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## Complementary pain management in endometriosis: a narrative review

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### ABSTRACT

**Objective.** Endometriosis is a gynaecological disease characterized mainly by infertility, chronic pelvic as well by the disability that generates. In 2020, the WHO established that it affects approximately 10% of women and girls of reproductive age worldwide. Multiple surgical and pharmacological treatments have been recommended by different clinical practice guidelines for pain relief. Complementary therapies such as acupuncture, electrotherapy, massage, physical exercise, or diet have not been established as strong recommendation. Nevertheless, studies demonstrated significant decrease in pain that support its use as an adjunct pain management.

The aim is to understand and expose the contribution of complementary therapies to pain relief in patients with endometriosis.

**Materials and Methods.** A search was carried out in PubMed, Web of Science, Scopus, and Ovid databases, with controlled descriptors in health, filtering 994 articles and including 12.

**Results.** It was found that medical management for pain relief in patients with endometriosis is the basis of the treatment of this health condition. However, with complementary therapies a decrease in pain was demonstrated. This includes transcutaneous electrical stimulation, neuromuscular pelvic floor manipulation, complementary alternative medical therapy, acupuncture technique on Ah Shi points, cognitive behavioural therapy, physical activity, diet and physiotherapy. Information was found in 16 articles of experimental, observational studies and narrative reviews which support the use of complementary therapy as an adjunct in the management of pelvic pain.

**Conclusions.** The use of complementary therapies are effective interventions for pain control in patients with endometriosis and should be recommended for pain improvements and quality of life.

## INTRODUCTION

Endometriosis is a disease defined by the presence of active endometrial tissue outside the uterus. The condition affects quality of life of the patient mostly because of pain, incapacity, infertility and obstetric complications [1-3]. It mainly affects women of reproductive age, causing infertility in 30% of them [4]. Although its aetiology is not completely elucidated, there are different theories that try to explain its origin [5]. Retrograde menstruation with transplacental of shed endometrium is considered the primary aetiopathogenic mechanism. However, its understanding is still incomplete [6-8]. Activity of macrophages causing proliferation of fibroblasts, formation of adhesive lesions and angiogenesis due to the inflammatory cascade has been reported [9]. Numerous biomarkers are potentially involved in the development of endometriosis including IL-31, IL-33, IL6, IL8, CD68, CD14, TGF- $\beta$ 1, COX-2, VEGF, ER-1 $\beta$ , aromatase, alarmins, CA-125, ABCG2, CD133 [10-13], TNF- $\alpha$ , MCP-1 [9], by causing an inflammatory response and some of them angiogenesis and growth of endometrial lesions potential. Their use as tool for diagnosis is limited by their lack of specificity and sensitivity for endometriosis [14]. Currently the diagnosis is primarily made through laparoscopy visualization [5]. Ultrasound is also used as an effective tool to detect and characterize lesions on the uterosacral ligament, parametrium and paracervix [3, 15]. Other methods being investigated as alternatives include measurement of anogenital distance length ( $22.8 \pm 4.6$  mm) and anti-Müllerian hormone (AMH) levels [16, 17] instead of surgical procedures which can cause pelvic adhesions and inflammation [18]. Before a definitive diagnosis is made, women often endure symptoms for years while negative effects on well-being and quality of life accumulate [5]. Scales such as the Depression Anxiety Stress Scales (DASS-21), the Visual Analogue Scale (VAS) and the Endometriosis Health Profile-5 (EHP-5) have demonstrated that infertility and pain had the highest possible negative impact on quality of life [19, 20]. Within the spectrum of current pain treatment are surgical and pharmacologic modalities. New hormonal treatments such as GnRH antagonists, aromatase inhibitors, SERMs, and SPRMs are currently under investigation. Nevertheless, there are side effects and some precautions and contraindications [21-23]. Some data have shown that non-surgical or pharmacological treatment for chronic pelvic pain

in endometriosis is safe, has hardly any adverse effects and improves the quality of life. These include physical therapy, acupuncture, massage, pilates, diet, and cognitive behavioural therapy. The few publications that are found in this regard on complementary therapies show positive and promising results over this topic [24-26]. Given the above, this study aims to describe and analyse the effects of complementary therapies for pain management in endometriosis.

## MATERIALS AND METHODS

This research is a scoping review, where a search for information on complementary treatment (non-pharmacological or surgical) of endometriosis was done in 4 databases in May 2022, following the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR). The following databases were searched: PubMed, Web of science, Scopus, and Ovid. A total of 941 articles were found. For the information search, the PICOT strategy was considered, where the population corresponded to patients with endometriosis, the intervention consisted of non-pharmacological or surgical treatment, without the presence of a comparator and the primary outcome to be measured was pain. The inclusion criteria were articles in English or Spanish, publications with empirical data (experimental, quasi-experimental, observational) and narrative (systematic, panoramic, integrative reviews, case studies), research on patients diagnosed with endometriosis who had some type of non-pharmacological treatment such as: physiotherapy, acupuncture, physical exercise, alternative therapy, among others, taking pelvic pain as the main outcome. The exclusion criteria were articles without full text available, research focused on the treatment of other pathologies such as dyspareunia or dysmenorrhea, as well as clinical trial protocols and systematic review protocols. The search equation was performed by a person with review training and is condensed as follows: endometriosis AND (“Non-pharmacological treatment” OR physiotherapy OR acupuncture OR “physical exercise” OR “physical activity”) AND pain. All the results were initially filtered through the Rayyan free software, where two independent reviewers evaluated all the articles by title and abstract and in case of disagreement, a third party intervened to make

the inclusion decision. 44 duplicates were eliminated for a total of 894 articles analysed, of which 22 were included. The second filter consisted of reading the full text where 14 investigations were selected, 2 were discarded because they did not meet all the inclusion criteria, for a total of 12 articles included in this review (Figure 1). The results were condensed in a table on the Microsoft Excel program, where the variables of author, year, country, objective of the study, and conclusions were analysed.

