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Psychiatric illness across the menstrual cycle

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Psychiatric illness across the menstrual cycle

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Editorial: Psychiatric illness across the menstrual cycle

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Editorial on the Research Topic
Psychiatric illness across the menstrual cycle

Premenstrual psychiatric symptoms are common and occur in several disorders including premenstrual dysphoric disorder (PMDD), premenstrual syndrome (PMS), and premenstrual exacerbation (PME) of psychiatric illness. In PMDD and PMS, symptoms are restricted to the luteal phase of the menstrual cycle; in PME, symptoms of an underlying affective disorder are exacerbated in the luteal phase. PMDD is a severe mood disorder characterized by affective symptoms with onset 1-2 weeks before menses and offset once menstruation begins, or shortly thereafter (1). In contrast, PMS is a broader term encompassing fewer and less impairing symptoms (2), and can be diagnosed based on physical symptoms *or* affective symptoms. Common affective symptoms in PMDD and PMS include irritability, low mood, anxiety, sensitivity to stressors, and mood lability. PME is the cyclic premenstrual worsening of a psychiatric disorder, such as major depressive disorder, in which existing symptoms become more severe in the week before menses, then return to an elevated baseline following menses onset or resolution (3). In PME, unlike PMDD and PMS, symptoms do not resolve in the follicular phase of the menstrual cycle.

Despite the associated prevalence and impairment, premenstrual disorders remain understudied relative to other psychiatric disorders, and even relative to other reproductive affective disorders such as postpartum depression (4). This Research Topic aims to increase awareness of menstrual cycle-related psychiatric conditions, to promote research in this understudied field, and to improve clinical recognition. Articles in this Research Topic focus on: 1) understanding clinical features and treatment of premenstrual disorders, 2) understanding the prevalence of PME across psychiatric disorders, 3) identifying risk factors for premenstrual disorders, and 4) predicting individual symptom onset in the menstrual cycle, which may enable rapid intervention.

Several articles in this Research Topic focus on clinical features and treatment of premenstrual disorders. An article by Brown D. et al. reviews the qualitative psychological experience of PMDs (PMS and PMDD). The authors highlight the distress and impairment women experience from PMDs and the limited information they receive to manage their symptoms, often requiring them to advocate for themselves in the healthcare setting and devise their own coping strategies, including both adaptive and maladaptive approaches. Premenstrual symptoms affected them across multiple domains of their lives, including

relationships and career. Importantly, a research paper in this Research Topic, also by Brown D. et al., finds that among women with PMDD surveyed, nearly half had deliberately harmed themselves during a PMDD crisis, 82% reported premenstrual suicidal ideation, and 26% had attempted suicide. SI was influenced by personal relationships affected by PMDD, diagnosis delays, and self-worth damaged by PMDD. This high rate of self-harm and suicidality emphasizes the seriousness of this disorder. Within reproductive mental health, gender-diverse individuals are particularly understudied and underserved. An article by Arshed et al. focuses on transgender and gender-diverse (TGD) menstruators. This population's experience of menstruation and associated mood symptoms is unique and deserves special consideration by clinicians and researchers. The authors provide suggestions for the psychiatric management of menstruation in TGD and promote gender-affirming menstrual care for transmenstruators. In addition, Islas-Preciado et al. review cultural attitudes and taboos toward premenstrual symptoms, and emphasize the need for an intersectional approach that acknowledges interacting social identities such as race, gender, and sexuality that may influence women's experiences of premenstrual mood symptoms. Modzelewski et al. explore treatment of premenstrual mood symptoms in general, including SSRIs, hormonal agents, and therapy.

PME affects a large number of women living with psychiatric illness. Lin et al. review PME of mood, anxiety, psychotic, obsessive-compulsive, personality, and trauma-related disorders. The authors review data on PME prevalence and describe treatment options. They note that there is little guidance on assessment of PME, resulting in a paucity of research and clinical recommendations. Guidelines and clinical tools for assessment of PME are needed, and awareness of PME in clinical practice is imperative for diagnosis and alleviation of associated distress and functional impairment. For those who require medication, treatment for PME differs from that for PMDD – so it is vital for clinicians to understand the distinction.

Risk factors for premenstrual disorders are a growing area of study. Adverse childhood experiences are known to increase risk for PMDD and PMS (5), but less is known about PME. A study by Standeven et al. finds that individuals with PME have a higher quantity and severity of childhood traumatic events compared to healthy controls, with a positive correlation between childhood trauma and premenstrual symptom burden.

While premenstrual disorders remain underrecognized and understudied, advances in research on premenstrual psychiatric symptoms are on the horizon. Brown R. et al. describe how wearable technologies may improve measures of physiologic features such as heart rate variability, sleep, and physical activity, to advance research in this area. They suggest that, in the future, remote digital monitoring paradigms may enable patients and physicians to monitor and respond to premenstrual symptoms in real-time. This would allow women to recognize and target premenstrual symptoms before they interfere in functioning, lead to harmful suicidal and non-suicidal behaviors, or harm interpersonal relationships. The articles discussed previously describe the distress and consequences of premenstrual disorders, demonstrating the urgent need for real-time detection and treatment. Relatedly, Tauseef et al. discuss possibilities for just-in-time adaptive interventions (JITAIs) to target premenstrual psychiatric symptoms, including affective dysregulation, irritability, and suicidality. They propose that JITAIs could use menstrual cycle data to identify points of vulnerability within individuals and strategically deploy interventions based upon their individual profile. This would provide a personalized medicine approach to managing premenstrual symptoms.

Together, this Research Topic suggests that, while research on psychiatric illness across the menstrual cycle is limited, it is a quickly growing area of research, with exciting horizons ahead that may include better characterization of risk factors, improved treatments based on a more advanced understanding of the biological features of premenstrual disorders, and use of cutting-edge technology to manage premenstrual disorders. Improvements in identification of at-risk populations, detection of symptom onset in individuals, and treatment can reduce the burden of premenstrual disorders on many women's lives.

Author contributions

LH: Writing – original draft, Writing – review & editing. LO: Writing – review & editing. LS: Writing – review & editing.

Conflict of interest

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Premenstrual syndrome: new insights into etiology and review of treatment methods

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Premenstrual syndrome (PMS) is a common disorder affecting women of reproductive age, with an estimated global prevalence of 47.8%, with severe symptoms occurring in 3-8%, significantly affecting daily functioning. GABA conductance and changes in neurosteroid levels, particularly allopregnanolone, are suspected to play a substantial role in the disorder's etiology. In this paper, we provide an overview of recent reports on the etiology and recognized therapeutic approaches, encompassing both pharmacological and non-pharmacological interventions. Our examination includes studies on SSRIs, hormonal agents, neurosteroids, supplementation, and therapeutic roles. We aim to determine the most favorable treatment regimen by comparing medication effects and alternative methods. The treatment of PMS is crucial for enhancing the quality of life for affected women. Medications used in PMS treatment should be individually selected to achieve the best therapeutic effect, considering the clinical situation of the patients.

KEYWORDS

PMS, PMDD, SSRI, allopregnanolone, treatment

1 Introduction

Many women of reproductive age experience dysphoria and physical symptoms approximately two weeks before menstruation (1). The mentioned discomfort, both physical and psychological, associated with the luteal phase of the menstrual cycle and typically resolving when menstruation ends, is defined as premenstrual syndrome (PMS) (2). The global prevalence of premenstrual syndrome is estimated at 47.8% (3), while the most severe form of PMS - premenstrual dysphoric disorder (PMDD) affects 3-8% of women of reproductive age (4). What is more, the PMDD is classified 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) (5). That indicates the complexity of the disorder and is a reminder of the widespread spectrum of symptoms. The most common mental symptoms of PMS include irritability, tearfulness, anxiety, and depressed mood. Physical ones, on the other hand, mainly involve abdominal bloating, breast tenderness, and headaches (6). Hormonal changes, stress, diet, and alterations in neurotransmission are considered the most significant

risk factors (7). It is also suspected that the severity of PMS is higher in unmarried women compared to married women, those with lower economic status, and those with a family history of similar cases (8). Behavioral and social factors also play a role, including medication use (including contraceptives), smoking, alcohol and caffeine consumption, and even education. Age, past pregnancies, and previous menstrual history have also been evaluated, but there is still no complete consensus on how they impact the development of the disorder (9). Diagnosing premenstrual syndrome is possible only after ruling out other conditions that could better explain the experienced discomforts (10). The treatment primarily focuses on alleviating symptoms, and we will delve into this aspect further in our discussion.

