

Artigo de Revisão

Premenstrual syndrome: possibilities of care for symptom attenuation

Síndrome pré-menstrual: possibilidades de cuidados para atenuação dos sintomas

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ABSTRACT: Introduction: Premenstrual syndrome (PMS), with beginning in one or two weeks before menstruation, includes a recurring pattern of physical, affective and behavioral symptoms that can be exacerbated by external factors as life habits and socioeconomic conditions, affecting negatively the daily activities. Objective: Identify the possibilities of care for PMS symptoms attenuation. Method: Integrative literature review performed through reading of official portals of public agencies and the electronic search in Biblioteca Virtual em Saúde (BVS), PubMed, Scientific Electronic Library Online (SciELO) and Cochrane Library. Results: In this integrative review, it was selected 246 primary studies published within the last 5 years, available for free and in English and Portuguese languages. Discussion: In regard of the non-pharmacological techniques, it was observed that physical exercise, diet, traditional Iranian medicine, vitamin D supplementation, cognitive behavioral therapy and phytoestrogens, mainly linseed, had good efficiency in the attenuation of the PMS symptoms, as dysmenorrhea and mood changes; the treatment with auriculotherapy has shown similar results as the use of placebo; others as acupuncture, acupressure and didn't bring conclusive results. Between the pharmacological methods, the standard treatment is with combined oral contraceptives. Furthermore, the use of selective serotonin reuptake inhibitors (SSRIs) can increase the amount of serotonin for neurotransmission and consequently improve PMS symptoms. The selective estrogen receptor modulator offers a safe strategy to handle the symptoms, including menopause. The use of selective progesterone receptor modulator, on the other hand, has shown better control of aggressive behaviors. At last, a multicentric study made in Sweden has shown promising results of endogenous neurosteroid when compared to the use of combined oral contraceptives. Conclusion: There are strong evidence of improvement of PMS symptoms in front of the many treatment possibilities, whether they are pharmacological or non-pharmacological.

KEYWORDS: Premenstrual Syndrome. Menstrual Cycle. Drug Therapy. Complementary Therapies.

RESUMO: Introdução: A Síndrome Pré-menstrual (SPM), com início de uma a duas semanas antes da menstruação, engloba um padrão recorrente de sintomas físicos, afetivos e comportamentais, podendo ser agravados por fatores externos, como hábitos de vida e condição socioeconômica, afetando negativamente as atividades diárias. Objetivo: Identificar as possibilidades de cuidados para atenuação dos sintomas da SPM. Método: Revisão integrativa realizada por meio da busca eletrônica na Biblioteca Virtual em Saúde (BVS), no PubMed, na Scientific Electronic Library Online (SciELO) e na Cochrane Library. Resultados: foram selecionados 246 estudos primários publicados nos últimos 5 anos, nos idiomas inglês e português. Discussão: Com relação às técnicas não farmacológicas, observou-se que os métodos de exercício físico, dieta, medicina tradicional iraniana, suplementação de vitamina D, terapia cognitivo-comportamental e uso de fitoestrógeno, sobretudo a linhaça, obtiveram boa eficácia na atenuação dos sintomas da SPM, como dismenorreia e alterações de humor; o tratamento com auriculoterapia mostrou resultados semelhantes ao uso de placebo; outros como acupuntura e acupressão não trouxeram resultados conclusivos. Entre os métodos farmacológicos, o tratamento padrão preconizado é por meio de anticoncepcionais orais combinados. Além disso, o uso de inibidores seletivos da recaptação da serotonina (ISRSs) pode aumentar a quantidade de serotonina para neurotransmissão e consequentemente melhorar os sintomas da SPM. Os moduladores seletivos do receptor de estrogênio oferecem uma estratégia segura para manejo de sintomas, inclusive os de menopausa. O uso de moduladores do receptor de progesterona, por outro lado, mostrou maior controle de comportamentos agressivos. Ademais, um estudo multicêntrico realizado na Suécia mostrou resultado promissor do neuroesteróide endógeno em comparação ao uso de anticoncepcionais orais combinados. Conclusão: Há fortes indícios de melhora dos sintomas da SPM diante das diversas possibilidades para seu tratamento sejam elas farmacológicas ou não-farmacológicas.

PALAVRAS-CHAVE: Síndrome Pré-Menstrual. Ciclo Menstrual. Tratamento Farmacológico. Terapias Complementares.

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INTRODUCTION

From childhood to aging, women experience physiological modifications and adaptations to establish the complete development and maturity of their organism. In this context, at puberty, menarche represents a fundamental milestone for the activation of the hypothalamic-pituitary-ovarian axis, with the secretion of follicle-stimulating hormones (FSH), luteinizing hormone (LH), estrogen and progesterone, which entails anatomical changes in the womb, tubes, ovaries and breasts. Furthermore, it consolidates the beginning of the menstrual cycle, with variations from 20 to 45 days and an average of 28 days^{1,2}.

Nonetheless, the hormonal oscillation inherent to the menstrual cycle is sometimes accompanied by undesirable signs and symptoms that can translate into a decrease in the woman's quality of life, characterizing the premenstrual syndrome (PMS). This manifests itself through a set of physical, affective and behavioral symptoms during the luteal phase of the menstrual cycle that vary in intensity and degree of repercussion, which can range from isolated mastalgia (breast tenderness) to the impossibility of carrying out daily activities. Epidemiological data infer that approximately 50% to 85% of women have, at some point in their reproductive life, at least one symptom of PMS and 30% to 40% have recurrent symptoms³.

