvic pain and infertility, cases in which empirical treatment has not had an effect, cases of drug intolerance and for immediate diagnosis/resolution of the disease [6]. In addition, it has been reported as the first treatment option for symptomatic intestinal endometriosis, as improves quality of life, especially regarding intestinal functioning [24].

Laparoscopy encompasses two distinct procedures, including conservative or definitive methods, involving hysterectomy with or without removal of the ovaries. Still, in the conservative method, two different techniques (ablation or excision) can be applied [6]. Ablation usually involves the application of an energy source (carbon dioxide laser), which destroys the lesions; or even performing mono or bipolar electrosurgery. In contrast, in excision the cysts are removed in the traditional way [40]. A greater reduction in pain scores has been reported in women with deep infiltrating disease undergoing laparoscopy compared with those with superficial endometriosis [40] [42]. In contrast, a higher incidence of recurrence of pain symptoms has been reported in women undergoing ablation compared to excision, particularly in women with deep endometriosis [40]. This finding is related to the fact that in deep endometriosis, only the most superficial lesions are treated, since in these cases deep penetration with ablation energy on the lesions is not recommended, due to the risk of damage to adjacent tissues [40].

A reduction in the recurrence of dysmenorrhea, dyspareunia, non-menstrual pelvic pain and an increase in the possibility of spontaneous pregnancy, as well as improvement in ovarian changes were found in women undergoing excision [6] [40]. On the other hand, the risk of the exciseive method has been reported for women who want a future pregnancy, as this procedure can lead to reductions in ovarian reserves. In more severe cases, in the presence of infiltrative ovarian lesions, there is a need for a thorough evaluation of the ureteric course, as well as infiltrations of the urinary tract, cul-de-sac or intestine. Surgical pro-

cedures are long and delicate, involve greater risk, in addition to demanding greater knowledge, experience and precision from the multidisciplinary team [40].

Hysterectomy methods themselves have been reported to be effective in treating severe pain, however, in women under 40 years of age, ovary conservation is indicated in order to avoid surgical menopause. In these cases, the possibilities of recurrence of symptoms and need for further surgery are also more common [6]. However, it is important to pay attention to the recurrence of symptoms and endometriotic foci in the late postoperative period, since recurrences of about 10% and 40% - 50% of symptoms were reported after 1 or 5 - 7 years, respectively [6]. A study comparing cyclic or continuous contraceptive use or non-use by patients undergoing laparoscopy reported the following rates of recurrence of ovarian endometriomas (29%, 14.7% and 8.2%) when not in use, in cyclical use or continuous use, respectively [43]. Thus, it is obvious that pharmacological measures, including the use of contraceptives in order to avoid relapses or to prolong the patients return to the operating room, are important and necessary.

In addition to laparoscopy, nerve transection has also been reported as a method for the management of endometriosis, since presacral neurectomy helps to reduce pain and dysmenorrhea, however, changes such as constipation and bladder dysfunction have been related to this procedure [6]. Also, more recently, robotic laparoscopic surgery has emerged, a method that has aroused scientific and commercial interest. It is reported as a differential of this method, the possibility of increasing precision, depth perception and wrist articulation compared to traditional laparoscopy. However, in practice, significant differences in length of stay, blood loss and possible intraoperative and postoperative complications were not reported, in addition to being an expensive procedure [44]. In addition, it requires longer surgical time, a fact related both to the profile of patients who, in these cases, present more severe conditions with deep infiltrations in the urinary and/or intestinal tract, and to the profile of professionals due to the lack of extensive experience in this field [44]. In this sense, robotic surgery is a viable and promising possibility for the treatment of endometriosis, but at the moment it does not present significant advantages over traditional laparoscopy [44].

There are several surgical procedures. However, it is noteworthy that, although these procedures do not involve major risks, they still exist; with emphasis on infections, hemorrhages and injuries in abdominal pelvic organs (intestine and bladder) [41]. Thus, a thorough clinical analysis is feasible to avoid performing undue procedures, which are relatively invasive and costly. In addition, it is also ideal that the choice of procedure is adapted to factors (age, infertility, sexual health, family planning, attempts at other treatments, among others) related to the patient, seeking to treat the whole.