2 Etiopathogenesis

The pathogenesis of PMS is intricate and not fully understood. Several theories attempt to explain the causes of its symptoms.

Classically, PMS has been linked to hormonal fluctuations during the monthly cycle, with mood deterioration and increased anxiety primarily associated with decreases in estrogen and progesterone (Figure 1).

2.1 The role of sex steroids and their derivatives - central role for allopregnanolone?

Recently, particular attention has been given to the progesterone metabolite allopregnanolone (11). Allopregnanolone is an allosteric modulator of the GABA receptor in the CNS, which binds to the alpha and beta subunits at residues m1-m3 (12), which explains its broad effects on multiple CNS pathways (13). Moreover, allopregnanolone synthesis can occur *de novo* not only in the brain but also in the ovaries and adrenal glands due to the presence of necessary enzymes in these organs needed for its production (14). Understanding the significance of allopregnanolone in alleviating PMS symptoms may provide crucial information about the cause of the disorder itself. Significantly, when utilized as a novel drug (brexanolone) for postpartum depression (PPD) treatment, it not only mitigates affective disorders (15) but also suppresses the inflammatory response. This dual action could potentially alleviate the severity of peripheral symptoms, including pain (16). The steroidal structure of progesterone and its metabolites enables them to penetrate the blood-brain barrier when formed peripherally, as observed in the ovaries (14). It is important to note that the presence of PMS is a risk factor for PPD (17). Both conditions are believed to be caused by hormonal changes, specifically the increase and subsequent withdrawal of sex hormones (18, 19), and the existence of subgroups of susceptible individuals (20, 21). Due to these associations and the increased interest in neurosteroids, allopregnanolone has become one of the most commonly linked substances to the etiology of PMS in recent years (20).

Women experiencing premenstrual symptoms demonstrate an impaired stress response (22). This may be precisely linked to the action of steroid hormones, which, through various mechanisms, inhibit the activity of the HPA axis, starting at the level of the PVN (23). Progesterone, or more specifically, its metabolite — allopregnanolone, enhances GABA conductance and suppresses CRH formation in hypothalamic cells. In contrast, estrogen inhibits the generation of free radicals, resulting in a reduction of oxidative stress in the body (24). What is more, Granda et al. suggest that abnormal oxidative and inflammatory activity may occur in PMS (25). It is possible that in PMS, there is an abnormal response to estradiol and an increase in oxidative stress, given that antioxidants in high concentrations have a pro-inflammatory effect

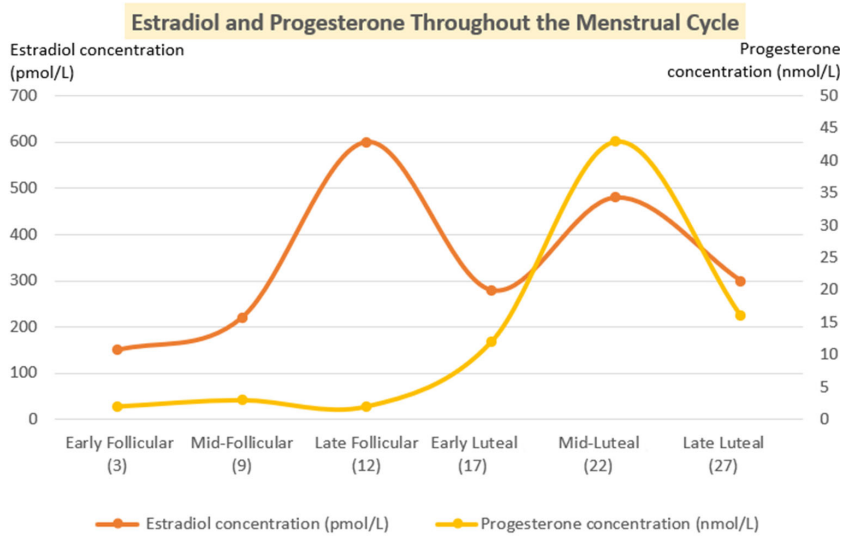

FIGURE 1
Concentrations of estradiol and progesterone during the menstrual cycle.

and estradiol has a second peak concentration in the early luteal phase (26). The significance of estrogen metabolites producing oxygen radicals (27) is noteworthy. However, the current research does not allow for a clear assessment of the role of oxidative stress (28–30). Interestingly, there are no discernible differences in hormone levels during the monthly cycle between healthy women and those suffering from PMS (31). However, concentrations of allopregnanolone and its conversion from progesterone are higher in women with the PMDD (32). This suggests a disturbance in the metabolic pathway of progesterone in women who are affected and implies the existence of a subgroup of women sensitive to hormone concentrations. This sensitivity is supported by the findings of Schmidt et al., who demonstrated that re-administration of progesterone to women suffering from PMS while taking a leuprolide resulted in a recurrence of symptoms (33).

Furthermore, women with PMS, after blocking 5-alpha-reductase, a crucial enzyme for allopregnanolone production, experienced significantly reduced premenstrual symptoms (34). In contrast, during the follicular phase, women with PMDD who took allopregnanolone as part of another study showed reduced GABA-A receptor sensitivity (35). These data underscore the crucial role of this metabolite in the described disorder: High allopregnanolone levels may explain why the stress response in women with premenstrual disorders is blunted (36), given the mentioned above impact of GABA conductance on CRH.

However, as explained above, blocking its synthesis provides relief to patients. The explanation for this situation may lie in the reaction to substances in the CNS itself. Due to their structure, steroid hormones can interact not only trans-membrane to the cell but also through the G-protein-bound receptor, leading to changes in the cell genome (37). Theoretically, with an increase in progesterone, there is an unimodal increase in allopregnanolone, and an adaptation - a down-regulation of the receptor to maintain constant inhibition of GABA (14). With a decrease in the concentration of the substance in the later luteal phase, the physiological GABA-glutamate balance could be disturbed: Adaptive changes do not keep up with the contraction in allopregnanolone, which was higher at baseline in affected women, and GABA receptors are not restored in time, leading to impaired GABA conductance. This could explain, among other things, the increased activity of the prefrontal cortex (38), as observed in imaging studies.

According to this assumption, it would not be the neurosteroid concentration itself that causes the onset of symptoms, but rather the decrease in concentration. The GABA-A receptor appears to adapt to neurosteroid concentrations through changes in its conformation (39). Women with PMDD have lower sensitivity to benzodiazepines, as well as pregnanolone, which may be related to receptor adaptation involving increased expression of the delta subunit. This subunit is insensitive to benzodiazepines but highly sensitive to allopregnanolone (40). Its increased expression, along with the other subunits, may reflect an attempt to adapt to falling allopregnanolone concentrations at the end of the luteal phase, especially since a study by Timby et al. indicates that women with PMDD have altered sensitivity to allopregnanolone (35). A similar theory regarding PPD was presented by Maguire et al. (41). In the case of the monthly cycle, it appears that the distinction lies not so much in the concept of abnormal adaptations taking place but in the severity of their proportions. The long-drawn modulation in PPD throughout the 3rd and 4th trimesters of pregnancy may be linked to both the effects of prolonged exposure of GABA cells to allopregnanolone, leading to adaptations at the level of the receptor and cell genome, and significantly higher progesterone concentrations than in the luteal phase (42). In contrast, changes in PMS may occur only through a pathway of rapid adaptation to allopregnanolone involving structural changes in the GABA A receptor, which would explain the lower severity of symptoms. Additionally, the relationship between the two pathologies is indicated by the fact that PMS predisposes to PPD (17), and similar to PPD, in PMS, we observe a subgroup of women sensitive to hormonal fluctuations (21) (Figure 2).

However, it is important to remain skeptical when discussing the connection between the onset of PMS and fluctuations in progesterone derivative levels. The studies by Schmidt et al. (33, 43) showed that eliminating hormone fluctuations during the luteal phase is not enough to prevent the onset of PMS symptoms. What is interesting, the researchers found that there was a subgroup that was sensitive to hormonal fluctuations: only patients with a history of PMS responded to hormonal interventions compared to a group of healthy women. Based on these findings and considering the abnormal response to BDZ in PMS patients, it can be concluded that abnormal adaptive responses of the GABA A receptor are one of the main, but not the only, problems faced by women with PMS. Furthermore, Schmid et al. also indicated in their more recent study that it is not high progesterone levels sustained over a long period, but changes in progesterone concentration that are key in triggering symptoms. This study provides a more complete understanding of the role of sex hormones in the disorder - the findings indicate that it is not re-administration but changes in sex hormone concentration that may be crucial. In both cases, this may indicate abnormal adaptations of the GABA A receptor (44).