**RESULTS**

Four experimental studies and eight observational studies and/or systematic reviews were included (n = 12).

*Synthesis of the findings of the included publications*

Randomized controlled trials (n = 2), narrative reviews (n = 5), retrospective cohort study (n = 1), a quasi-experimental study (n = 1), systematic re-

views (n = 2), and a case report (n = 1) were found. The countries of origin of the studies were Australia (n = 1), Switzerland (n = 1), United States (n = 2), Italy (n = 1), Germany (n = 1), England (n = 1), China (n = 2) and Brazil (n = 1).

**Experimental studies (Tables 1 and 2)**

Of the controlled clinical trials found Mikocka *et al.* [25] states that cognitive behavioural therapy and yoga may have benefits in alleviating the general well-being of patients with pain caused by endometriosis. Similarly, Mira *et al.* [26], in their trial that included 101 patients, showed improvement in chronic pelvic pain  $p < 0.001$  with a decrease of 36% in the intervention group, through transcutaneous electrical stimulation. This reduction in pain was observed from the third week to the end of treatment, as well as improvements in dyspareunia, sexual function, and quality of life of the participants. In turn, Ling Bi *et al.* [27] carried out a retrospective cohort study, highlighting the effect and safety of neuromuscular electrical stimulation (NES) in patients suffering from endometriosis after 10 weeks,

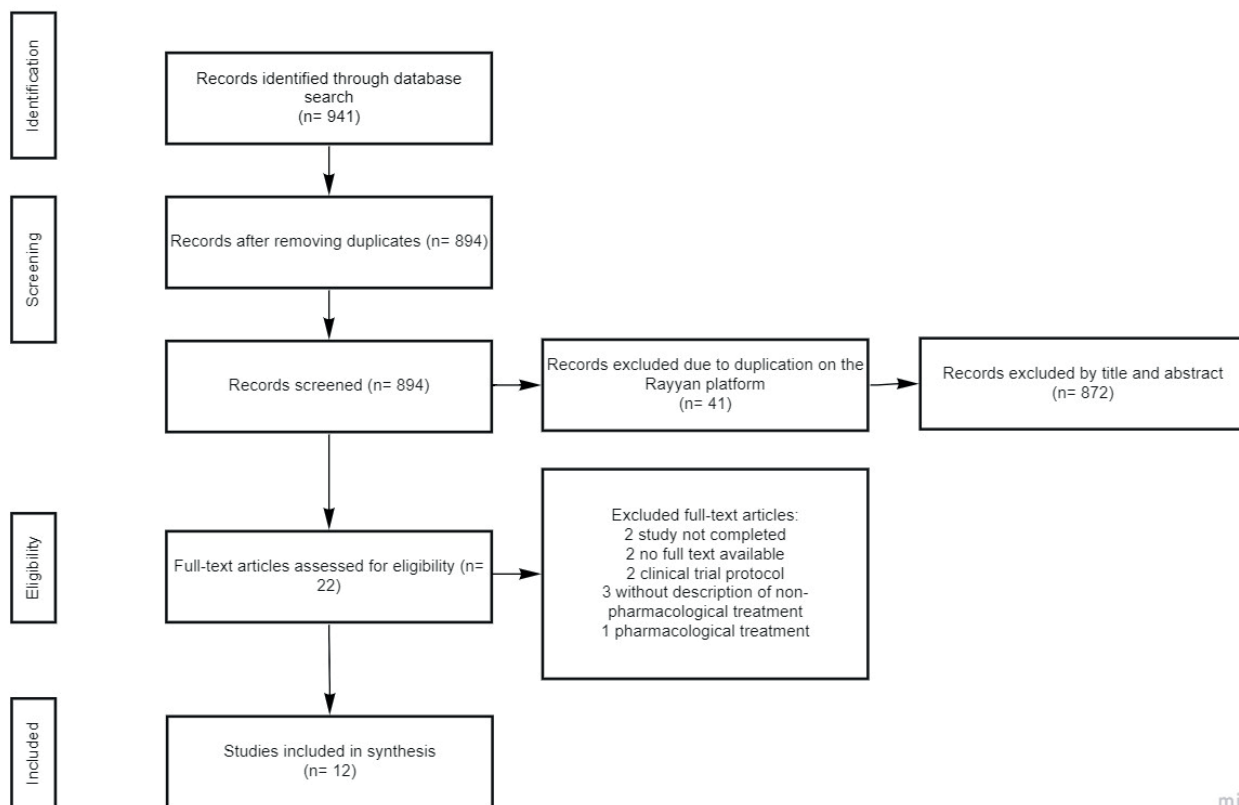


Figure 1. Flowchart of the article selection process (PRISMA).