The onset of symptoms commonly appears around one to two weeks before menstruation, with remission in the first few days of each cycle. It is important to highlight that, although its etiology remains unknown, the cause of PMS can be associated with hormonal oscillations of the menstrual cycle and its relationship with neurotransmitters, especially serotonin and gamma-aminobutyric acid (GABA)^{3,4}.

Among the most frequent complaints, one can mention depressive symptoms, easy crying, anxiety, irritability, mood changes, headache, myalgia, edema, mastalgia, exacerbation of appetite and weight gain^{3,4}. In addition, some factors such as genetics, socioeconomic status, nutrition, lifestyle, stress level and emotions experienced in their relationship with the environment can intensify the effects of PMS⁵. Studies carried out in the United States of America (USA)⁶, United Kingdom⁷ and Brazil⁸ with women affected by PMS revealed a higher prevalence in young, black and obese participants with unhealthy lifestyle habits, including alcohol consumption and smoking.

It is worth underlining that, in view of the high incidence, several strategies to alleviate symptoms are used with a view to promoting a better quality of life for women affected by PMS. Care management varies from lifestyle modification to the introduction of pharmacological and non-pharmacological methods. Therefore, the identification of the specific needs of each woman should be expanded

based on the different existing care methods.

Accordingly, considering the impact that PMS has and the scarce dissemination of methods for the alleviation of symptoms, the present study is justified by the need to recognize the various care options for women, respecting their individuality and autonomy. Thus, it has the objective of identifying the possibilities of care to alleviate the PMS symptoms.

METHODOLOGY

This is an Integrative Literature Review, i.e., this type of study is characterized by the synthesis of existing research results, in order to guide the choice of practices based on technical-scientific knowledge⁹.

The methodological route complied with the following steps: 1) definition of the problem to be studied; 2) selection of the literature sample; 3) characterization of the articles; 4) critical analysis of the included results; 5) discussion of results; and 6) presentation of the integrative review.

At first, in order to answer the proposed objective, the guiding question was elaborated, based on the PICOT strategy: In women with PMS, where (P), what are the possibilities of care (I), used with a focus on the alleviation of symptoms (C), are capable of contributing to the improvement of the quality of life? (O). It was carried out observing publications of the last five years (T).

The second phase of the study was carried out in September and October 2022 with the help of the databases: Virtual Health Library (VHL), PubMed, Scientific Electronic Library Online (SciELO) and the Cochrane Library. The search for an article was performed by consulting the *Descritores em Ciências da Saúde* (DeCS): *Síndrome Pré-Menstrual*; *Ciclo Menstrual*; *Tratamento Farmacológico*; *Terapias Complementares*; and the Medical Subject Headings (MESH): *Premenstrual Syndrome*; *Menstrual Cycle*; *Drug Therapy*; *Complementary Therapies*, combined with each other with the Boolean logical operator "AND".

Primary studies published in the last five years (2017-2022) that answered the guiding question were included. Duplicate articles, reviews, theses and/or dissertations and those that did not address the proposed theme were excluded.

In the first search, studies were excluded from the application of filters (year, type of study, language) in each database for those that did not meet the inclusion criteria, right after a careful reading of the titles and abstracts was carried out for eligibility of studies in this first stage. Duplicate articles were counted only once.

In the third phase, when evaluating the data, tables were designed to allow extracting the most relevant information from the articles included in this study. The first table consisted of the following data: identification of

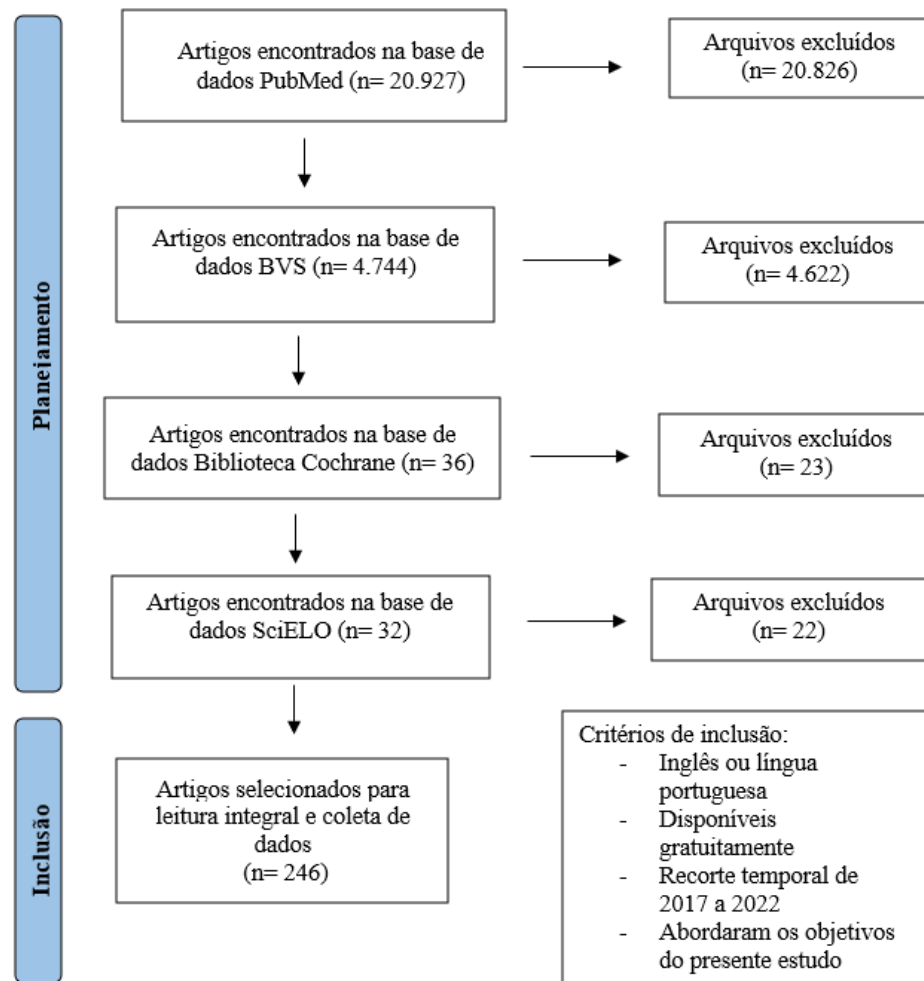
the main author, year, journal, *Qualis* and evidence level, while the second included the objective and the main results and conclusions found.