The additional importance of hormones is underscored by estrogen's ability to promote growth factors, such as BDNF (22, 45). SSRIs, used in the treatment of PMS, also stimulate its formation, and their effectiveness in treatment serves as indirect evidence of the importance of disturbances in serotonergic conduction in the etiopathogenesis of this pathology (46). Imaging studies further provide evidence of altered GABA and serotonergic conduction in the amygdaloid nucleus and prefrontal cortex in patients affected by PMDD (47).

2.2 Rapid action of SSRIs in PMS - potential mechanism

Due to the rapid response to treatment with SSRI drugs, a different mechanism should be considered compared to the classical model found in affective disorders (48). In the classical model, the drugs take effect after about 3 weeks, while in the case of PMS, no such time gap is observed. A strong argument for the importance of serotonergic conduction is the lower peripheral blood serotonin levels during the luteal phase in women with PMS (49, 50). Use of drugs from SSRI group, leads to an increase in serotonin

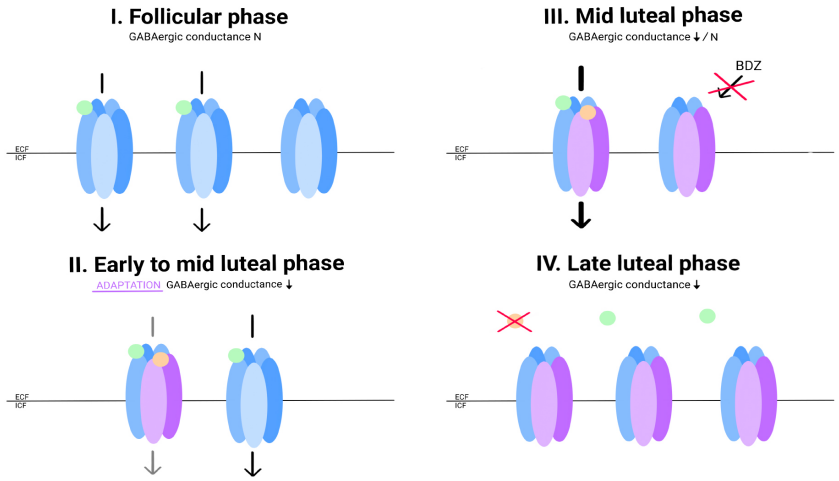

FIGURE 2
Allopregnanolone concentrations and hypothetical changes in GABA conductance in PMS patients. During the follicular phase, progesterone and allopregnanolone concentrations are low. Expression of selected GABA receptor subunits is not increased. GABA conductance functions properly (I). With increasing concentrations of allopregnanolone, the conformation of the GABA-A receptor is affected: the expression of the alpha4 subunit, and probably delta, is increased. In a group of women with PMS, there is a paradoxical decrease in GABA conductance under the influence of allopregnanolone (II). This condition explains the paradoxical effect of flumenazil in women with PPMD. The GABA-A receptor in this conformation is insensitive to BZDs. At the highest concentration of allopregnanolone in the cycle, GABA-A conductance is mainly regulated by it (III). Allopregnanolone does not reach high enough concentrations in the cycle to induce the expected allosteric modulator effect. Its concentration begins to fall, forcing readaptations within the GABA-A receptor. Until the conformation of the molecules returns to "physiological", inhibition may be impaired (IV). - Gamma-aminobutyric acid (GABA); - Allopregnanolone; - GABA receptor; - GABA receptor with altered subunit expression in response to allopregnanolone.

concentration in the synaptic cleft. An increase in serotonergic neurotransmission is the result (51). Furthermore, recent studies have shown that during the monthly cycle in women suffering from PMDD, there is an increase in serotonin uptake during the premenstrual period. Furthermore, increased serotonin transporter correlated with increased depressive symptoms. This indicates that the key may be the change in extracellular serotonin levels itself (52).

Another theory proposes the thesis that SSRIs promote an enzyme necessary for the production of allopregnanolone, and this enzyme is responsible for the immediate effect (53), which would explain the achievement of rapid clinical effects after brexanolone administration (54).

Within the allopregnanolone pathway, the enzyme 5α-reductase initiates the transformation of progesterone into 5α-dihydroprogesterone (5α-DHP). Subsequently, another enzyme, 3α-hydroxysteroid dehydrogenase (3α-HSD), facilitates the conversion of 5α-DHP to allopregnanolone (55, 56).

Progesterone can also be transformed into 5β-DHP with the enzyme 5β-reductase. Subsequently, 3α-HSD acts on 5β-DHP to produce pregnanolone (57).

Allopregnanolone and pregnanolone are positive allosteric modulators of GABAA, enhancing its function. Conversely, their isomers, isoallopregnanolone and epipregnanolone, are negative allosteric modulators, thereby inhibiting GABAergic neurotransmission. Dehydroepiandrosterone (DHEA) is another pregnanolone derivative and negative allosteric modulator, which potentially may compete with allopregnanolone for the substrate. Furthermore, a potential mechanism for PMS/PMDD could involve higher levels of negative allosteric modulators compared to positive allosteric modulators (57, 58).

Griffin et al. suggest that SSRIs (fluoxetine, paroxetine and sertraline were included in the study) may modulate the activity of neurosteroidogenic enzymes by enhancing their substrate affinity. For instance, they propose that SSRIs could increase the affinity of 3α-HSD for 5α-DHP, potentially augmenting its function. The specific mechanism of SSRIs influence on enzyme is currently unknown (51).

The mechanism of action of SSRIs in managing PMS/PMDD is convoluted, encompassing the modulation of GABA via neuroactive steroids. The SSRI's impact on neuroactive steroid levels involves processes such as the redirection of biosynthetic pathways from progesterone towards neuroactive metabolites. Additionally, substrates are directed towards enhancing GABAA function positively, while competitive inhibition of enzyme substrates also plays a role. These mechanisms may contribute to the modulation of neuroactive steroid levels, suggesting the impact of SSRIs in addressing PMS/PMDD symptoms (58, 59).

2.3 Inflammation in PMS

One clue to the development of the disorder is immune dysregulation in women experiencing PMS. A study by Gold et al. revealed elevated levels of hs-CRP in women with PMS, indicating an immune component to the disorder (60). This study confirms the theory about the role of inflammation in its development, but there is insufficient evidence indicating a central effect of these substances in PMS.

The strong correlation of hsCRP with abdominal pain may suggest a local inflammatory process. Still, the central levels of cytokines are unknown, even though hsCRP was associated with mood disorders in the study. Unfortunately, the study had several limitations that could impact the CRP result: the patients' status, prevalence, and BMI at the time the samples were taken were not considered (61). A relevant study by Puder et al. demonstrated that regardless of BMI, hsCRP levels are similar in women with high BMI and those within normal limits, and the course of low-grade inflammation is independent of BMI (62). It's important to note that the study sample included only 15 women. Furthermore, hsCRP concentrations correlated once again with women's mood, and hsCRP level itself was highest during the early follicular phase, associated with physiological processes. Another study, which excluded conditions such as smoking and a history of mood disorders, provided more robust evidence by demonstrating elevated levels of inflammatory cytokines in affected women (including IFN-gamma, IL-2, IL-10, IL-12, IL-4) (63). However, the study did not clarify the important time criterion for the appearance of these markers in the blood. The markers themselves, such as IFN-gamma, indirectly indicate T-lymphocyte activity, with correspondingly elevated IL-1 levels, highlighting the interconnectedness of anti- and pro-inflammatory factors. An additional argument supporting the importance of inflammation is the results of treatment of selected PMS using anti-inflammatory drugs (64).