**Table 1.** Characterization of experimental studies.

Study	Country	Design	Number of subjects (age)	Population characteristics	Purpose of the study
Mikocka, <i>et al.</i> (2021)	Australia	Randomized, parallel controlled trial	258 (> 18 yrs)	Women > 18 years old, with high level of English, internet access and endometriosis diagnosed in the last 6 months by US, histology or clinically. Pain included dysmenorrhea, dyschezia, dysuria or cyclic pain. Drug treatment was continued during the interventions.	To compare the cost-effectiveness and efficacy of cognitive behavioral therapy and yoga vs education in the treatment of endometriosis.
Mira, <i>et al.</i> (2020)	Not available	Multicenter randomized controlled trial	101 (28 to 43 yrs)	Menstruating women who present deep infiltrative endometriosis, in continuous hormonal treatment for the least 3 months and report symptoms of chronic pelvic pain or deep dyspareunia.	To evaluate the clinical effectiveness of complementary self-applied electrotherapy treatment for pain control compared to standard hormonal treatment alone for endometriosis and to describe its influence on quality of life and sexual function in women with deep infiltrative endometriosis.
Ling Bi, <i>et al.</i> (2018)	China	Retrospective cohort study	154 (18 to 42 yrs)	Women aged 18 to 42 years with a confirmed diagnosis of endometriosis-associated pain (EAP) and chronic pelvic pain (CPP).	To assess the effect of neuromuscular electrical stimulation (NMES) for the treatment of EAP.
Benedicto, <i>et al.</i> (2020)	Brazil	Quasi-experimental study	21 (18 to 50 yrs)	Sedentary women with chronic pelvic pain (CPP) associated with significant dysmenorrhea for the least 6 months.	To evaluate the influence of strength exercise on remote pain sensitivity in women with endometriosis-related symptoms.

$p < 0.01$ . However, the efficacy of NES was not studied, as a placebo control group was not included. Benedict *et al.* [28] conducted a quasi-experimental study in which it was shown that strength exercises have an effect of lowering the pain threshold in symptomatic patients with endometriosis compared to healthy women who did not have a long-term decrease in the pain threshold. They had the lowering of pain 20 minutes after performing strength exercise returning to normal values after this time compared with the decrease in pain threshold in symptomatic women with endometriosis which was evidenced in the first week. However, after this time in symptomatic women the thresholds remained stable, but still lower than those of healthy patients.

### Observational studies and systematic reviews (Table 3)

Within the observational studies and systematic reviews, the use of complementary therapies is highlighted, where two of the studies included in this review analysed transcutaneous electrical stimulation (TENS); acupuncture techniques were included in four studies, the prescription of activity and physical exercise was the focus of discussion in three investigations, as well as diet control was also described in three articles, osteopathic

manipulative therapy was present in one study as well as the yoga respectively.

Agarwal *et al.* [29] in his narrative review, gives a multidisciplinary perspective to intervene endometriosis, within this proposal, the pelvic floor approach performed by physiotherapy in synergy with the prescription of analgesics such as gabapentin for the management of endometriosis is mentioned. It highlighted the importance of an early intervention in mental health to prevent and, if necessary, treat clinical symptoms of anxiety and depression. On the other hand, Mechsner *et al.* [30] describes a multimodal approach with a series of interventions for pain management in patients with endometriosis. It exposes in the first place the use of pharmacology in acute stages of pain, mentioning the use of ibuprofen, naproxen and metamizole. On the other hand, a great emphasis is placed on diet control, suggesting a reduction in the consumption of gluten industrial sugars and meat to reduce the “endo-belly” syndrome, which refers to intestinal swelling, constipation or diarrhoea with abdominal distention. Finally, it proposes a physiotherapeutic approach. Muscle changes in the pelvic floor need to be managed because of trigger points and increased muscle tone, the above through manual therapy techniques, therapeutic exercise, and electrostimulation.

Yang *et al.* [31] in his systematic review analysed the use of acupuncture techniques finding a significant

Table 2. Description of intervention and results of experimental studies.