5.4.4. Alternative Treatments for Endometriosis

Although pharmacological and/or surgical means are the most used to treat endometriosis, it is noteworthy that both have more unwanted side effects. Thus,

alternative methods that can help to improve symptoms and promote better quality of life, in addition to presenting little or no side effects, are also reported.

Acupuncture methods

Regarding acupuncture, several methods (traditional Chinese or Japanese acupuncture, electroacupuncture and auriculoacupuncture) have been reported. They are relatively safe and widely indicated methods for pain relief in endometriosis, as they result in physiological and psychological benefits [45] [46].

Briefly, traditional Chinese acupuncture advocates the existence of a natural pattern of vital energy (Qi) throughout the body, thus, interruption and/or imbalance of this energy flow indicates illness and/or pain. Therefore, this method aims to correct these endometriosis-related changes [46]. Japanese acupuncture is similar to the Chinese method. The main difference is in the application of needles, performed only in the superficial layers of the dermis. Therefore, it is a well-accepted and commonly associated method of treating endometriosis in adolescents [45]. Electroacupuncture has characteristics similar to the previous methods; with a difference, the stimuli are performed through electric current. Auriculoacupuncture involves stimulation of specific points in the ears, the points being: Ting Zhong (cymbian auricle center), Pi Zhi Xia (hypocortex), Nei Fen Mi (endocrine), Jiao Gan (sympathetic) and Nei Sheng Zhi Qi (internal genital organs), traditionally addressed in pain relief and improvement of the reproductive system [46].

Studies report the ability of these methods to; increase the pain threshold by decreasing the expectation of symptoms and activating the brain's analgesic mechanisms to release neural and humoral factors, including adenosine, alpha-aminobutyric acid, opioid peptides, acetylcholine, nitric oxide, noradrenaline and dopamine [45] [46], as well as stimulating increased cytotoxicity of NK cells, promoting a cross-relationship between the neurotransmitter network and the immune system, mediated by nitric oxide, beta endorphins and cytokines [45]. Other positive effects were also reported: Acupuncture was able to decrease estrogen levels, with consequent reduction of endometriotic tissue and pain [45], as well as, auriculoacupuncture significantly improved dyspareunia and severe dysmenorrhea compared to chinese herbal medicine [46], in addition to promoting a decrease in menstrual flow and the size of endometriomas [47]. Furthermore, it has been hypothesized that acupuncture may play a role in ovulation induction and fertility treatment by normalizing the hypothalamic-pituitary-ovarian axis [46], as well as reducing plasma levels of CA-125 [45].

However, it should be noted that the appropriate moment for performing these methods must be considered individually. According to one study, an intervention was started in the week before the premenstrual period, including 3 weekly sessions, as during this period the regularization of Qi and blood flow would occur and the consequent achievement of pain relief [48]. Typically, 9 - 16 sessions are required, lasting about 15 - 25 minutes each [49].

Physical activity

The practice of physical activity has been associated with the improvement of chronic pain; however, studies exclusively related to endometriosis are scarce. A study was found comparing patients who underwent only pharmacological treatment with those who associated drugs (danazol and GnRH analogues) to the practice of physical activity. In this, a lower rate of disease recurrence was reported after discontinuation of the drug, as well as reduced androgenic side effects and testosterone levels and less bone mineral loss [50]. In this case, the explanation for the improvement in pain is still unclear. It is believed that, in part, there is a relationship with blood pressure, since physical exercise increases blood pressure by sympathetic activation, which activates baroreceptors and, consequently, triggers the nucleus of the solitary tract, a situation that in the long term, increases the peripheral pain threshold [51].

However, women with endometriosis, because they have a greater perception of pain, find physical exercise an extremely unpleasant situation, which makes it difficult for them to adhere to physical training programs for a long time, allowing them to experience the benefits of this practice, especially in the long term [51]. In this sense, the practice of physical activity should be encouraged, as promotes improvement of possible psychological changes (anxiety and depression) related to the disease, in addition to improving the life quality.

