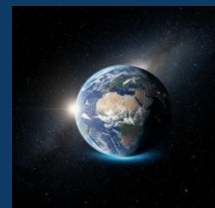




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Premenstrual Syndrome and Premenstrual Dysphoric Disorder: A Narrative Review of Recent Evidence on Physical Activity as an Adjunctive Management Strategy

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Abstract

Background Premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) affect substantial proportions of women of reproductive age, imposing significant burdens on quality of life, work productivity, and psychological wellbeing. Evidence suggests that physical activity may improve symptoms of these conditions.

Aim. To synthesise current evidence on physical activity and structured exercise as adjunctive interventions in the management of premenstrual disorders, examining mechanistic pathways, exercise modalities, and clinical implications.

Material and methods. A narrative review was conducted, focusing in particular on premenstrual syndrome and premenstrual dysphoric disorder, as well as the impact of physical activity on alleviating their symptoms. Randomized controlled trials, systematic reviews, and meta-analyses were prioritized and appraised qualitatively.

Results. Systematic reviews and meta-analyses demonstrate that physical activity, particularly aerobic exercise at moderate intensity, reduces both physical and psychological premenstrual symptoms. Identified mechanisms include modulation of ovarian hormone profiles, enhancement of endogenous opioid systems, regulation of neuroendocrine stress responses, fluid-electrolyte balance, and prostaglandin metabolism. Alternative modalities including Pilates and kinesio taping demonstrate comparable efficacy. Strength training performance fluctuates across menstrual cycle phases, with optimal performance during the late follicular phase.

Conclusions. Regular, preference-sensitive exercise provides a practical and sustainable method for managing PMS symptoms; however, it should not replace prospective diagnosis or appropriate treatment. Further research employing prospective symptom monitoring, standardized outcome measures, and mechanistic biomarkers is essential to refine personalized recommendations and identify optimal exercise prescriptions for individual women.

Keywords: premenstrual syndrome, premenstrual dysphoric disorder, physical activity, aerobic exercise, narrative review

1. Introduction

Cyclical hormonal fluctuations profoundly influence women's physical, emotional, and cognitive functioning [1]. The luteal phase is characterized by a constellation of symptoms termed premenstrual syndrome or, in severe presentations, premenstrual dysphoric disorder [2]. Physical activity emerges as a particularly valuable intervention, offering simultaneous benefits across multiple symptom domains including mood regulation, sleep quality, pain processing, stress reduction, and cardiovascular fitness [3]. Current evidence synthesis reveals substantial heterogeneity in trial populations, intervention modalities, and outcome measurement strategies, necessitating careful interpretation.

Research Objective. The objective of this review was focused on defining, etiology premenstrual disorders, distinguishing between premenstrual symptoms (PS), premenstrual syndrome (PMS), and premenstrual dysphoric disorder (PMDD). Furthermore, the study examines the mechanism by which physical activity alleviates premenstrual symptoms.

Research Problems. This narrative review addresses three critical questions:

1. What is the quality and magnitude of evidence that physical activity improves PMS or PMDD symptoms?
2. Which specific exercise modalities and doses have demonstrated efficacy?
3. How should these findings translate into clinically responsible recommendations for women and healthcare providers?

Research Hypotheses. The main hypothesis of this review is that exercise at moderate intensity reduces both physical and psychological symptoms of premenstrual syndrome and premenstrual dysphoric disorder. Various forms of physical activity offer similar benefits in reducing these symptoms. Furthermore, fluctuations in hormone levels across the menstrual cycle affect performance during exercise.

2. Materials and methods

This narrative review integrates clinical-trial evidence with mechanistic literature and generates hypotheses for future controlled research. A narrative approach was chosen deliberately because primary trial literature is heterogeneous in population definition, intervention specifications, and outcome measurement strategies. The review's purpose is interpretive synthesis across clinical and preclinical domains rather than computation of a single pooled effect estimate.