2.4 HPA axis in PMS

Meta-analysis by Klusmann et al., showed that the HPA axis exhibits stronger reactivity during the luteal phase compared to the follicular phase (65). This is also linked to elevated cortisol levels during the luteal phase. Additionally, Hou et al. found that there is a blunted morning cortisol response in PMS (66). The dysregulation of the HPA axis may be caused by cyclical stressors experienced over time. In addition, PMS has been found to result in an impaired cortisol response to stress (67). Affective disorders are also linked to altered HPA axis function (68). It is important to note that the cortisol response and sympathetic nervous system response are impaired in PMS, but only during the luteal phase (69). However, the study by Schmidt et al. mentioned earlier does not provide enough evidence to determine whether it is progesterone alone via allopregnanolone, or both progesterone and estrogen, that contribute to this dysregulation. However, the available data suggest that estradiol-containing drugs may be effective in improving HPA function, as demonstrated by the improvement in function following estrogen administration (70). In addition, regulation of progesterone levels may prevent abnormal adaptations of GABA-A receptors and thus prevent changes in the HPA axis.

2.5 Prolactin in PMS

In the context of the etiology of PMS, the role of prolactin was also considered. Studies with bromocriptine provide indirect evidence for the effect of prolactin on PMS (71, 72). Additionally, higher prolactin concentrations are observed during the luteal phase, which is associated with PMS symptoms (73). Elevated levels of prolactin have been linked to mastalgia, and decreasing these levels has been shown to result in clinical improvement in patients (74). Based on the concentrations of estrogen and progesterone, high levels of prolactin may exacerbate PMS symptoms, in line with the theory proposed by Carroll and Steiner (72).

2.6 Genes in PMS

Genetic studies have not provided clear conclusions regarding the specific genes that are reliably involved in the development of PMS. However, family studies suggest a discernible genetic component and align with the theory of the existence of a subgroup of susceptible patients (75). Research conducted by Widholm et Kantero found that children of mothers with PMS have a higher likelihood of developing the disorder (76). Additionally, a study on monozygotic and dizygotic twins highlighted a greater than 40% probability of developing the disorder if one of the twins suffers from PMS (77).

Although etiopathogenesis remains incompletely understood, studies on PMS markers and advancements in imaging techniques provide a rationale for the use of many drugs in the treatment of PMS (Figure 3).

3 Hormone treatment

Hormone treatment aims to eliminate fluctuations in sex hormones during the menstrual cycle. This can prevent adaptive changes in the Central Nervous System that occur under the influence of progesterone and estrogen derivatives. Theoretically, this could eliminate a group of women particularly sensitive to hormonal fluctuations. The attempted maladaptation of GABA-A receptors to allopregnanolone could be prevented by the absence of a progesterone peak (34, 78). Eliminating this phenomenon could potentially increase serotonin levels in women who suffer from PMS (50). Based on these interactions, monophasic COC preparations seem to be a better treatment option than multiphasic preparations. Biphasic and triphasic formulations gradually increase the amount of gestagens in the second half of the cycle, corresponding to the physiological fluctuations of sex hormones. This removes the progesterone peak, making abnormal adaptation of the body impossible. Monophasic preparations are recommended for controlling mood disorders during PMS, according to guidelines (10). A more detailed description of endocrine disruption is described above.

3.1 Contraceptive treatment

The most effective drug in the oral contraceptive (OC) group seems to be formulations containing ethinylestradiol and drospirenone. This preparation is FDA-approved for the treatment of PMDD (79). These drugs are intended to improve the patient's condition through several mechanisms, including the

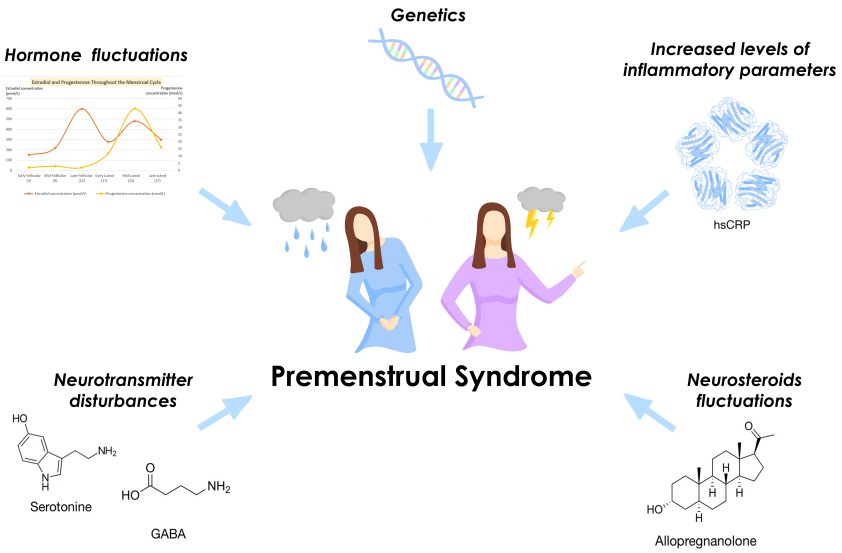

FIGURE 3
Selected factors influencing the development of PMS.

suppression of ovulation, which results from the stabilization of hormone levels by both components of the pill. Theoretically, this is also expected to lead to an improvement in mood. The preparation is also intended to have an anti-androgenic effect, which would reduce symptoms such as irritability and aggression. However, the role of androgen hormones in PMS is not yet fully understood. Eriksson et al. found higher serum testosterone concentrations in women with premenstrual symptoms regardless of cycle (80), while another study (81) found no differences in testosterone concentrations between sick and healthy women. However, it should be noted that the latter study was limited by a small sample size. In addition, the heightened levels of DHEA during the periovulatory period in women with PMS highlight the significance of neurosteroids in the disorder. DHEA is a precursor for the synthesis of neurosteroids and has a protective effect on the CNS (82). However, the concentration of DHEA is higher for a short period during the cycle, indicating a different DHEA processing pathway in affected women.

Additionally, drospirenone is responsible for the anti-androgenic effect in the cited preparation (83). This substance is a progesterone derivative with up to 10 times the anti-androgenic effect. Drospirenone has been found to have a beneficial effect in reducing PMS and PMDD symptoms due to its antagonism to the mineralocorticoid receptor (84). This substance is an analog of spironolactone, a diuretic, which has been shown to nullify symptoms related to water retention and also has mood-enhancing effects (85). It is important to note that in the natural cycle, progesterone competes with aldosterone for access to the mineralocorticoid receptor, thereby antagonizing its action. While most progesterone analogs do not mimic this action, drospirenone is an exception. Spironolactone inhibits the action that results from the earlier dominance of estrogens in the cycle, which leads to the promotion of angiotensin formation (86). This is particularly relevant because angiotensin is responsible for various changes in the body, including its influence on the Central Nervous System. For instance, it regulates acetylcholinergic conductance (68). The earlier-mentioned improvement in mood after spironolactone may be correlated with its ability to lower and normalize progesterone concentrations (87). This suggests that spironolactone may block the body's abnormal adaptation to progesterone and allopregnanolone. Drospirenone is an analog of spironolactone that performs the important function of progesterone in the periphery more effectively, with anti-androgenic and anti-mineral corticosteroid actions. Additionally, drospirenone lowers the concentration of progesterone in the body, which prevents abnormal adaptation reactions in the CNS. The initial studies on drospirenone were inconclusive. The relatively long period of placebo intake (21/7 days) may have been related to these observations: improvements in aspects of acne, appetite and hunger, and breast pain, but no significant improvement in mood was achieved (88, 89). Only studies using a shorter duration of placebo intake (24/4 days) demonstrated significant improvement in physical symptoms such as breast tenderness, swelling, bloating, headaches, and muscle pain, as well as mood. However, the authors highlighted that previous studies on the use of contraception in PMDD indicate its superiority in treating physical symptoms over mood, where SSRIs are still more potent (79). Lopez et al. (2008) demonstrated significant improvements in productivity and social relationships following a three-month treatment with ethyl estradiol and drospirenone (90). Additionally, this drug can reduce the risk of PMDD recurrence (79). To achieve maximum treatment efficacy, it is recommended to administer the specified preparation for 24 days with a 4-day interval. The preparation contains 20ug of ethinylestradiol and 3mg of drospirenone. If treatment is ineffective, increase the dose of ethinylestradiol to 30ug and take the preparation in a cycle of 21 days with a 7-day interval, along with 3mg of drospirenone. According to the cited data, a shorter medication interval improves the mood of sufferers

(10, 79). Therapy with this contraceptive, like other drugs, may cause side effects (Table 1). Patients may experience nausea, breast pain, and intermenstrual bleeding (95).