In the analysis of the articles, the findings were classified according to the level of scientific evidence. To this end, a classification system consisting of seven levels was used: Level I - evidence from systematic reviews or meta-analysis of relevant clinical trials; Level II - evidence derived from at least one well-designed and controlled randomized clinical trial; Level III - well-designed clinical trials without randomization; Level IV - cohort and case-control studies; Level V - systematic review of descriptive and qualitative studies; Level VI - evidence derived from a single descriptive or qualitative study; and Level VII

- opinion of authorities or report of expert committees⁸.

Still in the analysis stage, a reflective and careful reading was carried out with a view to identifying convergences and divergences between the authors. Finally, in phase five, the presentation of data and the discussion of articles were related to interventions in the studied population. A flowchart was organized focusing on the objectivity and clarity of the articles that imply their validation.

Finally, the remaining articles were read in full and, again, those that were not directly related to the purpose of this study were excluded. In the end, 246 articles were eligible for this study (Figure 1).



Inclusion, Planning, Articles found in the PubMed database, Articles found in the VHL database, Articles found in the Cochrane Library database, Articles found in the SciELO database, Files selected for full reading and data collection, Excluded files, Inclusion criteria: English or Portuguese languages, Freely available, Time frame from 2017 to 2022, Addressed the objectives of this study.

Figure 1 - Flowchart of the phases of the integrative review

RESULTS

In the present study, 246 articles were analyzed that met the eligibility criteria, as follows: 101 found in PUBMED, 122 in VHL, 10 in SciELO and 13 in the Cochrane Library. Of these, after reflective and careful reading with a focus on objectivity and clarity, 27 articles were selected. There was a predominance of publications in international journals, with 22 appearing in English and 5 in Portuguese. Table 1 and Table 2 show information about the listed studies.

It was noticed that the possibilities of care for the alleviation of Premenstrual Tension (PMS) more frequently included: Acupuncture, Combined oral contraceptives, Auriculotherapy, Lecithin phosphatidic acid and phosphatidylserine complex (PAS), Aerobic physical exercise and diet, Phytoestrogens, Selective Serotonin Reuptake Inhibitors (SSRIs), Traditional Iranian Medicine, Selective Estrogen Receptor Modulators (SERMs), Selective Progesterone Receptor Modulators (SPRMs), Vitamin D Supplementation and Cognitive-Behavioral Therapy.

Table 1 - Selected articles

Main Author	Year	Journal	Qualis	Evidence Level
Da Silva JD	2018	Pensar a Prática	C	Level IV
Henz A	2018	Revista Brasileira de Ginecologia e Obstetrícia	B3	Level IV
Yilmaz-Akyuz E	2019	Revista de Nutrição	B3	Level II
Rezende APR	2022	Revista Brasileira de Ginecologia e Obstetrícia	B3	Level IV
Masho SW	2005	Journal of Psychosomatic Obstetrics & Gynecology	B2	Level IV
Sadler C	2011	Journal of Women's Health	A1	Level IV
Longo SCM	2006	Revista de Saúde Pública	B2	Level IV
Armour M	2018	Cochrane Library	C	Level I
Korelo RIG	2022	Complementary Therapies in Medicine	B2	Level II
Schmidt K	2018	Clinical Nutrition ESPEN	B4	Level II
Prazeres LMA	2018	Fisioterapia em Movimento	B4	Level IV
Farahmand M	2020	Complementary Therapies in Medicine	B2	Level II
Heidari H	2019	Scientific Reports	A1	Level II
Alkhalaf Z	2021	Human Reproduction	A1	Level IV
Arabnezhad L	2022	BMC Complementary Medicine and Therapies	B1	Level II
Borji-Navan S	2022	BMC Women's Health	B2	Level II
Ussher JM	2017	Plos One	A2	Level II
Santos DPC	2022	Revista Saúde & Ciência Online	C	Level VI
Frigo M	2022	Cochrane Library	C	Level II
De Oliveira MT	2022	Sistemas de Bibliotecas da UFCG	C	Level V
De Wit AE	2021	American Journal of Obstetrics & Gynecology	A1	Level I
Shehata NAA	2020	Reproductive Sciences	B1	Level II
Takeda T	2018	BMJ Open	B1	Level II
Kaltsouni E	2021	Neuropsychopharmacology	A1	Level II
Bixo M	2017	Psychoneuroendocrinology	A1	Level II
Comasco E	2021	The American Journal of Psychiatry	A1	Level II