Author(s)	Control intervention	Experimental intervention	Main outcomes	Pain measurement scale	Results
Mikocka, et al.	Education brochures via email with education about endometriosis: symptoms and their causes, diagnosis, management and treatment, fertility and pregnancy, emotions, complications and risks, relationships, and sexuality	Cognitive behavioral therapy: weekly 120-minute therapy with groups of 10-13. They were encouraged to understand, educate, and manage pain. They were also required to have at least 3 times a week 20 minutes of practice at home. Yoga: yoga classes once a week of 60 minutes in groups of 10-13 people. Physical postures, conscious breathing techniques, relaxation and meditation were done. Participants were required to complete at least 20 sessions at home 3 times a week of movements and breathing techniques.	<ol style="list-style-type: none"> <li>1.Quality of life</li> <li>2.Quality of sleep</li> <li>3.Psychological symptoms,</li> <li>4.Fatigue 5.Menstrual symptoms,</li> <li>6.Pain</li> <li>7.Functionality and pain 8.Catastrophic pain</li> <li>9.Self-efficacy</li> <li>10.Central sensitization.</li> </ol>	<p>Pain VAS (0-10)</p> <ol style="list-style-type: none"> <li>1.Pain and functionality: brief pain inventory</li> <li>2.Pain catastrophizing: Pain Catastrophizing Scale</li> <li>3.Pain Self-Efficacy: Pain Self-Efficacy Questionnaire 4.Central sensitization: E Fibromyalgia Criteria-2016</li> </ol>	<p>Cognitive behavioral therapy and yoga improve general well-being, pain, psychological symptoms, and satisfaction in patients with endometriosis. Yoga and cognitive behavioral therapy were found to be more effective than education in improving quality of life in patients with endometriosis.</p>
Mira et al.	Hormonal treatment	Transcutaneous electrical nerve stimulation (TENS) in the presacral region (S3-S4 position) twice a day, 20 min per application + hormonal treatment.	<ol style="list-style-type: none"> <li>1.Chronic pelvic pain (EVA)</li> <li>2.Deep dyspareunia (DDS)</li> <li>3.Dyschezia (EVA)</li> <li>4.Frequency of bowel movement (per week) 5.Dysuria (EVA)</li> <li>6.Pain during spotting (EVA)</li> <li>7.Quality of life (Endometriosis Health Profile Endometriosis Health Profile (EHP-30)</li> <li>8.Sexual Function (Female Sexual Function Index (FSFI).</li> </ol>	EVA	<p>The TENS proved to be a good complement for the reduction of chronic pelvic pain and deep dyspareunia. Also, it has an improvement in quality of life and sexual function of patients. It can be considered a good complementary tool for the treatment of deep infiltrative endometriosis in this case in menstruating women.</p>
Ling Bi, et al.	No intervention	Neuromuscular electrical stimulation in acupuncture points at the level of the abdomen and lower limb. From 2 to 100 Hz for 30 minutes; once a day, 3 weekly sessions for a total of 10 weeks.	<ol style="list-style-type: none"> <li>1.Pain measured by numerical rating scale (NRS) and endometriosis symptom severity score (ESSS).</li> <li>2.Quality of life measured by the 36-item Short Form Health Survey (SF-36). It included 2 main subscales of physical component summary (PCS) and mental component summary (MCS).</li> </ol>	NRS	<p>Neuromuscular electrical stimulation (NMES) is shown to be effective in Chinese women with endometriosis-associated pain after 10 weeks of treatment. More studies are needed to corroborate this result.</p>
Benedicto, et al.	Chair leg extension strength exercises were performed in healthy women. The phases were preparation and experimentation. In the preparation phase, a mock session was performed to acquire a correct posture; in the experimental phase, a light warm-up of 3 minutes was started, and when the exercise was performed, a 1RM test was estimated, consisting of 10 repetitions to measure sub-maximal strength with a load of 60%. The protocol included 4 sets of 15 repetitions with intervals of 1 to 2 minutes.	Leg extension strength exercises in a chair were performed in symptomatic women with endometriosis. The phases were preparation and experimentation, in the preparation phase a mock session was performed to acquire a correct posture, in the experimentation phase it began with a light warm-up of 3 minutes, when arriving to the exercise a 1RM test was estimated, consisting of 10 repetitions to measure sub maximal strength with a load of 60%. The protocol included 4 series of 15 repetitions with intervals of 1 to 2 minutes.	<p>Sub-maximal strength (1RM), Pressure pain (algometry), heart rate, Blood pressure.</p>	Visual Analog Scale (VAS)	<p>The results of two groups with the same intervention were considered. It was observed that women with endometriosis-related symptoms had lower pain thresholds than women in the control group who were asymptomatic and healthy. In the control group the pressure pain thresholds increased immediately after exercise and returned to baseline after 20 minutes. In the experimental group, there were increases in heart rate and systolic pressure immediately after exercise, but significant alterations in the pressure pain threshold were not seen until the first week when the threshold decreased..</p>

Table 3. Characteristics of observational studies and systematic reviews.

Study	Country	Design	Objective	Conclusions
Kalaitzopoulos, et al. (2021)	Switzerland	Narrative review	Give an overview of therapeutic approaches from eight widely used national and international guidelines	All the guidelines of different gynaecology and obstetrics associations agree that the combined oral contraceptive pill and progestogens are recommended therapies for pain associated with endometriosis. Acupuncture proved to be effective as a complementary therapy for the significant reduction of pelvic pain and improvement in the quality of life of patients. Likewise, Transcutaneous Electrical Nerve Stimulation (TENS) is the most widely used electrical stimulation for pain therapy by directly blocking the transmission of pain signals along the nerves.
Agarwal, et al. (2019)	United States	Narrative review	Describe long-term clinical outcomes for women with endometriosis-associated pain. The multidisciplinary model of care is considered as an alternative to the single provider model and is considered to offer counselling as part of treatment	To improve long-term clinical outcomes, a multidisciplinary approach, including pain medicine, psychology, pelvic physiotherapy, nutrition, and other disciplines, will be helpful. Pelvic physiotherapy intervention can improve pelvic pain by internal manipulation of the pelvic floor muscles and ligaments.
Tennford, et al. (2021)	Carpen-ter, et al. United States Figgi Sebe Petrelluzzi, et al. Brazil Goncalves et al. Brazil,	Systematic review	To determine the effect of physical activity (PA) in patients with endometriosis	There may be a beneficial association between physical activity and endometriosis symptoms, however the exact impact cannot be determined from the existing literature. The benefits of PA should be communicated to patients with endometriosis and future studies should be RCTs that measure and report pain, quality of life and patient satisfaction.
Ball, et al. (2020)	Not available	Narrative review	To disseminate scientific and innovative information on the approach to chronic pelvic pain	Holistic, self-care and psychological approaches were shown to have positive or protective factors for endometriosis. Low red meat diet and exercise are a protective factor for endometriosis and acupuncture and psychological interventions were effective for pain relief and quality of life.
Buggio, et al. (2017)	Italy	Narrative review	To examine the evidence for new alternative approaches such as osteopathic manipulative therapy (OMT), massage, acupuncture, transcutaneous electrical nerve stimulation (TENS), vitamins, and dietary supplementation for the management of endometriosis	It is observed within the review the importance of factors such as diet and physical exercise, complementary alternative medical therapy (CAMT) could be a good complement to hormonal therapy even more in those patients with some contraindication. Finally, the importance of an interdisciplinary intervention to obtain integral results in the treatment is analysed.
Mechsner, et al. (2022)	Germany	Narrative review	To describe the different interventional techniques for chronic endometriosis and to give an overview of the pathology	The main cause of pain was analysed as peripheral and central sensitization leading the patient to suffer chronic pain. Pelvic myofascial pain reduces the quality of life of patients and can overlap with other types of chronic pain such as irritable bowel syndrome, vulvodynia, and painful bladder syndrome. In these cases, it is recognized by a very low pain threshold and multimodal therapy is needed.
Yang, et al. (2017)	China	Systematic review and meta-analysis	To determine the effectiveness of acupuncture as a treatment for endometriosis pain	Acupuncture reduces pain and serum CA-125 levels. There is very little evidence from randomized blinded clinical trials.
Payne, et al. (2019)	United States	Case Report	To detail the possible effects of Traditional Chinese Medicine on pelvic pain secondary to endometriosis through the presentation of a single case	Significant changes in pain levels were observed after the patient underwent acupuncture using Ah Shi points. However, the patient used a series of formulations and medications, and no way was found to determine the effectiveness of these for the reduction of fibroids and bleeding. The use of points other than Ah Shi is being considered for future studies.