PubMed/MEDLINE was searched from 2020 to 2026. Search strings combined condition terms ("premenstrual dysphoric disorder", "PMDD", "premenstrual syndrome", "PMS", "premenstrual tension") with intervention terms ("exercise", "physical activity", "aerobic", "resistance training"). Reference lists of key reviews were hand-searched to identify additional sources.

3. Result

3.1. Menstrual Cycle Physiology

The menstrual cycle represents a fundamental physiological rhythm in women's reproductive health, regulated through complex endocrine interactions between the hypothalamus, anterior pituitary gland, and ovaries [4-6]. This system operates through two distinct phases, each characterised by specific hormonal dynamics and physiological adaptations.

The follicular phase begins on the first day of menstruation and extends approximately 14 days until ovulation [7]. During this phase, the hypothalamus releases gonadotropin-releasing hormone (GnRH), stimulating pituitary secretion of follicle-stimulating hormone (FSH). FSH promotes ovarian follicle growth and maturation, leading to progressive increases in estradiol production [8]. Estradiol reaches peak concentrations in the late follicular phase, triggering a surge in luteinising hormone (LH) that initiates ovulation [7].

The luteal phase follows ovulation and persists until menstrual onset, lasting 10 to 14 days [7]. Following ovulation, the remnant follicle transforms into the corpus luteum, producing substantial quantities of progesterone with secondary estrogen production. Should pregnancy not occur, corpus luteum regression precipitates declining progesterone and estrogen concentrations, culminating in menstrual bleeding [6,7].

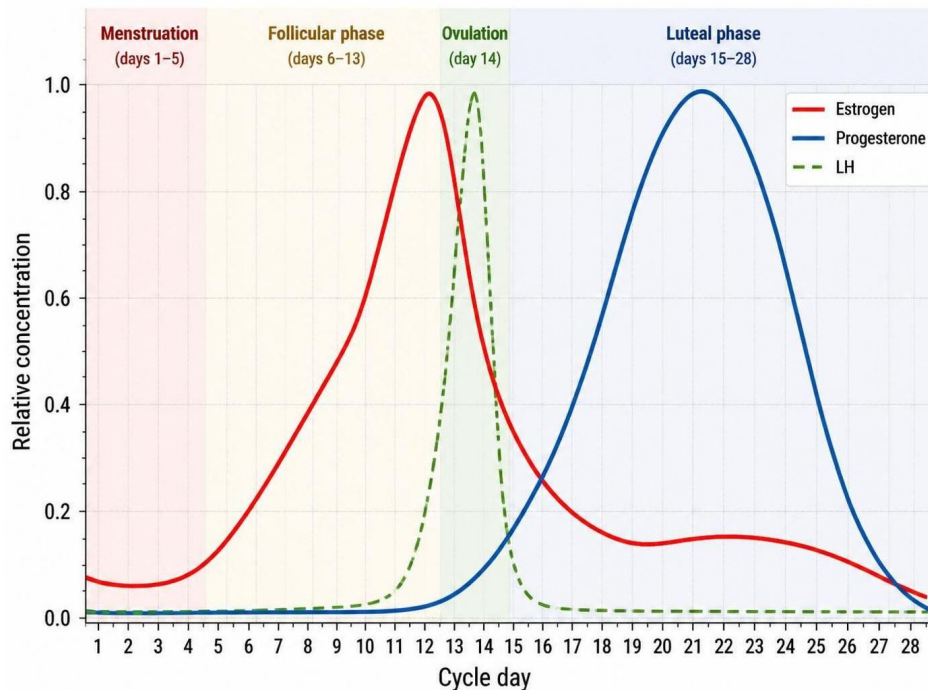


Figure 1. Typical hormone concentration changes across the menstrual cycle

3.2. Premenstrual Symptoms, Premenstrual Syndrome and Premenstrual Dysphoric Disorder

3.2.1. Definitions

The luteal phase, which begins after ovulation and continues until the onset of menstruation, is the period during which premenstrual disorders manifest. These disorders present as psychiatric or physical symptoms that impair the individual's normal daily functioning and generally resolve shortly after menstruation begins. A distinction must be established between premenstrual symptoms (PS), premenstrual syndrome (PMS), and premenstrual dysphoric disorder (PMDD) [9].