Table 2 - Selected articles

Main Author	Objectives	Results	Conclusion
Da Silva JD	To investigate the effects of the menstrual cycle (MC) phases on physical fitness variables and the subjective perception of exertion in young women	There were no significant differences in physical fitness tests between the MC phases	The different MC phases do not influence the performance of physical fitness components
Henz A	To validate the Premenstrual Symptom Screening Tool (PSST) concerning the daily recording of problem severity for PMS diagnoses	The PSST showed high sensitivity (79%) and low specificity (33.3%) for the PMS diagnosis	The PSST should be considered a diagnostic screening tool
Yilmaz-Akyuz E	To determine the effectiveness of aerobic exercises and diets in students with premenstrual syndrome	There was a significant reduction in PMS symptoms, in addition to a decrease in the intensity of dysmenorrhea compared to the control group.	Aerobic exercise and diet are effective in terms of reducing the symptoms of premenstrual syndrome and the intensity of dysmenorrhea
Rezende APR	To investigate the prevalence of PMS in university students, the associated factors, the most prevalent symptoms and the interference of symptoms in academic, family, social and work activities	The most prevalent symptoms were physical, followed by psychological. More than 30% of patients reported that the symptoms moderately to severely interfered with their social and academic activities	Identifying risk factors for PMS is essential to prevent symptoms and reduce the impact of this syndrome.
Masho SW	To determine the association between obesity and Premenstrual Syndrome (PMS)	Obese women (BMI ≥ 30) had an almost 3x greater risk of PMS than non-obese women	PMS management strategies should consider not only factors such as high stress and smoking, but also obesity
Sadler C	To estimate the prevalence of premenstrual symptoms in women from the general population in Southampton, the United Kingdom, and to examine its association with lifestyle factors and contraceptive use	Use of any form of hormonal contraceptive was associated with a lower prevalence of premenstrual symptoms	Premenstrual symptoms were common in this cohort and the use of hormonal contraceptives revealed good results.
Longo SCM	To study the prevalence and factors associated with premenstrual syndrome, comparing the frequency found with the self-reported	The prevalence found was 25.2% and self-reported was 60.3%. Users of psychiatric drugs and those who did not use hormonal contraception had a higher prevalence	25% of women had premenstrual syndrome. The self-reported perception of women was higher.
Armour M	To evaluate the effectiveness and safety of acupuncture or acupressure for women with PMS or premenstrual dysphoric disorder (PMDD)	Five trials were included in this review. None of the studies compared acupuncture or acupressure with other active treatments	Acupuncture and acupressure can improve physical and psychological symptoms of PMS when compared to simulated control
Korelo RIG	To investigate the effect of auriculotherapy on the intensity of physical and mood symptoms of premenstrual syndrome (PMS)	The group treated with auriculotherapy and placebo had significantly lower PMS symptom scores.	Auriculotherapy can be used as an adjunctive therapy to reduce the physical and mood symptoms of PMS
Schmidt K	To confirm observations regarding the effects of PAS on PMS symptom severity in a controlled clinical trial setting	A daily intake of PAS, containing 400 mg of phosphatidylserine and 400 mg of phosphatidic acid complex, can be considered safe	The results prove the effectiveness of PAS in terms of reducing PMS symptoms
Prazeres LMA	To compare the signs and symptoms of menstrual disorders in women who practice regular physical exercise or not	Negative impacts on the psychological, social and physical state of interviewed with PMS was significantly higher among sedentary women	The prevalence of signs and symptoms associated with dysmenorrhea was significantly higher in the sedentary group
Farahmand M	To evaluate the effect of <i>Echium amoenum</i> (EA) on the severity of premenstrual syndrome (PMS) compared to placebo	After adjusting for age and body mass index, the average scores of premenstrual syndrome, through the GEE analysis, decreased to 6.2 and 11.6, respectively	Compared with the placebo group, EA proved to be more effective in terms of improving PMS symptoms, being recommended for the treatment
Heidari H	To investigate the effect of vitamin D supplementation on inflammatory and antioxidant markers in vitamin D-deficient students with PMS	Vitamin D has effects on inflammatory markers, increasing serum levels of antioxidant capacity, and leads to improvements in PMS symptoms	There are beneficial effects of using 50,000 IU of vitamin D3 biweekly in vitamin D-deficient patients with PMS
Alkhalaf Z	To evaluate whether insufficient concentrations of 25-hydroxyvitamin D (25(OH)D) and other markers of vitamin D metabolism are associated with premenstrual symptoms in healthy women with regular menstrual cycles	Women with five or more moderate/severe premenstrual symptoms scored higher on the depression scale than women with fewer symptoms	There is an association between insufficient serum levels of 25(OH)D and physical symptoms. Vitamin D has the power to influence specific symptoms among women with regular menstrual cycles