The use of oral contraceptives that contain only progesterone is not recommended for the treatment of PMS and PMDD symptoms. This is because such therapy may exacerbate mood fluctuations and other PMS-related symptoms (91, 96). Evidence supporting this position comes from a study that found that patients with mood disorders have higher levels of progesterone in their blood compared to the control group (97). It is known that the development of progesterone-induced mood disorders is strongly dependent on the individual's sensitivity to the hormone, its

TABLE 1 Collected research on hormone treatment in PMS.

Author, year of publication	Substance, dosage form and total daily dose	Study design	Dosage, total duration of administration	First test group	Second test group	Third test group
Pearlstein et al. 2005 (79)	oral contraceptive (OC) containing drospirenone 3 mg and ethinyl estradiol (EE) 20 µg pills	multicenter, double-blind, placebo- controlled, crossover	3 mg drospirenone + 20 EE µg/ dayfrom day 1 of the cycle to day 24 during 3 menstrual cycles	**OC formulation (3 cycles)->washout (1 cycle) -> placebo (3 cycles)**34 women [18-40 years old](14 completed study)	**placebo (3 cycles) -> washout (1 cycle) -> OC formulation (3 cycles)**30 women [18-40 years old] (11 completed study)	-
Freeman et al. 2001 (88)	oral contraceptive (OC) drospirenone (DRSP, 3 mg) and ethinyl estradiol (EE, 30 µg)	multicenter, double-blind, randomized, placebo- controlled	3 mg DRSP + 30 µg EEduring 3 cycles	**DRSP/ EE**42 women [18-40 years old]	**Placebo**40 women [18-40 years old]	–
Graham and Sherwin 1992 (89)	triphasic OCethinyl estradiol 0.035 mg, norethindrone 2 mg tablets	double-blind, controlled	ethinyl estradiol 0.035 mg from days l-21 and norethindrone,0.5 mg during days l-7, 1 mg during days 8-16,and 0.5 mg during days 17-21. 1 tablets of O.C. /dayduring 3 cycles	**OC**20 women [18-35 years old]	**Placebo**25 women [18-35 years old]	-
Lundin et al. 2016 (93)	combined oral contraceptive (COC)1.5 mg estradiol and 2.5 mg nomegestrolacetate pills	investigator- initiated, multi-center, randomized,double-blinded, placebo-controlled	COC pill/ dayfrom day 1 to day 24 of cycle during 3 cycles	**COC**84 women [18 – 35 years old]	**Placebo**94 women [18 – 35 years old]	-
Halbreich et al. 2011 (105)	oral contraceptive (OC) Levonorgestrel 90 mcg/ethinyl estradiol 20 mcg (LNG/EE) tablets	multicenter, randomized, double-blind, placebo- controlled	4 consecutive 28-day pill packsfor 112 days	**LNG/EE**186 women [18-49 years old](127 women completed)	**Placebo**181 women[18-49 years old] (128 women completed)	–
Comasco et al. 2021 (117)	Ulipristal acetate (UPA) 5 mg	investigator- initiated, multicenter, double-blind, randomized, parallel-group	5 mg UPA/ day for 28 daysduring 3 menstrual cycles	**UPA**48 women [18-46 years old](41 women icluded in analys)	**Placebo**47 women [18-46 years old] (39 women icluded in analys)	-
Bäckström et al. 2021 (142)	Sepranolone 10 or 16 mg	parallel, randomized, double-blind, placebo-control	10 or 16 mg sepranolone/ dayduring 14 days prior to the next estimated menstruation for 3 menstrual cycles	**Sepranolone 10 mg**64 women [18-45 years old](50 women icluded inanalys)	**Sepranolone 16 mg**68 women [18-45 years old] (49 women icluded inanalys)	**Placebo**70 women [18-45 years old] (44 women icluded in analys)

(Continued)

TABLE 1 Continued

Author, year of publication	Method of data collection	Outcomes	Adverse events/ side effects	Limitations	Overall effect
Pearlstein et al. 2005 (79)	Daily Record of Severity of Problems (DRSP) scores	Significantly reduce PMS symptoms and improved DRSP total score while using drospirenone/EE than placebo. the greatest improvementswere found for the physical symptoms of breast tenderness,swelling, bloating, headache and muscle pain and also improved mood	7 womens discontinued the study due to AEs (4 while using drospirenone/EE and 3 while taking placebo)Reasons for discontinuation from drospirenone/EE were spotting/ dysmenorrhea/vomiting, breast tenderness/clumsiness/ nervousness, spotting and severe nervousness/increased irritability, and from placebo were severe nervousness/increased irritability, migraine	-the sample size was modest,-the length of the study led to considerable subject attrition-OCs potentially change the characteristics of the menstrual cycle (e.g., cycle length, increased intermenstrual bleeding), which could potentially unblind both subjects and study personnel	positive
Freeman et al. 2001 (88)	Calendar of Premenstrual Experiences (COPE) scale Beck Depression Inventory (BDI) and the Profile of Mood States (POMS)	There was greater improvement in the total COPE scores in the DRSP/EE group compared with the placebo group (appetite, acne, and food cravings) but the difference did not reach statistical significance	The most commonly reported adverse events were nausea, headache, sinusitis, upper respiratory infection, malaise, and depression in both groups	-high placebo response rate-the COPE instrument, which was used as a primary outcome measure, has a range of 0–3, which may not have been sensitive enough to detect differences between active and placebo treatment over time	positive
Graham and Sherwin 1992 (89)	the Daily Ratings Form (DRF) visual analogue scales (VAS)	Premenstrual breast pain and bloating were significantly reduced with O.C. there were no beneficial effects of theO.C. over placebo for any of the mood symptoms.	decreased sexual interest after starting treatment with O.C.	-small sample size,- women were only observed for 3 menstrual cycles	positive
Lundin et al. 2016 (93)	the Daily Record of Severity of Problems (DRSP) the self-rated version of the Montgomery-Åsberg Depression RatingScale (MADRS-S)	COC use is associated with small but statistically significant mood side effects in the intermenstrual phase.Significant treatment by menstrual cycle phase interactions were noted for mood swing, irritability and anxiety, also minimal for mood change, depression, and sense of being overwhelmed	COC users reported a clinically significant mood worsening and 15 placebo users	the placebo response was substantial, and many women also improved throughout the trial.	slightly positive
Halbreich et al. 2011 (105)	Daily Record of Severity of Problems (DRSP) Work Limitations Questionnaire (WLQ)	LNG/EE may be useful for managing the physical, psychological and behavioral symptoms and loss of work productivity related to PMDD.LNG/EE decreased PMDD symptoms in the late luteal phase as well as on worst symptomatic days, reduced severity of the predefined physical, depressive and irritability symptom clusters and reduced work limitation.	Headache was the most commonly reported AE with both treatments. metrorrhagia, menorrhagia and vaginal and uterine hemorrhage and flulike syndrome more often in LNG/ EE group	-a high number of subjects failed screening (maybe because of challenging to complete a daily-rating questionnaire for 7 months)-high placebo response(the placebo run-in cycle only partially addressed this issue),- small sample size	positive
Comasco et al. 2021 (117)	Daily Record of Severity of Problems (DRSP)	Treatment effects were also noted for the DRSP depressive symptom subscale	7 women in the UPA group discontinued because of mild/ moderate side effects (headache,	-small sample size,- women were only	positive

(Continued)