decrease in pain. This strategy creates a type of analgesia which suppresses serum levels of estradiol, inhibits the growth of the ectopic endometrium, and allows the release of neurological factors humoral such as adenosine,  $\gamma$ -aminobutyric acid, opioid peptide, acetylcholine, nitric oxide, norepinephrine, and dopamine. Additionally, Payne *et al.* [32] support what was found by Yang *et al.* It is described that the use of acupuncture and the Ah Shi technique on pelvic floor trigger points substantially improves pain and pelvic perineal muscle tone.

Buggio *et al.* [33] expose physical activity as a protective factor against the pain presented in endometriosis since high-intensity exercise can reduce the level of estrogen, and it helps to reduce the proliferation, migration, and differentiation of endometriotic tissue. The odds ratio for endometriosis for any physical activity *versus* no physical activity was 0.85 (95% confidence interval (CI) 0.67-1.07). Similarly, they stated that, through the practice of yoga, through learning postures, breathing techniques and meditation, patients improved their ability to relief pain and thus control their symptoms. However, they propose another series of alternative interventions such as osteopathic manipulative therapy and massage. This is mainly based on the control of inflammation of internal organs that can cause symptoms in the musculoskeletal system. Jointly electro acupuncture is proposed where the use of acupuncture is combined with electrostimulation, this is based on the pituitary stimulation and production of cortisol and adrenocorticotrophic hormone generating an anti-inflammatory effect. In the same way, the use of non-invasive TENS is suggested, with the main objective of performing nerve stimulation to control pain and generate a release of endogenous opioids.

## DISCUSSION

This Scoping review describes complementary therapeutic strategies and their effect on pain management in patients with endometriosis. Within the heterogeneity of these interventions, it is evident that non-pharmacological treatment for pain management works as an adjuvant to main medical treatments such as combined oral contraceptives, progestogens, anti-inflammatories, and laparoscopic surgery. Although in this review only one case report is exposed where the efficacy of acupuncture and herbal therapy for pain in endometriosis is seen after 6 months, being the only

therapeutic strategy, most of the clinical trials and reviews describe the efficacy mainly of acupuncture and electrical stimulation after a treatment time greater than 4 weeks. This as a complement of medical or/and pharmacological treatment, mentioning that it is not replaced in any circumstance due to its limited evidence. However, other alternative therapies such as cognitive behavioural therapy, yoga, low-red meat diet, exercise and psychological interventions not only help improve pain but also improve the quality of life of patients. This wide range of therapeutic possibilities stems from the different mechanisms that can harm women with endometriosis. Endometriomas activate nociceptive fibres from all the inflammation they generate through a localized inflammatory response [5], which, over a long period of time, can cause central sensitization and thus lower pain thresholds leading to a pathology of stress and chronic pain [34]. This leads to problems that are triggered by the chronicity of pain and chronic inflammatory state such as the adoption of incorrect postures due to muscle spasms, inflammation at the gastrointestinal systemic level and psychological symptoms with a consequent decrease in quality of life. Chronic pain and consequent stress have been seen to decrease muscle tone and strength as well as decrease muscle relaxation capacity, generating changes in the pelvic floor due to muscle hypertonicity, causing trigger points of myofascial pain. This being one of the reasons why electrical stimulation and acupuncture can work [35].

On the other hand, it has been postulated that the chronic proinflammatory state generates changes in the microbiota that lead to symptoms of diarrhoea, abdominal distention, vomiting, or cyclical constipation. Taking this into account, diet has an important role. It has been postulated that the consumption of vegetarian products rich in fibre, fruits and vegetables has an anti-inflammatory role compared to a diet rich in protein, which has a pro-inflammatory role emphasizing pork and red meats [36]. Many times, these symptoms cause additional abdominal pain, discomfort and a feeling of heaviness. Therefore, diet can be a point of help to manage these symptoms and impact quality of life.