continue

continuation

Main Author	Objectives	Results	Conclusion
Arabnezhad L	To evaluate the effects of curcumin on vitamin D levels in young women with PMS and dysmenorrhea	Curcumin significantly increased average serum vitamin D levels compared to placebo	Curcumin supplementation in women with PMS and dysmenorrhea led to significant improvement in vitamin D and liver function enzyme tests
Borji-Navan S	To evaluate whether cognitive-behavioral therapy can reduce the severity of symptoms in women with PMS and improve their quality of life during the premenstrual and late follicular phases of the menstrual cycle	After the intervention, the average total PMS symptom score was significantly lower in the intervention group than in the control group, and the premenstrual quality of life score was significantly higher	Cognitive-behavioral therapy could reduce the severity of symptoms for women suffering from PMS. Therefore, this intervention can be used for women with PMS
Ussher JM	To examine the effectiveness of couple-based cognitive behavioral therapy (CBT) for premenstrual disorders (PMD) compared to individual CBT and a waitlist control	In all groups, women reported greater awareness and understanding of post-intervention premenstrual change	Individual and couple CBT interventions can reduce women's premenstrual symptoms and suffering, as well as improving premenstrual coping
Santos DPC	To analyze which are the prevalent symptoms of the climacteric period, their intensity and relationship with the consumption of food sources of phytoestrogens in women in the Southwest of Paraná	The intensity of symptoms in the sample was predominantly moderate and the frequency of intake of phytoestrogen-rich foods was low	There was no significant association between phytoestrogen consumption and symptom intensity
Frigo M	To evaluate whether the consumption of a cereal bar combining different phytoestrogens could contribute to the reduction of climacteric symptoms in women	Significant improvement in symptoms in premenopausal and postmenopausal women who received phytoestrogen over time	Consumption of a cereal bar containing phytoestrogens was able to improve symptoms of climacteric syndrome
De Oliveira MT	To introduce the benefits promoted by linseed flour for the prevention and treatment of diabetes, hypertension and obesity, through a literature review	The antioxidant properties of linseed promote the reduction of cardiovascular risks and generate benefits in the treatment and prevention of chronic diseases	Linseed generates, through a balanced diet, improvement of physiological functions, benefiting the prevention and treatment of obesity, hypertension and diabetes
De Wit AE	To determine the level of evidence for the effectiveness of combined oral contraceptives in the management of premenstrual depressive symptoms and general premenstrual symptoms and the comparative effectiveness of combined oral contraceptives	Combined oral contraceptives were more effective than placebo in terms of treating general premenstrual symptoms, but not specifically premenstrual depressive symptoms	Combined oral contraceptives can improve overall premenstrual symptoms in women with PMS, but there is no evidence that one combined oral contraceptive is more effective than any other
Shehata NAA	To compare the effectiveness of the combined use of fluoxetine and combined oral contraceptives (COC) versus COC alone in the treatment of severe premenstrual syndrome (PMS)	The main outcome was the number of women with improvement in relation to PMS in the final treatment cycle	Combined use of fluoxetine and COC containing drospirenone is superior to COC in severe PMS
Takeda T	To analyze the effect of natural S-equol supplements on premenstrual symptoms	Diet with S-equol supplementation can be a safe treatment strategy for PMS	S-equol supplement (SE5-OH) has been reported to be effective in terms of treating menopausal symptoms
Kaltsouni E	To investigate the psychoneurobiological signatures of SPRM treatment in relation to reactive aggression in women with PMDD	SPRM treatment was associated with increased frontocingulate reactivity, offering an anovulation-associated mechanism that facilitates emotion regulation in PMDD	SPRM treatment, which reduced symptom severity, was associated with greater control of aggressive behavior
Bixo M	To check whether repeated subcutaneous UC1010 dosing in the luteal phase is superior to placebo in terms of reducing mood symptoms in women with PMDD	The use of UC1010 as a potential treatment for PMS was well tolerated and safe when compared with the current standard treatment	UC1010 reduces symptom severity and impairment more effectively than placebo
Comasco E	To investigate ongoing treatment with a selective progesterone receptor modulator, ulipristal acetate (UPA), as a potential treatment for PMDD	The average improvement in daily problem severity scores after 3 months was 41%. Symptom remission was achieved by 20 women in the UPA group and 8 women in the placebo group	UPA is a promising drug for the treatment of PMDD, particularly for the psychological symptoms associated with the syndrome and as an alternative pharmacological treatment

DISCUSSION

Acupuncture and acupressure

Chinese acupuncture and acupressure techniques have been used as a medical treatment for Premenstrual Syndrome for millennia. However, despite its history, due

to the low quality of evidence, its effectiveness in terms of reducing PMS symptoms remains uncertain. In addition, it is not possible to determine the safety of such techniques, which require further research seeking to reflect on the validation of these practices in the context of premenstrual syndrome¹⁰.