TABLE 1 Continued

Author, year of publication	Method of data collection	Outcomes	Adverse events/ side effects	Limitations	Overall effect
	EuroQoL visual analogue scale (EQ- VAS) Montgomery-Åsberg Depression Rating Scale, self-rated version (MADRS-S)	(anger/irritability), but not for the DRSP physical symptom subscale.UPA could be a useful treatment for PMDD, particularly for the psychological symptoms of PMDD	fatigue, and nausea) and 3 women in the placebo group discontinued because of depressive symptoms or anxiety.Nausea was significantly more common among women in the UPA group than in the placebo group.Other most commonly reported side effects in the UPA group were headache, nausea, and fatigue.	observed for 3 menstrual cycles	
Bäckström et al. 2021 (142)	Daily Record of Severity of Problems (DRSP) scale in an eDiary	Sepranolone 10 mg reduced PMDD symptoms significantly more than placebo. The effect of sepranolone 16 mg dosage did not statistically differ from placebo.10 mg sepranolone could ameliorate negative mood symptoms, improve distress and impairment occurring in the premenstrual phase to a greater degreethan placebo	14 subjects discontinued the study due to a treatment-emergent adverse event (3 in placebo group, 5 in sepranolone 10 mg group and 6 in sepranolone 16 mg group)The most prevalent AE was injection site pain (8 in sepranolone 16 mg group).	-small sample size-women were only observed for 3 menstrual cycles	positive

concentration in the blood, and the timing of exposure. It is worth noting that it is progesterone administered in doses that mimic the luteal phase, and therefore in lower concentrations comparatively to pregnancy, that may be associated with mood side effects in OC users (91, 98–100). In contrast, during pregnancy, high concentrations of the substance exhibit anti-anxiety and sedative effects (101–104). Consequently, the effectiveness of progesterone in alleviating premenstrual symptoms strongly depends on its blood concentration. In conclusion, the use of progesterone alone in the treatment of PMS and PMDD does not show the same efficacy as therapy with oral contraceptives containing drospirenone with ethinylestradiol. Furthermore, it appears that premenstrual symptoms may be induced by the use of progestogen as part of hormone replacement therapy (105). In terms of targeted treatment, dutasteride may be a more suitable option as it inhibits the conversion of progesterone to allopregnanolone (34). However, there is limited data on the efficacy of this substance, and as an androgen, it may have negative effects on male fetal development in women who are planning pregnancies.

The use of oral contraceptives containing only estrogens is not recommended for the treatment of PMS and PMDD symptoms. Studies suggest that such preparations may be ineffective in alleviating premenstrual symptoms or may even worsen them (106). In addition, it has been shown that estrogens are significantly associated with an increased risk of endometrial cancer. However, this risk can be effectively reduced by concomitant use of progesterone (106). Therefore, a more effective and safer approach would be the use of combination preparations, such as the OC and COC preparations cited earlier (107).

Researchers have also considered the issue of the placebo-drug interval. Although OC treatment is effective, it does not fully eliminate hormonal fluctuations. This may be related to a treatment regimen involving a placebo (92). The use of COC - continued contraception - could eliminate LH, FSH, oestradiol, and progesterone fluctuations, thus improving patient comfort (108). Halbreich et al. (2011) studied the effectiveness of levonorgestrel (LNG) 90 mcg/EE 20 mcg for 4 cycles of 28 days. The study found that over half of the patients experienced a significant improvement, defined as a 50% reduction in symptom intensity (92). Furthermore, as the therapy duration increased, more patients responded positively to the treatment. In the initial cycle, during the late luteal phase, typically associated with the onset of symptoms, there was a decrease in symptom intensity according to the DRSP scale. However, according to Freeman et al.'s analysis of studies, the efficacy of COC treatment is similar to that of SSRIs. It should be noted that the effect of COC treatment is not as well demonstrated for low symptom severity (109). One possible reason for the PMS trials showing less clear outcomes than the PMDD trials is that the PMS trials had lower criteria for symptom severity at the start of the study. This could have made it harder to see the differences in how much the LNG/EE and placebo groups improved, compared to the PMDD trials where the participants had more severe symptoms and more room for improvement. It is important to note that these studies are limited by high responses in the placebo group, ranging from 27-53% for PMDD. Additionally, COC treatment offers better control of bleeding days and reduces pain associated with the 5 most severe days of the cycle (110). Therefore, these drugs appear to be particularly effective in more severe cases of PMS - PMDD, especially when physical symptoms are inadequately controlled.

COCs have been shown to improve patients' mood and physical symptoms.

It is noteworthy that the use of a levonorgestrel-releasing IUD may increase stress sensitivity. Women using this type of IUD exhibited significantly higher blood cortisol levels than those who took oral levonorgestrel in combination with estrogen. This phenomenon may be due to the potential effect of this type of contraception on increasing autonomic system reactivity to stimuli such as stress (111). It is worth noting that several studies have suggested that the use of levonorgestrel-releasing IUDs may worsen mood disorders (111–115). In conclusion, it is important to note that the effectiveness of levonorgestrel in alleviating PMS symptoms appears to depend on its method of administration. Oral formulations containing levonorgestrel demonstrate greater efficacy than IUDs, which may even exacerbate symptoms associated with the disorder.

3.2 GnRH agonist treatment

Alongside oral contraceptives, gonadotropin-releasing hormone (GnRH) agonists also play a significant role in the treatment of PMS and PMDD. The mechanism of action involves inhibiting the central hypothalamic-pituitary-ovarian system, which leads to the inhibition of ovulation. This has been confirmed in studies (116). Inhibiting ovulation is expected to reduce hormonal fluctuations in the menstrual cycle. However, it is important to note that these drugs induce a menopausal state, which can cause symptoms such as bone mass loss and hot flashes. To minimize the side effects of therapy, progestogens or tibolone are often added. Another option is to use a progesterone receptor blocker, which, if given early enough in the cycle, also prevents ovulation. Ulipristal acetate is a progesterone receptor blocker used to treat uterine myoma. Receptors for progesterone are present in the hippocampus and frontal cortex (117). This highlights the significance of this steroid in the disorder. Blocking its receptor would prevent interactions between progesterone and the genome, inhibiting potential negative changes (118). Comasco et al. (2020) conducted a study that found that taking ulipristal significantly improved psychiatric/mental symptoms in PMDD sufferers compared to placebo. The study lasted for three months and outcomes were measured using the Daily Record of Severity of Problems (DRSP) scale (93).

The group of GnRH agonists match the efficacy of first-line drugs - SSRIs. Due to their induction of the perimenopausal state/suppression of estrogen and progesterone synthesis (mentioned above), they cause several side effects characteristic of the menopausal period (119) These side effects limit the duration of therapy to a maximum of 6 months, with the main limitation being the loss of bone mass (120). To address the problems of therapy with GnRH analogs, attempts are being made to use add-back hormone therapy to reduce the incidence of side effects (121).

However, this is a controversial approach due to the etiology of PMS in which hormonal fluctuations seem to be the predominant problem. In theory, this could lead to counteracting the therapeutic effect of GnRH. Progestogens themselves can trigger a worsening of mood in women, presumably through their effect on the GABAa receptor (82). According to Schmidt et al.'s theory, not only progesterone but also estradiol administered alone can induce a relapse of PMS symptoms (33). Similar conclusions were reached by Leathear et al. in whose study of GnRH with add-back hormone therapy as many as nine out of 20 subjects discontinued therapy, when in the case of the GnRH analog alone it was three out of 20, including only one for medical indications. The entire study lasted six months and showed that people on add-back hormone therapy did not achieve clinically significant improvements compared to placebo (121). Given that progestogen was given only for one week into a cycle in this study, it is debatable to use add-back therapy alone with estrogen. This would eliminate the effect of progestogen, which, when administered during the luteal phase, can mimic premenstrual symptoms (122). On top of this, a study by Erkkola et al. indicates that progestogen supply every 3 months for 14 days was sufficient in menopausal women to prevent endometrial hyperplasia (123). Furthermore, in a study by Mezrow et al, it was shown that add-back estrogen was also effective, however, each time Medroxyprogesterone acetate (MPA) was administered for 10 days every 4 cycles, this was accompanied by a worsening of mood (124). Further studies, on a group of PMS and PMDD patients, are needed to confirm these reports and effectively apply this type of therapy in selected patients. In agreement with the data presented here correlates with the study by Segebladh et al. who showed that the addition of HRT in women with PMDD specifically worsened the control of mood-related symptoms, however, the addition of 1.5mg of oestradiol alone (gel, daily) least interfered with the outcome of leuprolide acetate treatment (125). Furthermore, the higher the concentration of estradiol relative to progesterone in the other groups of the study, the more pronounced the premenstrual symptoms were. This evidence indirectly suggests that the co-occurrence of hormones in the cycle potentiates their interaction with mood, lowering it even more strongly in predisposed women. This also challenges the approach that progesterone metabolites alone are crucial for the development of the premenstrual disorders (126).