Cognitive Behavioral Therapy

Commonly, much is studied and search for means of treatment of the physical symptoms of pain and infertility, however, little is addressed about the psychological effects such as; anxiety, depression, social aversion and difficulties in socializing and/or socializing, which many women with endometriosis experience in everyday life [7] [13] [52].

Cognitive Behavioral Therapy (CBT) was reported as a means to improve the recognition and treatment of both psychological and physical impacts with the same relevance, seeking to treat the whole. Recent studies show significant reductions in pain and depression scores, as well as an improvement in the quality of life of women undergoing pharmacological treatments associated with CBT, a fact due to a better understanding and ways of dealing with the disease [7] [13] [52].

Anti-inflammatory nutritional therapy

It is known that the severity of endometriosis and its symptoms are closely related to an extensive degree of inflammation observed in patients. In addition, nutrient-deficient diets, diets based on red meat and industrialized products, trigger lipid changes, generation of free radicals and oxidative stress, intensifying inflammatory processes, as well as triggering epigenetic abnormalities, involved with the development and progression of the disease [53]. However, the adoption of a balanced diet, including foods with anti-inflammatory properties, has been gaining relevance, as well as the search for the identification and understanding of its mechanisms of action.

Foods rich in omega 3, supplementation of N-acetylcysteine, vitamin D and

resveratrol, associated with greater consumption of preferably organic fruits and vegetables, as well as whole grains, turmeric and ginger, have been reported as protective foods and reduce the risks of development of endometriosis and related to possible regression of the disease [53]. The consumption of vegetables was reported as the highlight of the moment in relation to their benefits, due to their anti-inflammatory, detoxifying and antitumor properties [54]. Brassic vegetables (cauliflower, broccoli, cabbage, kale and arugula) were associated with a significant reduction in the chronic inflammatory process, a benefit that is due to the glucosinolates present in these foods. After ingestion, these substances are converted to bioactive degradation products, which associate with inflammatory receptors [54].

In addition, there is great scientific interest in curcumin, a phenolic component derived from turmeric, which has activities; antioxidant, anti-inflammatory, hypoglycemic, antimicrobial, antitumor, antiangiogenic and antimetastatic [55]. Studies have reported its ability to reduce the growth and number of endometriotic stromal cells and the development of peritoneal endometrial glands, induce the expression of apoptotic mitochondrial factors such as cytochrome C, increase the expression of p53 protein and inhibit the secretion of interleukins (IL-6 and IL-8) and monocyte chemotactic protein 1 (MCP-1) [55] [56]. In this sense, the approach of nutritional measures that prevent and/or alleviate the inflammatory picture in endometriosis becomes essential.

Medicinal plants

Some plants with medicinal properties and/or their derivatives with great potential to treat pain have also been addressed in the treatment of endometriosis. Resveratrol, a polyphenol commonly found in the seeds and skin of grapes, is endowed with anti-angiogenic and anti-inflammatory properties. It is capable of inducing apoptosis of endometrial stromal cells by suppressing the expression of survivin, an apoptosis-inhibiting protein, as well as inhibiting the synthesis of prostaglandins, attenuating the peritoneal inflammatory response and decreasing the development of endometriosis [42] [56]. In another study, it is reported that cotton (*Gossypium* sp), commonly used as a tonic in the stimulation of uterine contractions, demonstrated efficacy in the treatment of endometriosis, in the short (90%) and long term (54% - 63%), after 1 and 3 years respectively. This effectiveness is due to the mechanism of action related to the active substance (gossypol), which antagonizes the effects of estrogen and progesterone [57].

Another plant, *Cannabis sativa*, is also addressed in pain management, due to the direct and/or indirect effects of its active principles D9-tetrahydrocannabinol (THC) and cannabidiol (CBD) on specific receptors in the endocannabinoid system. Although several different receptors are present in this system, cannabinoid receptors 1 (CB1) and 2 (CB2) present mostly in central and peripheral presynaptic neurons are the most explored, with anandamide being its main neurotransmitter [58].