Auriculotherapy

Regarding the use of auriculotherapy for the rehabilitation of Premenstrual Syndrome, a study followed-up women who had moderate/intense symptoms of PMS, dividing them into 3 groups, so that 1 received the treatment, 1 received a placebo and 1 was used as a control group¹¹.

Accordingly, it was possible to observe a significant improvement in PMS changes (mood and physical) between the groups that underwent auriculotherapy or placebo treatment. In the group that received the auriculotherapy treatment, the improvement in the symptoms could be observed mainly after the 4th session. Thus, regarding the evolution of physical symptoms, the study shows that there was an improvement in musculoskeletal pain, especially with respect to headache, mastalgia and low back pain, during the menstrual cycle¹¹.

In addition, regarding anxiety, when comparing the effect of this therapy in relation to treatments considered conventional for PMS, such as vitamin B6 supplementation, it was possible to observe that, despite both having positive results, there was a greater reduction in the level of stress with the use of alternative therapy. It is worth underlining that, even in this study, due to the good results in the group that received the placebo treatment, it is possible to classify its introduction as an opportunity for rehabilitation of PMS¹¹.

Lecithin phosphatidic acid and phosphatidylserine complex (PAS)

An association between nutritional factors and PMS has been observed and, consequently, the search for a nutritional supplement that is effective in terms of alleviating PMS symptoms is of great interest¹².

The lecithin phosphatidic acid and phosphatidylserine complex (PAS) corresponds to the acidic forms of phosphatides, which are part of common phospholipids, acting as a precursor of other lipids and signaling cell membranes. Previous studies have shown that its long-term administration dampens cortisol responses to acute exercise and mental stress, improving memory, learning, mood and stress management¹².

Additionally, it has been linked to an improvement in psychiatric disorders, such as bipolar and major depressive disorders. The symptom-reducing effects of daily intake of lecithin phosphatidic acid and phosphatidylserine complex (PAS) over three menstrual cycles, as evaluated by various instruments for evaluating PMS, are beneficial and provide a safe alternative to the standard pharmacological treatment¹².

Physical exercise and diet

Concerning diet and physical exercise, studies

show beneficial effects in the significant reduction of PMS symptoms in women who maintain a diet during the premenstrual period with approximately 50% carbohydrates, 25% to 30% fat and 15% to 30% protein^{5,13}.

Added to this, there is evidence that regular physical exercise for 30 minutes a day, at least 3 times a week, decreases the prevalence of signs and symptoms of premenstrual syndrome and dysmenorrhea^{4,13}.

Traditional Iranian Medicine

Echium amoenum (EA) is one of the important medicinal herbs in the traditional Iranian medicine. The Romans, around 300 BC, already used EA as a drug, proving its effectiveness. In Iran, it was already documented in ancient Persian medicine books its sedative, anti-inflammatory, analgesic, antioxidant and neuroprotective effects, working to treat coughs, sore throats and pneumonia, as well as anxiety and depression¹⁴.

From a randomized, double-blind and controlled study carried out in Iran, a reduction in PMS severity was observed with the use of EA compared to the use of placebo, confirming its effectiveness and safety in terms of reducing PMS symptoms, whose severity was measured and classified using the Premenstrual Symptom Screening Tool (PSST). The generalized estimating equation (GEE) was used to compare the total PMS severity score between the two groups¹⁴.

Vitamin D supplementation

It is possible to say that vitamin D has, due to its performance in the regulation of interleukins, an anti-inflammatory immune function, in addition to behavioral effects related to anxiety, depression and mood modulations¹⁵.

Accordingly, in order to identify the effects of vitamin D supplementation on PMS, a study followed-up women for 4 months, dividing them into 2 groups, where one received supplementation and the other received placebo, so that an improvement in the clinical symptoms of PMS was perceived in the first cited group¹⁵.

A study carried out in the United States also analyzed 1,267 women aged between 18 and 44 years, proving that insufficient levels of 25-dihydroxyvitamin D (25 (OH) D) have a direct relationship with PMS symptoms, specifically related to breast tenderness and generalized pain¹⁶. In addition, another article also brought up the possibility that curcumin, a bioactive that stimulates vitamin D receptors, has a beneficial effect on PMS symptoms¹⁷.

Cognitive-behavioral therapy

Studies performed in Iran report improvement in premenstrual syndrome symptoms after weekly cognitive-behavioral therapy (CBT) sessions for 2 months. Two

randomized groups of women were analyzed, where one received online CBT sessions and the other was kept under observation, without interventions¹⁸.

The results showed a significant progress in the average of PMS symptoms, being lower when compared to women in the group without interventions. In addition, there was an increase in their quality of life during the menstrual period, from 5 days before menstruation to about 2 days after it¹⁸.

Another study carried out in Australia used cognitive-behavioral therapy sessions over a period of 5 months as a method, with women randomized into 3 groups. The first group participated in CBT done as a couple, the second received individualized sessions and the last one remained under observation¹⁹.

The results showed a significant decrease in PMS symptoms in both groups that underwent therapy, with lower levels of loss of interest and emotional symptoms such as depression and anxiety, which shows a positive impact on the psychological well-being of women¹⁹.