There are only a limited number of studies that have examined the effect of GnRH agonists along with add-back hormone treatment, which makes it difficult to draw clear conclusions. A meta-analysis conducted by Wyatt et al. indicated that add-back therapy does not reduce the effectiveness of GnRH agonists based on several studies (127). However, more recent studies have raised doubts about these findings. Ultimately, a high placebo effect, typical of PMS studies, reduces the quality of the results. The mere administration of a placebo may suggest the reappearance of hormone fluctuations and subsequent symptoms in female patients (128). Additionally, it should be noted that the effectiveness of GnRH therapy decreases in patients with a co-existing psychiatric diagnosis, which is more frequent in the PMS population than in the general population. There is no doubt that the problem of adverse effects of GnRH analogs requires replacement therapy, and studies suggest that the best combination would be oestradiol alone with progesterone administered approximately every 3–4 cycles. However, it should be noted that progesterone administration may be accompanied by an increase in symptoms, and this should be brought to the patient's attention when attempting such therapy. On top of this, the small amount of evidence limits such an approach.

When discussing GnRH agonists, GnRH antagonists should also be considered. GnRH antagonists rapidly inhibit pituitary gonadotropin secretion through competition for GnRH receptors, eliminating the initial stimulatory phase typical of agonists. They have indications, among others, in the treatment of endometriosis (129).

The reason why they can be considered for use is their rapid onset of action and rapid return of pituitary function after cessation of therapy (130). GnRH agonists must be administered for a longer period and on a relatively continuous basis to maintain their effect. While the therapeutic regimen would not differ in terms of continuity of therapy in the case of GnRH antagonists for PMS and PMDD, these drugs are more predictable in their use. However, they can be expensive and may require hormone replacement therapy (131). While there are no studies that discuss the use of these drugs for PMS and PMDD, they may become more convenient for clinicians to use in the future.

3.3 Future directions

As blocking the synthesis of progesterone metabolites, including allopregnanolone, has been found to provide relief to patients with PMDD, it is important to attempt to normalize the concentration of this substance (132). Low concentrations of allopregnanolone can worsen mood in certain cases (133). Conversely, when its concentration peaks, its activity has been associated with a decrease in amygdala impulsivity (134).

The appearance of allopregnanolone appears to affect GABA receptor modulation, with only high concentrations being beneficial in a therapeutic context. This is observed in the group where a paradoxical anxiety mechanism is described at low concentrations (135). However, a potential issue in this scenario is determining the appropriate timing for terminating treatment with the drug. The decrease in allopregnanolone concentration appears to trigger the re-conformation of the GABA receptor (39). Our current knowledge is insufficient to use the substance that is blamed for mood fluctuations. The abnormal receptor response appears to underlie the pathogenesis of the disorder, given the somewhat common paradoxical mechanism of action of GABA-A modulators, which also involves the action of benzodiazepines (136) and ethanol (135). Another issue is blocking progesterone metabolism to inhibit allopregnanolone synthesis. SSRI drugs appear to normalize allopregnanolone concentrations, which may explain their rapid effect in women with premenstrual symptoms (137). In contrast, isoallopregnanolone is a negative modulator of GABA, unlike allopregnanolone, but its effect on GABA is small (138, 139). In studies conducted on rats, isoallopregnanolone was found to reverse the effects of allopregnanolone (140). Additionally, even a half dose of isoallopregnanolone was able to reverse the sedative effects of allopregnanolone as well as the SEV test, which measures the intensity of anesthesia (141). To ensure the drug's effectiveness, it should be administered based on the predicted concentrations of allopregnanolone during the cycle. This means that its concentration should be highest in the later luteal phase to counteract the fall of allopregnanolone. Bäckström et al.'s study showed the greatest improvement in patients with the highest concentrations of the drug in the late luteal phase. Despite methodological errors, such as administering the drug outside of the late luteal phase, it still demonstrated efficacy (142). A recent study found that women who took isoallopregnanolone had a lower incidence of PMDD symptoms than those who took a placebo (94). However, both studies have methodological problems. In the first study, inaccurate adjustment of the drug's administration timing to the luteal phase and an unselective inclusion criterion were noted. Women with symptoms outside the luteal phase were also admitted. Furthermore, the initial analysis in the second study only considered the 5 days of the cycle with the most severe symptoms. It was not until the extension to 9 days that a significant benefit from the drug was observed. Additional research is required to establish definitive conclusions. Currently, it is understood that isoallopregnanolone is particularly effective in improving mood, reducing tension, and alleviating anxiety. The medication appears to be beneficial for patients with mental disorders during their menstrual cycle.

3.4 Conclusion

In conclusion, for PMS therapy, oral contraceptives containing drospirenone and ethinylestradiol (at a dose of 3 mg drospirenone and 20 mcg ethinylestradiol) are the most effective. If bleeding and abdominal pain are not controlled, an alternative solution is to use COCs with levonorgestrel and EE. Transdermal patches may be used as an alternative to oral contraceptive pills for patients who have difficulty taking them regularly. However, the effectiveness of transdermal patches is still a matter of debate (106). It is not recommended to use formulations that contain only progesterone or only estrogen. The available research on the effectiveness of new treatments that selectively target progesterone and its metabolites is insufficient to draw firm conclusions.

It is important to note that many PMS and PMDD symptoms, including breast tenderness, depression, and headaches, can occur as side effects of taking contraception, which limits the effectiveness of this approach (143). Although side effects were rare in most of the studies cited, it is still necessary to consider alternative therapeutic approaches for premenstrual disorders. It is worth noting that the preparations discussed above mainly affected physical symptoms, and only some had a clear effect on improving mood.

4 Antidepressant medication

The treatment of PMS and PMDD uses drugs from the SSRI group, which block serotonin reuptake in the presynaptic area. This leads to an increase in serotonin concentration in the synaptic cleft, increasing serotonergic neurotransmission (46).

According to the latest guidelines from the Royal College of Obstetricians and Gynaecologists, SSRIs should be used as first-line drugs in the pharmacotherapy of severe PMS (144). Primarily because they are considered most effective in alleviating the anxiety and irritability symptoms characteristic of the disorder (145). Studies on the use of SSRIs to treat PMDD have shown a

beneficial effect of the therapy in 60% to 90% of patients, with a range of 30% to 40% to placebo (22).

The exact percentages depended on the criteria the patients met. Among the most important were the severity, type, and number of symptoms reported (50). Such criteria limit the determination of the percentage beneficial therapeutic effect for the entire group of women suffering from PMS.

An advantage of the use of SSRIs in the course of PMS, as opposed to their use in the treatment of depression, is their rapid effect, achieved even within days of starting medication. This indicates a different mechanism of activity than that observed in depression therapy, where measurable improvement can be observed after a few weeks of taking the drugs (46, 146, 147).

The rapid effects of SSRIs in women with PMS or PMDD are likely due to their simultaneous effects on serotonin receptors and allopregnanolone levels in the brain, thereby indirectly modulating GABAA receptor function. Increasing the efficiency of DHP conversion to allopregnanolone SSRI group drugs also alters the levels of this neurosteroid (22, 148).

The swift effects of SSRIs in treating PMS and PMDD allow them to be used not only continuously, but also intermittently (only during the luteal phase) (149). Currently, there are no studies that show a clear difference in the efficacy of SSRIs in relieving PMS, comparing administration either continuously or only during the luteal phase. However, it should be noted that at this point the number of studies is insufficient to draw confident conclusions (46). Taking SSRIs only in the luteal phase avoids the withdrawal syndrome associated with long-term antidepressant use (150).

The choice of route of administration, i.e.: continuously or only in the luteal phase in women with severe PMS or PMDD without comorbidities, may be based on patient or physician preference and individual experience of side effects occurring in a given patient (151). It is worth mentioning that it is necessary to gradually discontinue the intake of SSRI drugs when they are administered continuously (144). Otherwise, there is a risk of adverse effects, the most common of which are nausea and weakness. Marjoribanks et al. showed that there is a correlation between the dose of an SSRI and the appearance of side effects. It seems that higher doses of the drug are associated with an increased likelihood of experiencing its side effects (46).

The entire group of SSRI drugs can be used to treat premenstrual symptoms. According to the Marjoribanks et al. (46), too few studies have been conducted using a specific drug from the SSRI group to indicate significant differences in the effectiveness of PMS treatment. The choice of drug should be based on the individual clinical situation of the patient, this is to minimize the severity and frequency of adverse effects.