CB1 receptors are highly expressed in the uterus and other non-reproductive

tissues, while CB2 receptors are expressed in the immune system, uterus, intestines, lungs, pancreas, and skin tissue. The presence of CB1 and CB2 receptors was reported in different regions of the oocytes, according to the stage of maturation, as well as the presence of anandamide in the reproductive tract fluids. In the secretory phase, an important increase in CB1, mRNA and endometrial proteins was observed, a fact associated with the ability of progesterone to regulate the expression of these receptors [58]. In addition, a significant increase in anandamide associated with a decrease in CB1 expression has been observed in women with endometriosis, a situation that can impair the control of pain symptoms, aggravating chronic pelvic pain, dysmenorrhea and dyspareunia [58].

Other interesting aspects are the time of absorption and improvement of symptoms, since THC has an immediate noticeable effect a few minutes after administration, while CBD requires a longer period. However, when administered together, improvement in acute and/or severe conditions, as well as in chronic symptoms, has been reported [59], a fact that may play a vital role in pain management. Regarding dose, one study reported less pain, as well as fewer gastrointestinal symptoms, psychological and mood changes in women who received high concentrations of THC (inhaled) and CBD (orally), respectively [58]. A significant improvement in symptoms in response to medications was also reported in older women; however, this reason was not exactly clear. It is believed to be associated with factors that change with age, such as: hormonal changes, increased drug sensitivity, possible decline in the endocannabinoid system, and/or changes in pain perception [58]. CBD, in addition to acting on the chronic inflammatory process in the reproductive tract, also exhibits anxiolytic and antidepressant activities, through modulation of the serotonin receptor (5HT1A) [59]. Most synthetic cannabinoid ligands are found to ensure beneficial effects by acting as CB1 cannabinoid receptor agonists [58]. Furthermore, side effects associated with the use of these drugs are rarely reported [58].

It is also important to highlight the existence of other medicinal plants (*Angelica sinensis*, *Achillea biebersteinii*, *Hypericum perforatum*, *Uncaria tomentosa*, *Verbena hastata* and *Alchemilla mollis*) with therapeutic potential for treating pain and improving the quality of life of women with endometriosis [57]. However, their applications in clinical practice are limited due to the scarcity of studies that address them more comprehensively.

This review discusses more recent research data published between 2010 and 2021 and related to pain management in women with endometriosis. However, this study has limitations, due to the inclusion only of articles published in English and Portuguese, thus excluding, to a large extent, relevant studies published in other languages. Another limitation is the lack of studies comparing the different means and/or methods, which makes it difficult to present positive and negative points regarding the use of techniques/treatments in isolation and divides the opinion of professionals, interfering in the development of a conduct pattern. There were studies that used a small number of patients or still did not distinguish their particularities such as age, time of diagnosis of endometriosis

and comorbidities. Most of the time, the distinction was just the endometriosis site and symptoms. In addition, there were few studies focused exclusively on endometriosis pain management, which is a drawback of the retrospective design.

6. Conclusions

Endometriosis is a multifactorial disease, with a high prevalence among the female population of reproductive age. Pain associated with the clinical condition was reported as one of the most negative symptoms that profoundly impact the quality of life of these women, affecting their physical and mental health. In addition, other factors, such as difficulty and/or late diagnosis, discrediting symptomatic complaints and trivialization by health professionals were identified as facilitators for the worsening of this scenario.

Regarding pain management, several classes of drugs, as well as different surgical procedures and alternative therapies are available for the treatment of endometriosis, which have been shown to have very positive effects when administered and/or performed either alone or in association.

Thus, it is obvious the need for a better understanding of the disease, as well as the adoption of new measures and/or conducts by the multi-professional team. Thus, welcoming and active listening by professionals, early diagnosis and comprehensive and individualized treatment of these women are attitudes that need attention. These actions will certainly bring greater comfort and better prognosis for this population. Furthermore, it is also important to emphasize the need for more research, especially with regard to alternative therapies, aiming to expand the scientific evidence of the benefits related to them.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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