The group participating in the couple-based sessions showed more benefits when compared to the individualized therapy group, with an improvement in the relationship context. As for women who did not receive interventions, they continued with a high number of premenstrual syndrome symptoms, without significant changes. After 2 months of the intervention, a follow-up session was held that reported the continuing decline in total symptoms, as

well as in premenstrual distress and emotional reactivity¹⁹.

Phytoestrogens

There are two types of treatments involving estrogen: drug hormone therapy and natural therapy with phytoestrogens, molecules present in certain foods, such as soy, sesame and linseed. Such particles bind to an estrogen receptor, due to their chemical similarity, with antioxidant effects and enzymatic inhibition properties. Among the main phytoestrogens, one can mention isoflavones and lignans²⁰.

Its main use is directed towards climacteric women as an alternative to the use of estrogens for hormone replacement therapy. Nevertheless, there is no safety in terms of indicating the use of phytoestrogens in patients with any formal contraindication for hormone replacement therapy. More clinical, randomized and long-term trials are needed to answer these questions²¹.

Among the main phytoestrogens, linseed is a component that has been heavily studied for its health benefits, including the prevention of cardiovascular risks, obesity and diabetes. Furthermore, through the balance of hormonal oscillations, antioxidant properties and the release of immunological and anti-inflammatory factors, its important role in terms of mitigating symptoms related to premenstrual tension should be highlighted²².

Table 3 - Non-pharmacological methods

	Author/Year	Observation Method	Results
Acupuncture and Acupressure	Armour M, 2018	Meta-analysis	Reduction in PMS symptoms remains unclear
Auriculotherapy	Korelo RIG, 2022	Randomized and single-blind study	Significant improvement in PMS (mood and physical) changes between treatment and placebo groups
Lecithin phosphatidic acid and phosphatidylserine complex (PAS)	Schmidt K, 2018	Randomized and double-blind study	The current study clearly proves the effectiveness and safety of treating PMS with PAS, providing a safe alternative to the standard pharmacological treatment
Physical exercise and diet	Elvan Y, 2019	Randomly controlled trial	There was a significant difference in the visual analogue scale score between the groups after the intervention, with less severe dysmenorrhea than the control group
	Prazeres L, 2018	Cross-sectional study	When analyzing the behavior of PMS in relation to the practice of physical exercises, it was found that the signs and symptoms of: depressive mood, fatigue, difficulty concentrating, lack of interest in social and domestic activities were significantly more expressive in the sedentary group
Traditional Iranian Medicine	Farahmand M, 2020	Randomized, double-blind and controlled study	EA was more effective than placebo in terms of reducing PMS symptoms, the severity of which was measured and classified using a premenstrual symptom screening tool
Vitamin D Supplementation	Heidari H., 2019	Randomized study	Improvement of PMS symptoms in the group that received supplementation when compared to the use of placebo
	Alkhalaf Z, 2021	Cohort study	Insufficient levels of 25-dihydroxyvitamin D (25(OH) D) have a direct relationship to PMS symptoms related specifically to breast tenderness and generalized pain

continue

continuation

	Author/Year	Observation Method	Results
Cognitive-Behavioral Therapy	Sanam B, 2022	Randomized study	Decrease in the number of symptoms, such as depression, anxiety, concentration, lethargy, appetite, sleep, overload and physical symptoms, in addition to an improvement in quality of life during the premenstrual period
	Jane M. Ussher, 2017	Randomized controlled study	Significant decrease in PMS symptoms in both groups undergoing therapy. The group participating in the couple-based sessions showed better benefits when compared to the individualized therapy group, with an improvement in the relationship context
Phytoestrogens	Frigo M, 2022	Randomized clinical trial	Its main use is directed towards climacteric women as an alternative to the use of estrogens for hormone replacement therapy. There is no safety in terms of indicating the use of phytoestrogens in patients with any formal contraindication for hormone replacement therapy
	Santos DPC, 2022	Cross-sectional and observational study	
	De Oliveira MT, 2022	Literature review	Linseed has shown to improve symptoms related to PMS

Combined oral contraceptives

Combined oral contraceptives are made with synthetic estradiol and progestin, suppressing the the hypothalamic-pituitary-ovarian axis. Therefore, they are widely used by women who, in addition to seeking their contraceptive effect, try to reduce the symptoms of premenstrual syndrome²³.

According to a study carried out in the Netherlands, the use of combined oral contraceptives showed moderate effectiveness in terms of reducing the symptoms of premenstrual syndrome, when compared to the use of placebo. However, no improvement was identified in the depressive symptoms suffered by women with PMS²³.

In addition, no difference was seen in the use of different types of combined oral contraceptives, so that there was no emphasis on a specific drug formulation²³.

Selective serotonin reuptake inhibitors (SSRIs)

Serotonin levels fluctuate during the menstrual cycle under the influence of ovarian hormones. Accordingly, the use of selective serotonin reuptake inhibitors (SSRIs) can increase the amount of serotonin for neurotransmission and, consequently, improve PMS symptoms, with fluoxetine as the drug of choice²⁴.

A study carried out in Cairo divided women aged between 20 and 40 years into 3 groups. Group one received fluoxetine along with combined oral contraceptives (COC), group two received COC alone, while group three received placebo. The results showed that the addition of fluoxetine to combined oral contraceptives (COC) significantly reduced the average scores of the Daily Record of Severity of Problems (DRSP), a questionnaire developed to help

diagnose and evaluate PMS, so that the first group obtained improvements more significant in relation to the severity of the symptoms. Moreover, it was possible to observe that the improvement with the use of COC was superior to placebo in the reduction of DRSP scores²⁴.