Premenstrual symptoms typically encompass a spectrum of physical, emotional, and behavioral manifestations. Psychological symptoms include depressed mood, aggressive outbursts, irritable behavior, lacrimation, anxious feelings, disorientation, social isolation, difficulties with concentration, sleep disturbances, and modifications in appetite and thirst perception [9]. Common somatic manifestations involve breast sensitivity, abdominal bloating, body mass increase, cephalgia, peripheral edema, and musculoskeletal discomfort [10]. Between 50 and 80 percent of premenopausal women are estimated to experience at

least one physical or emotional symptom during the fortnight preceding menstrual onset [11,12].

Premenstrual syndrome is characterized by recurrent physical, emotional and behavioral symptoms that manifest during the luteal phase of the menstrual cycle and resolve upon menstrual onset, affecting a considerable proportion of females of reproductive age [13]. Premenstrual dysphoric disorder represents an extreme variant of premenstrual syndrome and constitutes a severe mood disorder predominantly manifested through psychological symptoms [14]. PMDD is characterized by cognitive-affective and physical symptoms that occur during the luteal phase and remit with the onset of menstruation [13]. According to classification systems, PMDD is designated as a gynecological diagnosis in the ICD-11 classification and as a psychiatric diagnosis in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [15]. The diagnosis of PMS and PMDD requires the exclusion of alternative conditions that might better account for the reported discomforts [16,17].

3.2.2. Epidemiology and Etiology

The global prevalence of PMS varies widely, with estimates ranging from 5.0% to 47.8%, depending on the diagnostic criteria and population studied [17], while the most severe form of PMS - PMDD affects 3-8% of women of reproductive age [17,18].

Multiple factors contribute to PMS etiology, which remains incompletely understood. During the menstrual cycle, fluctuations in estrogen and progesterone levels are believed to play a pivotal role in the pathophysiology of PMS. Serotonin and gamma-aminobutyric acid neurotransmitter systems may be influenced by these hormonal changes, resulting in the manifestation of PMS symptoms [13]. The underlying mechanisms for differential sensitivity to hormonal fluctuations among women remain incompletely understood [19].

Premenstrual dysphoric disorder etiology involves complex, multifactorial interactions between hormonal fluctuations and neurotransmitter systems [20,21]. Although precise mechanisms remain under investigation, neurosteroids, particularly those modulating the gamma-aminobutyric acid system, are hypothesized to play a pivotal role in PMDD pathophysiology [22-24]. A recent study established a link between progesterone and exacerbation of PMDD symptoms during the late-luteal phase, with affected females demonstrating relatively elevated cortisol levels during this phase [25].

Genetic factors contribute to premenstrual disorder etiology. Recent research has provided evidence supporting the participation of the gene responsible for coding the serotonergic 5HT1A receptor and allelic variations in the estrogen receptor alpha gene (ESR1) at the onset of PMS/PMDD [26,27]. Further investigation is necessary to elucidate the complex interplay of hormonal, genetic, and additional factors contributing to premenstrual disorder etiology.

3.3. Physical Activity and Premenstrual Symptoms: Evidence from Clinical Trials and Meta-Analysis

3.3.1. Mechanisms of Action

Different physiological systems, including the cardiovascular, central nervous, endocrine, and female reproductive systems, are implicated in PMS symptoms across emotional, physical, cognitive, and behavioral domains. Physical exercise is recognized for its ability to elevate endorphin levels, regulate the synthesis of progesterone and estrogen, and stimulate the production of naturally occurring anti-inflammatory substances [28]. Additionally, exercise offers enhanced overall fitness, opportunities for social interaction, and the potential to alleviate depressive feelings [29].