The complementary treatment exposed above could be a strong point of help in pain in patients with the most difficult medical conditions to treat such as deep endometriomas and extrapelvic endometriosis [37]. It represents a clinical and surgical challenge, considering that therapeutic strategy should be modulated and tailored on patient's characteristics. Surgeon has

to look for deep-seated lesions in the uterus, uterosacral ligaments, pelvic peritoneum, ovaries and ureters, sigmoid colon, and the upper rectum being the extraperitoneal surgical approach sometimes necessary [38]. To prevent recurrence rates, formation of postoperative lesions and improve fertility a total removal of endometrial implants without compromising ovarian function, protect and preserve the vasculature and nerve structures is mandatory [39, 40], what can be a winding road for patients.

Finally, it has been seen that 15-87% of patients with endometriosis have depressive and 29-88% anxious symptoms [4, 42]. This is where the effectiveness of cognitive behavioural therapy, yoga and exercises of self-modulation of pain are postulated. It is assumed that it helps with acupuncture to release endogenous opioids (pain reduction) and endogenous cortisol (anti-inflammatory) deactivating brain areas linked to pain perception. It also helps to release adenosine and to modulate the brain local blood flow which can contribute to pain modulation [43]. This is how, based on what can trigger the disease, the need arises for a multidisciplinary care approach that comprehensively manages women from the moment of diagnosis and the first symptoms, involving, in turn, the participation of different bodies of knowledge in health, such as gynaecology, nutrition, physiotherapy, psychiatry and psychology, as well as urology and gastroenterology. The foregoing suggests that the use of complementary therapies is not exclusively limited to being an adjunct to traditional management, on the contrary, alternative interventions to the usual praxis may have a potential leading role in pain management and therefore in the prevention of pain, optimization of the well-being and quality of life in women with endometriosis.

This review exposes the need of randomized clinical trials and studies of high methodological quality which representatively evaluate the efficacy of the different complementary interventions. Also, we highlight the importance of doing investigations where the percentage of patient satisfaction regarding the therapeutic complementary management can be shown *vs* the conventional one or combining those. On the other hand, it is necessary to delve into the impact of a complementary therapeutic arsenal as a primary option for treating pain in endometriosis with medical and surgical treatment and not leave them as an option. However, we need more information about its side effects, recommendations, and long-term effectiveness.

Additionally, this review denotes the absence of recommendations from clinical practice guidelines for non-pharmacological strategies for endometriosis, limiting the external validity of its implementation due to the lack of a prescription supported by high standards of evidence.

## CONCLUSIONS

The use of complementary strategies such as physical exercise, acupuncture, electrostimulation, cognitive behavioural therapy and diet are effective interventions for pain control in patients with endometriosis. More interdisciplinary research is required to promote understanding and the long-term effects of these currents of intervention, but its implementation should be recommended for pain improvements and quality of life in endometriosis patients from the beginning.

## COMPLIANCE WITH ETHICAL STANDARDS

### *Authors contribution*

M.A.S.V.: Methodology, project administration, supervision, writing – original draft, writing – review & editing. O.I.R.C.: Project administration, supervision, writing – review & editing. SOZ: Investigation, supervision, writing – original draft, writing review & editing. J.D.B., Z.Y.S..R, O.F.C.D.: Investigation, writing – original draft.

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### *Study registration*

N/A.

### *Disclosure of interests*

The authors declare that they have no conflict of interests.

### *Ethical approval*

The authors declare that no experiments have been performed on humans or animals for this research and no patient data appear in this article.



## Informed consent

The authors declare that no patient data appear in this article.

## Data sharing

All data are referred in the current review.