Selective estrogen receptor modulator (SERMs)

Selective estrogen receptor modulators (SERMs) are molecules that bind to the estrogen receptor with agonist and antagonist actions in specific tissues. Agonistic effects on bone tissue are relevant in the treatment of osteoporosis after menopause. In turn, central or breast tissue antagonistic effects make these molecules useful in the treatment of infertility and breast cancer²⁵.

S-equol is a metabolite of a soy isoflavone converted from daidzein by specific intestinal bacteria, functioning as an SERM. Currently, its ability to prevent estrogen-related diseases such as menopausal symptoms, breast cancer, osteoporosis and cardiovascular diseases is known. Recent studies have proven that the decrease in S-equol production works as a risk factor for the development of PMS²⁵.

Accordingly, its supplementation can be a safe treatment strategy for PMS, as well as being effective in terms of treating menopausal symptoms without adverse effects²⁵.

Selective progesterone receptor modulator (SPRMs)

Selective progesterone receptor modulators (SPRMs) are synthetic substances derived from steroids that can occupy progesterone receptors and act as an antagonist, agonist-antagonist or agonist of this hormone, depending on the target tissue²⁶.

There is a relationship between PMS symptoms

and progesterone fluctuations during the luteal phase, along with evidence from ovarian suppression studies. Indeed, inhibition of ovulation leads to remission of symptoms, whereas the addition of ovarian hormone restores them²⁶.

Progesterone derivatives, such as pregnenolone and allopregnanolone, work on emotion processing brain regions as allosteric modulators of the GABA receptor, which is at increased levels in patients with PMS. Recent studies have shown that treatment with selective progesterone receptor modulators led to a 41% reduction in symptoms, including greater control of aggressive behavior. The results further highlight the prospects for MSRP-based treatment to target brain circuits of clinical and behavioral relevance²⁶.

As mentioned, allopregnanolone is a progesterone metabolite and a positive GABA modulator, and is closely associated with symptoms that occur in premenstrual syndrome, especially those related to women's mood. Its inhibition through a GABA receptor-modulating steroid antagonist called isoallopregnanolone or sepranolone (UC1010) is questioned as to its effectiveness in terms of

mitigating these symptoms²⁷.

Accordingly, seeking to analyze the possibility of reducing PMS symptoms, a study was carried out in Sweden that randomized women into 2 groups, one receiving placebo and the other receiving sepranolone subcutaneously in 5 doses during the menstrual cycle. The results showed a significant reduction in symptoms in women who used isoallopregnanolone compared to those who received placebo²⁷.

Therefore, the study indicates the possibility of using UC1010 as an alternative treatment to those currently used for PMS, with combined oral contraceptives, for example. This is mainly due to its easy tolerability when compared to those used, as well as its safety and fewer side effects²⁷.

Ulipristal acetate (UPA) is also a SPRM that works as a progesterone antagonist in some organs, particularly the brain. Continuous low-dose treatment leads to anovulation in approximately 80% of women and, together with progesterone receptor antagonism, explains the alleviation of symptoms in women with PMS²⁸.

Table 4 - Pharmacological methods

	Author/Year	Method	Results
Combined oral contraceptives	Wit A, 2021	Meta-analysis	Moderate effectiveness in terms of reducing the symptoms of premenstrual syndrome, when compared to the use of placebo. However, when comparing the use of different types of combined oral contraceptives, no difference was seen in the results
	Shehata N, 2020	Randomized and double-blind study	There was an increase in the number of women with PMS improvement, as well as its severity, when the use of fluoxetine was associated with combined oral contraceptives
	Takeda T., 2018	Randomized and double-blind study	Supplementation can be considered a safe treatment strategy for PMS and is also effective in terms of treating menopausal symptoms without adverse effects
Selective serotonin reuptake inhibitors (SSRIs)	Kaltsouni E., 2021	Multicenter, double-blind and randomized study	There was a 41% reduction in symptoms, including greater control of aggressive behavior. In addition, the results show its clinical and behavioral relevance by acting on brain circuits
	Bixo M, 2021	Exploratory randomized, double-blind and placebo-controlled study	The study shows promising results of UC1010 as a potential treatment for PMS, being well tolerated and safe when compared to treatments currently used with combined oral contraceptives
	Comasco, E, 2021	Proof-of-concept randomized controlled trial	Continuous treatment with low-dose ulipristal acetate (UPA) leads to anovulation in approximately 80% of women and, together with progesterone receptor antagonism, explains the alleviation of symptoms in women with PMS

CONCLUSION

The evidence showed a vast list of possibilities for carrying out care focused on alleviating PMS. Accordingly, non-pharmacological technologies were observed as an important enhancer in the quality of health care for women with PMS due to their acceptability and, mainly, in view

of the reduction of possible side effects.

The knowledge and dissemination of these methods of care and interventions for PMS can favor the improvement of the quality and satisfaction of life of women who are in the reproductive phase. Nonetheless, it is suggested that further studies be carried out to strengthen the already extensive knowledge on the theme.

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