Physical activity influences premenstrual symptoms through multiple interconnected physiological pathways:

- **Endocrine Modulation:** Physical exercise regulates progesterone and estrogen synthesis and metabolism. The possible mechanism could be due to the potential of aerobic exercise to increase sex hormone-binding globulin, a plasma protein that binds circulating free estrogen, thereby reducing bioavailable estrogen [30].
- **Fluid-Electrolyte Balance:** Physical symptoms such as bloating, oedema, weight gain, and headache relate to dysregulation of the renin-angiotensin-aldosterone system, elevated serum aldosterone, increased prostaglandin E2 and prolactin concentrations, and deficiency of vitamin B6 and magnesium [31]. The late luteal phase demonstrates elevated renin-angiotensinogenic activity and depressed estrogen/progesterone ratios, increasing serum aldosterone and promoting sodium and water reabsorption [32]. Aerobic exercise lowers renin levels, increases estrogen and progesterone, and reduces serum aldosterone, thereby improving fluid retention and associated physical symptoms [33].

- **Prostaglandin Metabolism:** Repeated muscular contractions during physical activity enhance venous return and lymphatic circulation, promoting prostaglandin drainage from the pelvis and preventing pathological accumulation. This mechanism reduces abdominal discomfort, back pain, and dysmenorrhoea [34].
- **Opioidergic System:** Beta-endorphin concentrations diminish during the premenstrual phase, contributing to pain symptoms, mood disturbance, and food craving. Aerobic exercise at moderate intensity increases circulating beta-endorphins, enhancing pain tolerance and contributing to analgesic effects [35].
- **Neuroendocrine Stress Response:** Physical and psychological stress during PMS associates with altered cortisol awakening response. Aerobic exercise modulates the hypothalamic-pituitary-adrenal axis, facilitating healthy stress response cycling and reducing symptoms including anger, mood lability, anxiety, sadness, depression, and fatigue [36].

Table 1: Biochemical and hematological changes associated with aerobic exercise

Biochemical Parameter	Direction of Change	Clinical Consequence		PMS-Related Symptom Improvement	
Hemoglobin concentration	Increase	Enhanced oxygen-carrying capacity		Reduced fatigue, improved energy	
Hematocrit	Increase	Increased blood viscosity and oxygenation		Improved clarity, reduced dizziness	mental reduced
Erythrocyte count	Increase	Enhanced capacity	aerobic	Increased tolerance	exercise
Platelet count	Increase	Improved hemostasis		Potentially reduced abnormal bleeding	
Prolactin	Decrease	Reduced stimulation	lactotroph	Decreased tenderness, improvement	breast mood
Estradiol (E ₂)	Decrease	Reduced estrogenic stimulation	systemic	Decreased retention, mood	water improved
Progesterone	Decrease	Modulated elevation	luteal-phase	Improved stability	emotional

Serum aldosterone	Decrease	Reduced sodium-water reabsorption	Decreased bloating, edema, weight gain
Renin activity	Decrease	Downregulated renin-angiotensin-aldosterone system	Reduced fluid retention, peripheral edema

3.3.2. Evidence from Systematic Reviews and Randomized Controlled Trials

Ravichandran and Janakiraman showed in a systematic review of five randomised trials (n=492) that 30 minutes of moderate-intensity aerobic exercise performed 3–5 times weekly effectively reduced physical premenstrual symptoms. Walking, swimming, and running represented the most commonly performed modalities. Statistical analyses indicated greater exercise efficacy for physiological compared with psychological symptoms. Aerobic exercise effectiveness for specific symptoms included headache, nausea, bowel disturbances, abdominal bloating, appetite changes, and menstrual cramps [30].

The most influential quantitative synthesis to date is the systematic review and meta-analysis by Pearce and colleagues, which searched eight databases and two trial registries and identified 15 randomised controlled trials (n = 717) comparing exercise interventions of at least eight weeks with non-exercise comparators in women with premenstrual symptoms. Seven trials (n=265) contributed to the primary outcome, showing that exercise reduced global premenstrual symptom scores versus controls (large SMD = -1.08; 95% CI -1.88 to -0.29). Effects were also large and consistent across symptom domains: psychological (SMD = -1.67), physical (SMD = -1.62) and behavioural (SMD = -1.94). The authors noted substantial heterogeneity and a high risk of bias in most included trials (~87%) [37].