## REFERENCES

- Laganà AS, Garzon S, Götte M, Viganò P, Franchi M, Ghezzi F, et al. The Pathogenesis of Endometriosis: Molecular and Cell Biology Insights. *Int J Mol Sci.* 2019;20(22):5615. doi: 10.3390/ijms20225615.
- Bianco B, Loureiro F, Trevisan C, Peluso C, Cristofolini D, Montagna E, et al. Effects of FSHR and FSHB Variants on Hormonal Profile and Reproductive Outcomes of Infertile Women with Endometriosis. *Front Endocrinol (Lausanne).* 2021;12:760616. doi: 10.3389/fendo.2021.760616.
- Laganà AS, Vitagliano A, Chiantera V, Cicinelli E. Diagnosis and Treatment of Endometriosis and Endometriosis-Associated Infertility: Novel Approaches to an Old Problem. *J Clin Med.* 2022;11(13):3914. doi: 10.3390/jcm11133914.
- Matsuzaki S, Darcha C. Epithelial to mesenchymal transition-like and mesenchymal to epithelial transition-like processes might be involved in the pathogenesis of pelvic endometriosis. *Hum Reprod.* 2012;27(3):712-21. doi: 10.1093/humrep/der442.
- Zondervan K, Becker C, Missmer S. Endometriosis. *N Engl J Med.* 2020;382(13):1244-56. doi:10.1056/NEJMra1810764.
- Králíčková M, Vetvicka V, Fiala L, Laganà AS, Garzon S. The Search for Biomarkers in Endometriosis: a Long and Windy Road. *Reprod Sci.* 2022;29(6):1667-73. doi: 10.1007/s43032-021-00668-2.
- Baldi A, Campioni M, Signorile PG. Endometriosis: pathogenesis, diagnosis, therapy and association with cancer (review). *Oncol Rep.* 2008;19(4):843-46. doi: 10.3892/or.19.4.843.
- D'Hooghe TM, Debrock S. Endometriosis, retrograde menstruation and peritoneal inflammation in women and in baboons. *Hum Reprod Update.* 2002;8(1):84-8. doi: 10.1093/humupd/8.1.84.
- Hortu I, Ozceltik G, Karadadas E, Erbas O, Yigiturk G, Ulukus M. The Role of Ankaferd Blood Stopper and Oxytocin as Potential Therapeutic Agents in Endometriosis: A Rat Model. *Curr Med Sci.* 2020;40(3):556-62. doi: 10.1007/s11596-020-2213-1.
- Miller JE, Monsanto SP, Ahn SH, Khalaj K, Fazleabas AT, Young SL, et al. Interleukin-33 modulates inflammation in endometriosis. *Sci Rep.* 2017;7(1):17903. doi: 10.1038/s41598-017-18224-x.
- Hudson QJ, Ashjaei K, Perricos A, Kuessel L, Hussein H, Wenzl R, et al. Endometriosis patients show an increased M2 response in the peritoneal CD14+low/CD68+low macrophage subpopulation coupled with an increase in the T-helper 2 and T-regulatory cells. *Reprod Sci.* 2020;27(10):1920-31. doi: 10.1007/s43032-020-00211-9.
- Meng Q, Sun W, Jiang J, Fletcher NM, Diamond MP, Saed GM. Identification of common mechanisms between endometriosis and ovarian cancer. *J Assist Reprod Genet.* 2011;28(10):917-23. doi: 10.1007/s10815-011-9573-1.
- Liu S, Zhou J, Wen J. Expression and significance of CD133 and ABCG2 in endometriosis. *Clin Exp Obstet Gynecol.* 2015;42(6):771-5. Available at: <https://europepmc.org/article/MED/26753483>.
- Králíčková M, Vetvicka V, Fiala L, Laganà AS, Garzon S. The Search for Biomarkers in Endometriosis: a Long and Windy Road. *Reprod Sci.* 2022;29(6):1667-73. doi: 10.1007/s43032-021-00668-2.
- Noventa M, Scioscia M, Schincariol M, Cavallin F, Pontrelli G, Virgilio B, et al. Imaging Modalities for Diagnosis of Deep Pelvic Endometriosis: Comparison between Trans-Vaginal Sonography, Rectal Endoscopy Sonography and Magnetic Resonance Imaging. A Head-to-Head Meta-Analysis. *Diagnostics (Basel).* 2019;9(4):225. doi: 10.3390/diagnostics9040225.
- Buggio L, Barbara G, Dridi D, Ottolini F, Sergenti G, Facchin F, et al. Anogenital distance and Gynaecological diseases: a narrative review. *Ital J Gynaecol Obstet.* 2020;32(3):200-7. doi: 10.36129/jog.32.03.06.
- Nie J, Zhao C, Laganà AS, Liu X, Guo SW. Identification of lesional attributes of dysmenorrhea severity and the serum antimüllerian hormone levels in women with ovarian endometriomas. *Fertil Steril.* 2022;118(1):191-202. doi: 10.1016/j.fertnstert.2022.04.016.
- Serafino P, Palumbo M, Viciglione F, Mercorio A, Cafas V, Boccia D, et al. Surgical adhesions after laparoscopic myomectomy: methods of preven-