In a randomised clinical trial conducted by Mohebbi Dehnavi et al. enrolled 65 university students with PMS diagnosis. Participants randomised to 8 weeks of aerobic exercise (3 sessions weekly, 20-30 minutes per session) demonstrated significant reductions in headache (p = 0.001), bloating, vomiting, appetite changes, and other physical symptoms compared with usual activity controls [31].

In the study of El-Lithy et al. showed an aerobic exercise increased haemoglobin, haematocrit, red cell count, and platelet count while decreasing prolactin, oestradiol, and progesterone concentrations, resulting in improvement of fatigue, impaired concentration, confusion, and multiple premenstrual symptoms [38].

Elbandrawy et al. found that tele-Pilates and kinesio taping had comparable efficacy in adolescents with PMS, both reducing overall PMS symptoms, other PMS-related complaints, and menstrual cramps and back pain. Pilates may help by improving venous return via rhythmic muscle contractions and promoting fluid drainage, reducing bloating and tenderness; it also strengthens abdominal muscles and supports prostaglandin elimination, which can lessen abdominal/pelvic discomfort and backache [39].

Table 2: Characteristics of principal randomized controlled trials and systematic reviews

Author(s), Year	Study Design	Sample Characteristics	Intervention Type	Duration	Effect Size or Main Findings
Ravichandran & Janakiraman (2022) [30]	Systematic review of RCTs	Multiple studies, healthy women	Aerobic exercise	Varied (≥ 8 weeks)	Effective for physical PMS symptoms; 30 min, 3–5 times/week optimal
Pearce et al. (2020) [37]	Meta-analysis of RCTs	Multiple trials	Exercise (mixed modalities)	≥ 8 weeks	SMD -1.08 to -1.94 ; large effect sizes
El-Lithy et al. (2015) [38]	RCT	Young women with PMS	Aerobic exercise	12 weeks	Decreased prolactin, estradiol, progesterone; improved fatigue, concentration
Maged et al. (2018) [40]	RCT	Women with PMS	Swimming	8 weeks	Significant PMS symptom reduction
Mohebbi Dehnavi et al. (2018) [31]	Clinical trial	Healthy women	Aerobic exercise	8 weeks	Reduced severity of physical premenstrual symptoms
Koçak & Şevgin (2025) [41]	RCT	Women of reproductive age	Mixed exercise modalities	Regular participation	Significant menstrual symptom reduction
Elbandrawy et al. (2025) [39]	Comparative trial	Adolescents with PMS	Tele-Pilates vs. kinesio taping	Multiple sessions	Comparable efficacy; both reduced cramps and back pain

Kroll-Desrosiers et al. (2017) [42]	Cross-sectional study	Young adult women	Recreational physical activity	Regular	Inverse association with PMS severity
Ayyub et al. (2024) [3]	Systematic review	Multiple studies	Physical activity (varied)	Varied	Systematic evidence for PMS symptom reduction

Since various forms of physical activity appear to produce comparable symptomatic benefits, encouraging individuals to select modalities aligned with their preferences, lifestyle, and tolerability represents a rational clinical approach. However, the determinant of sustained clinical improvement is not the specific exercise modality chosen, but rather consistent, long-term engagement in regularized physical activity programs.

3.4. Strength Training and Menstrual Cycle Considerations

Fluctuations in estrogen and progesterone across the menstrual cycle are proposed to influence exercise performance. Estrogen may promote muscle glycogen storage and fat utilization, whereas progesterone may exert anti-estrogenic effects. Therefore, hormonal fluctuations may lead to differences in performance. Research has indicated that strength training in the late follicular phase is associated with larger gains in muscle strength [43,44].

This phase is characterized by anabolic dominance of estrogen, potentially rising from mid-follicular phase, whereas progesterone predominates in the luteal phase and is linked to catabolic effects [45]. Together with testosterone increases around ovulation, these findings suggest higher strength performance during the first half of the menstrual cycle than in the latter half [4,46]. The breaking point coincides with the shift from the follicular to the luteal phase, when estrogen, FSH, and LH levels decline rapidly following ovulation. This hormonal change may account for the participants' perceived drop in strength and energy [4].

A study was carried out to investigate how women perceive the results of strength training performance depending on the phase of their menstrual cycle. Women reported that the late follicular phase was the period in which they experienced the highest energy and motivation for strength training. Participants reported their greatest strength and power during this phase. They also perceived better strength and performance prior to ovulation, with a subsequent decline afterward, characterized by reduced energy and weakness [4].

Nevertheless, participants also described a rise in energy a few days into menstruation during the early follicular phase. They reported feeling renewed in terms of strength, performance, and energy, alongside renewed motivation to engage in strength training. This renewed drive may be related to the gradual increase in estrogen, FSH, and LH across the follicular phase [46-48]. Perceived strength training performance differed across the late luteal phase. Most participants reported lower motivation and reduced willingness to train. Fluctuations in ovarian hormones, especially estrogen and progesterone, may influence neurotransmitter regulation and intensify PMS-related symptoms, including fatigue and diminished strength. As the predominant luteal-phase hormone, progesterone is often considered catabolic and may suppress force production, which could account for the weakness described by several participants [43,46,49].

Table 3: Phases of the menstrual cycle and training performance

Menstrual Phase	Cycle	Dominant Hormones	Hormonal Characteristics	Exercise Performance Observations
Menstrual Phase (Days 1–5)		Estrogen Progesterone ↓	↓ Nadir hormone levels; acute inflammatory response	Variable performance; reduced energy; increased pain perception
Early Phase (Days 1–7)	Follicular	FSH ↑ Estrogen (gradually)	↑ Rising estrogen; minimal progesterone	Improving performance; increasing energy
Late Phase (Days 8–14)	Follicular	Estrogen (peak) LH surge	↑↑ Peak anabolic environment; elevated testosterone (around ovulation)	Maximum performance; strength optimal; greatest feeling of power and capability
Early Luteal Phase (Days 15–21)		Progesterone Estrogen (secondary peak)	↑ Dual hormone elevation; metabolism increases	Initially maintained performance; gradual decline in motivation
Late Luteal Phase (Days 22–28)		Progesterone (peak) Cortisol ↑	↑↑ Catabolic milieu; adrenal premenstrual manifestation	Reduced performance; weakness; motivation; symptom intensification

Strength training performance seems to vary across menstrual cycle phases, although the pattern is not identical for every individual. These findings highlight the value of recognizing

one's own cycle characteristics to tailor training effectively, and they suggest that a training log documenting MC phase may be useful. Overall, the results support a comprehensive approach that addresses both physiological and psychological demands across the MC, including the role of social support. For coaches and physical therapists, understanding how the MC can differentially affect women's experiences may help guide strategies for supporting and motivating athletes to perform even when energy levels fluctuate [4].

4. Discussion

4.1. Clinical interpretation and practical application

Physical activity can appropriately be integrated into a broader, multi-faceted treatment approach, especially for patients who enjoy it or have a sedentary lifestyle. The discussion should start by monitoring expected symptoms over time and identifying what the patient hopes to achieve: reducing overall symptom burden, improving mood, alleviating pain, boosting energy, enhancing sleep quality, or preserving the ability to perform everyday tasks. Allowing patients to choose between activities they find manageable – such as walking, swimming, cycling, Pilates, or similar options – is more justified than asserting that any single form of exercise works best for everyone.

While there is no established exercise prescription specifically validated for premenstrual syndrome, published studies frequently involve moderate-intensity cardiovascular exercise lasting 20 to 60 minutes, done at least three times weekly, over a period of 8 to 12 weeks [30,50]. These parameters can serve as a starting point for cautious experimentation, with incremental increases and reassessment following at least two menstrual cycles – though this should not be treated as a fixed, evidence-based standard. The WHO recommends 150-300 minutes of moderate aerobic activity weekly (or 75-150 minutes of vigorous activity), combined with resistance training on two or more days, but this is general guidance for adult health rather than a specific PMS treatment target [51].