- tion. *Ital J Gynaecol Obstet.* 2022;35(1):120-30. doi:10.36129/2022.56.
19. Mikuš M, Matak L, Vujić G, Škegro B, Škegro I, Augustin G, et al. The short form endometriosis health profile questionnaire (EHP-5): psychometric validity assessment of a Croatian version. *Arch Gynecol Obstet.* 2023;307(1):87-92. doi: 10.1007/s00404-022-06691-1.
  20. Škegro B, Bjedov S, Mikuš M, Mustać F, Lešin J, Matijević V, et al. Endometriosis, Pain and Mental Health. *Psychiatr Danub.* 2021;33(Suppl 4):632-6. Available at: [https://www.psychiatria-danubina.com/UserDocsImages/pdf/dnb\\_vol33\\_noSuppl%204/dnb\\_vol33\\_noSuppl%204\\_632.pdf](https://www.psychiatria-danubina.com/UserDocsImages/pdf/dnb_vol33_noSuppl%204/dnb_vol33_noSuppl%204_632.pdf).
  21. Kalaitzopoulos D, Samatriz N, Kolovos N, Mareti E, Samartzis E, Eberhard M, et al. Treatment of endometriosis: a review with comparison of 8 guidelines. *BMC Womens Health.* 2021;21(1):397. doi: 10.1186/s12905-021-01545-5.
  22. Angioni S, Cofelice V, Sedda F. Progestins for symptomatic endometriosis: results of clinical studies. *Curr Drug Ther.* 2015;10(2):91-104. doi: 10.3109/09513590.2014.950646.
  23. Zajec, V, Mikuš. M, Vitale, S. G. D'alterio, M. N. Gregov, M. Šarić, M. J. Carugno, J. Angioni, S. & Ćorić M. Current status and challenges of drug development for hormonal treatment of endometriosis: a systematic review of randomized control trials. *Gynecol Endocrinol.* 2022;38(9):713-20. doi: 10.1080/09513590.2022.2109145.
  24. Trovo de Marqui Bernadete A. Non-pharmacological approach to pain in endometriosis. *Rev Dor São Paulo. SciELO.* 2014;15(4):300-3. doi:10.5935/1806-0013.20140065.
  25. Mikocka-Walus A, Druitt M, O'Shea M, Skvarc D, Watts JJ, Esterman A, et al. Yoga, cognitive-behavioural therapy versus education to improve quality of life and reduce healthcare costs in people with endometriosis: a randomised controlled trial. *BMJ Open.* 2021;11(8):e046603. doi: 10.1136/bmjopen-2020-046603.
  26. Mira TAA, Yela DA, Podgaec S, Baracat EC, Benetti-Pinto CL. Hormonal treatment isolated versus hormonal treatment associated with electrotherapy for pelvic pain control in deep endometriosis: Randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol.* 2020;255(5):134-41. doi: 10.1016/j.ejogrb.2020.10.018.
  27. BiXL, XieCX. Effect of neuromuscular electrical stimulation for endometriosis-associated pain: A retrospective study. *Medicine (Baltimore).* 2018;97(26):e11266. doi: 10.1097/MD.00000000000011266.
  28. Poli-Neto OB, Oliveira AMZ, Salata MC, Rosa-E-Silva JC, Machado DRL, Salata MC, et al. Strength exercise has different effects on pressure pain thresholds in women with endometriosis-related symptoms and healthy controls: A quasi-experimental study. *Pain Med.* 2020;21(10):2280-7. doi: 10.1093/PM/PNZ310.
  29. Agarwal SK, Foster WG, Groessl EJ. Rethinking endometriosis care: Applying the chronic care model via a multidisciplinary program for the care of women with endometriosis. *Int J Womens Health.* 2019;11:405-10. doi: 10.2147/IJWH.S207373.
  30. Mechsner S. Endometriosis, an Ongoing Pain-Step-by-Step Treatment. *J Clin Med.* 2022;11(2):467. doi: 10.3390/jcm11020467.
  31. Xu Y, Zhao W, Li T, Zhao Y, Bu H, Song S. Effects of acupuncture for the treatment of endometriosis-related pain: A systematic review and meta-analysis. *PLoS One.* 2017;12(10):e0186616. doi: 10.1371/journal.pone.0186616.
  32. Payne JA. Acupuncture for Endometriosis: A Case Study. *Med Acupunct.* 2019;31(6):392-4. doi: 10.1089/acu.2019.1379.
  33. Buggio L, Barbara G, Facchin F, Frattaruolo MP, Aimi G, Berlanda N, et al. Self-management and psychological-sexological interventions in patients with endometriosis: strategies, outcomes, and integration into clinical care. *Int J Womens Health.* 2017;2(9):281-93. doi: 10.2147/IJWH.S119724.
  34. Borrelli GM, Carvalho KI, Kallas EG, Mechsner S, Baracat EC, Abrão MS, et al. Chemokines in the pathogenesis of endometriosis and infertility. *J Reprod Immunol.* 2013;98(1-2):1-9. doi: 10.1016/j.jri.2013.03.003.
  35. Finas D, Hüppe M, Diedrich K, Kowalcek I. Chronischer Unterbauchschmerz Am. Beispiel der Endometriose Problempatientin in der Gynäkologie? *Geburtshilfe Frauenheilkd.* 2005;65(2):156-63 doi: 10.1055/s-2004-830535.
  36. Ata B, Yildiz S, Turkgeldi E, Brocal VP, Dinleyici EC, Moya A, et al. The Endo-biota Study: Comparison of Vaginal, Cervical and Gut Microbiota Between Women with Stage 3/4 Endometriosis and Healthy Controls. *Sci Rep.* 2019;9(1):2204. doi: 10.1038/s41598-019-39700-6.
  37. Laganà AS, Vitale SG, Granese R, Palmara V, Ban Frangež H, Vrtačnik-Bokal E, et al. Clinical dynamics of Dienogest for the treatment of endometriosis: from bench to bedside. *Expert Opin Drug Metab Toxicol.* 2017;13(6):593-6. doi: 10.1080/17425255.2017.1297421.
  38. Sansone A, De Rosa N, Giampaolino P, Guida M, Laganà AS, Di Carlo C, et al. Effects of etonogest-

- tre implant on quality of life, sexual function, and pelvic pain in women suffering from endometriosis: results from a multicenter, prospective, observational study. *Arch Gynecol Obstet.* 2018;298(4):731-6. doi: 10.1007/s00404-018-4851-0.
39. Laganà AS, Vitale SG, Trovato MA, Palmara VI, Rapisarda AM, Granese R, et al. Full-Thickness Excision versus Shaving by Laparoscopy for Intestinal Deep Infiltrating Endometriosis: Rationale and Potential Treatment Options. *Biomed Res Int.* 2016;2016:3617179. doi: 10.1155/2016/3617179.
  40. Campo S, Campo V, Benagiano G. Adenomyosis and infertility. *Reprod Biomed Online.* 2012;24(1):35-46. doi: 10.1016/j.rbmo.2011.10.003.
  41. Chapron C, Pietin-Vialle C, Borghese B, Davy C, Foulot H, Chopin N, et al. Associated ovarian endometrioma is a marker for greater severity of deeply infiltrating endometriosis. *Fertil Steril.* 2009;92(2):453-7. doi: 10.1016/j.fertnstert.2008.06.003.
  42. Cousins FL, Dorien FO, Gargett CE. Endometrial stem/progenitor cells and their role in the pathogenesis of endometriosis. *Best Pract Res Clin Obstet Gynaecol.* 2018;50:27-38. doi: 10.1016/j.bpobgyn.2018.01.011.
  43. Berman BM, Langevin HM, Witt CM, Dubner R. Acupuncture for chronic low back pain. *N Engl J Med.* 2010;363(5):454-61. doi: 10.1056/NEJMct0806114.