Exercise recommendations must take into account individual circumstances: current fitness level, potential pregnancy, iron deficiency, disordered eating, heart or bone problems, and other medical concerns. Patients can reduce activity intensity on days with severe symptoms.

Lifestyle interventions should not replace treatments with stronger scientific backing when symptoms are severe or disabling. If depression or anxiety persists beyond the menstrual cycle phase, this may indicate a separate mental-health condition. Severe disruption to

functioning, unclear diagnosis, poor response to initial approaches, or suspected PMDD requires evaluation by a gynecologist and/or mental-health professional. Suicidal ideation, intent or planning requires immediate risk assessment and an appropriate emergency pathway [52,53].

4.2. Recommendations for future research directions

Upcoming clinical trials must collect daily symptom data throughout at least two pre-treatment cycles and must clearly differentiate between premenstrual syndrome, premenstrual dysphoric disorder, and perimenstrual exacerbation of underlying conditions. Rigorous methodological standards are essential, including: properly powered sample sizes based on statistical calculations, random assignment kept hidden from researchers, blinded evaluation of outcomes wherever possible, comparison against active interventions rather than placebo alone, transparent reporting of adherence and adverse events are needed.

A core outcome set should include global symptoms, emotional and mood-related symptoms, pain severity, energy levels, fatigue, ability to function in daily life, quality of life and clinically meaningful response, measured at standardised cycle phases.

Studies need to directly compare different types and amounts of physical activity, examine strength training as a standalone treatment, and assess the relative effectiveness of in-person supervision versus unsupervised home practice versus digital or remote coaching. Research must track outcomes well after the intervention period ends to determine whether benefits persist. Subgroup analyses should explore how results vary based on participants' baseline activity levels, specific symptom patterns, psychiatric comorbidity, use of hormonal contraceptives, and age or life stage.

Future investigations of how exercise works should test proposed biological pathways through prospective measurement rather than simply comparing biological markers before and after treatment without establishing a causal link.

5. Conclusions

The management of premenstrual syndrome necessitates a comprehensive, multimodal intervention strategy. Existing literature demonstrates the therapeutic potential of structured physical activity in mitigating the symptomatology associated with premenstrual disorders. The documented mechanisms supporting these benefits include enhanced endorphin

production and activation of endogenous anti-inflammatory pathways, both of which contribute to symptom amelioration. Furthermore, systematic engagement in regular physical activity has been associated with improved hormonal homeostasis, optimized reproductive physiology, enhanced menstrual regularity, and augmented ovulatory function across diverse female populations.

Contemporary evidence indicates that programmed exercise interventions during the luteal phase correlate with measurable improvements in hematological parameters and significant reductions in circulating concentrations of prolactin, estradiol, and progesterone. Beyond somatic improvements, empirical investigations consistently document that physical training contributes to enhanced psychological well-being, increased self-regard, reduced depressive symptomatology, and decreased anxiety manifestations in women with premenstrual complaints.

Although exercise interventions show promise in ameliorating specific premenstrual symptom clusters and overall health outcomes, the heterogeneity of individual responses necessitates continued investigation to elucidate differential treatment responses and establish evidence-based, personalized exercise prescriptions tailored to different individuals.

Clinical advice should therefore be individualised, gradual and linked to prospectively tracked goals. Exercise should complement, not replace, diagnostic assessment and established treatment for clinically significant PMS or PMDD. High-quality trials using prospective case confirmation, standardised outcomes and longer follow-up are required before precise exercise prescriptions can be recommended.

Disclosure

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Declaration of the use of generative AI and AI-assisted technologies in the writing process

In preparing this work, the authors used ChatGPT (OpenAI) for linguistic refinement, grammar correction, and structural editing of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the scientific content, interpretation of the data, and final version of the manuscript

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