In the literature, it is possible to distinguish SSRI drugs for the treatment of PMS such as fluoxetine, sertraline, paroxetine, citalopram, and escitalopram, the first 3 of which are approved by the FDA (50).

The criteria for selecting patients for the study were most often similar. They included aspects such as an age range of 18 to 45 years, regular menstrual cycles of 22 to 35 days, and evidence of probable ovulation. They also included meeting the criteria for a diagnosis of PMS/PMDD, and the absence of psychiatric comorbidities. Side effects that can occur with specific SSRI drugs are typically common to the entire group. Such adverse effects as decreased libido, nausea, weakness, drowsiness, fatigue, and sweating can be mentioned (46, 50).

4.1 Fluoxetine

Preclinical studies suggest that low doses of fluoxetine may increase allopregnanolone concentrations in the brain (152).

A pilot study on the use of fluoxetine to treat PMS conducted on 40 women showed the potential to alleviate the emotional symptoms of PMS. The administration of a dose of 10 mg/day during the luteal phase of the menstrual cycle, 7 days before the probable date of menstruation, was found to yield the most favorable outcomes. This led to a reduction of emotional PMS symptoms by more than 40% in 70% of the study participants, in comparison to placebo. The study was a randomized, double-blind, placebo-controlled trial (152).

Another double-blind pilot study of 39 women reported the efficacy of fluoxetine compared to placebo and calcium. Fluoxetine and calcium carbonate were administered for a period of 4 menstrual cycles. The dose taken by the patients was 10 mg of fluoxetine twice daily. Calcium carbonate was administered at 600 mg twice a day. The study shows noticeable benefits in treating PMS with fluoxetine. Efficacy with calcium was significantly lower, although higher than with placebo. Limitations of this study were the significance achieved in only 2 of the 5 symptom assessment instruments and the small study sample. According to the authors, there is no need to further compare the efficacy of fluoxetine with calcium in the treatment of PMS (153).

A study by Hedayat et al. conducted on 100 women compared the efficacy of fluoxetine and buspirone in treating PMS. The study was single-blind. The doses the patients were given were 20 mg/d of fluoxetine in one group and 10 mg/d of buspirone in the other. In both cases, the administration period was 2 months. Both drugs showed significant efficacy in treating PMS, with no significant differences between them. The authors believe that buspirone may be a better choice for treatment, due to fewer side effects. However, a limitation related to the lack of a placebo group should be taken into account here (154).

Hunter et al. demonstrated that fluoxetine, used in the treatment of PMDD, had a faster and more effective impact on alleviating anxiety-related symptoms compared to CBT therapy. However, after six months, the effectiveness of CBT therapy and fluoxetine use yielded similar results. The combination of both treatments showed no additional benefits. Such findings may contribute to better-tailoring therapy to the unique requirements of each patient. The female participants in the study were administered a daily dose of 20 mg for six months, and the study included forty-five women (155).

A study comparing the efficacy of fluoxetine with placebo in the treatment of PMDD showed that of the side effects, only decreased libido was observed with a statistically significant higher frequency among patients taking fluoxetine. Efficacy in alleviating physical symptoms was observed only among those administered a daily dose of 20 mg of fluoxetine. The reduction in the severity of problems was estimated at 38% for the 20 mg/d group, administering the drug daily only during the luteal phase (156).

According to a study from 2003, the difference in efficacy between a dose of 20 mg/d and 60 mg/d of fluoxetine was not statistically significant. In both cases, compared to placebo, efficacy was higher. At the 60 mg/d dose, adverse effects were more common (157).

Another clinical trial also proves there are no statistical differences between the efficacy of a 20 mg/d dose and a 60 mg/d dose in treating the physical symptoms of PMDD. Statistically significant differences were observed when tolerance to fluoxetine developed, favoring the 20 mg/d dose. At the 60 mg/d dose, patients were significantly more likely to discontinue treatment due to side effects (158).

Another study involving 405 women also reported that a 60 mg/d dose of fluoxetine resulted in a higher incidence of side effects compared to a 20 mg/d dose (159).

Fluoxetine, due to its high efficacy and the relatively high number of studies compared to other SSRI drugs in the treatment of PMS/PMDD, appears to be an appropriate form of medication as a first-line drug. It is worth noting that using the lowest effective dose is advisable, considering that, in selected studies, doses as low as 10 mg effectively controlled symptoms and carried a lower risk of side effects (Table 2).

4.2 Sertraline

A 1997 study observed significant improvement in PMDD symptom relief with sertraline administered continuously. The overall evaluation showed a great or very great improvement in 62% of those given sertraline and 34% of those in the placebo group (160).

A study by Freeman et al. on the use of sertraline to treat PMS found improvements in mood and relief of physical symptoms in women using sertraline. Doses ranged from 50 mg/d to 100 mg/d. Improvements occurred as early as the first month of treatment. The study was randomized, double-blind, and placebo-controlled (151).

In a 3-month, placebo-controlled comparison of sertraline and desipramine, the study revealed a significant advantage of the SSRI drug over the noradrenergic affinity drug. The degree of improvement was measured using the Penn Daily Symptom

TABLE 2 Collected research on fluoxetine treatment in PMS.

Author, year of publication	Drug, dosage form and total daily dose	Study design	Dosage, total duration of administration	First test group	Second test group	Third test group	Fourth test group
Maranho et al. 2023 (152)	Fluoxetine capsules 2 mg or 5 mg or 10 mg	randomized, double-blind, placebo-controlled pilot	2 or 5 or 10 mg/day,7 days before the first day of cycle to the first day of following cycle	**Fluoxetine** (2 mg)10 women[18-40 years old]	**Fluoxetine** (5 mg)10 women[18-40 years old]	**Fluoxetine** (10 mg)10 women[18-40 years old]	**Placebo**10 women[18-40 years old]
Yonkers et al. 2013 (153)	Fluoxetine capsules 20 mg	randomized, double-blind, placebo-controlled, parallel	2 x 10 mg/dayduring 4 cycles	**Fluoxetine**13 women[25-45 years old]	**Calcium carbonate**13 women[25-45 years old]	**Placebo**13 women[25-45 years old]	–
Nazari et al. 2013 (154)	Fluoxetine 20 mg	randomized, single-blind	20 mg/dayfor 2 consecutive moths	**Fluoxetine**50 women[18-49 years old](38 women were included in the analysis)	**Buspirone**50 women[18-49 years old](37 women were included in the analysis)	–	–
Hunter et al. 2002 (155)	Fluoxetine tablets 20 mg	randomized, open label	20 mg/dayduring cycle for consecutive 6 moths	**CBT**24 women[20-45 years old](21 women were included in theanalysis)	**Fluoxetine**21 women[20-45 years old](19 women were included in theanalysis)	–	–
Cohen et al. 2002 (156)	Fluoxetine capsules 10 mgor 20 mg	randomized, multicenter, double-blind, placebo-controlled, parallel-group	10 or 20 mg/day, during the luteal phaseand 3 cycles (in a double-blind manner)	**Fluoxetine** (10 mg)88 women[18-45 years old](77 women were included in the analysis)	**Fluoxetine** (20 mg)86 women[18-45 years old](64 women were included in the analysis)	**Placebo**88 women[18-45 years old](75 women were included in the analysis)	–
Steiner et al. 2003 (157)	Fluoxetine20 mg or 60 mg	randomized, double-blind, placebo-	20 or 60 mg/dayduring 6 cycles	**Fluoxetine** (20 mg)104 women[18-45	**Fluoxetine** (60 mg)108 women[18-45	**Placebo**108 women[18-45 years old](94 included in analysis)	–

(Continued)

TABLE 2 Continued

Author, year of publication	Drug, dosage form and total daily dose	Study design	Dosage, total duration of administration	First test group	Second test group	Third test group	Fourth test group
		controlled, parallel		years old](94 included in analysis)	years old](85 included in analysis)		
Steiner et al. 2001 (158)	Fluoxetine20 mg or 60 mg	randomized, double-blind, placebo controlled, parallel	20 or 60 mg/ dayduring 6 cycles	**Fluoxetine** (20 mg)104 women[18-45 years old](95 included in analysis)	**Fluoxetine** (60 mg)108 women[18-45 years old](85 included in analysis)	**Placebo**108 women[18-45 years old](94 included in analysis)	–
Steiner et al. 1995 (159)	Fluoxetine20 mg or 60 mg	randomized, double-blind, placebo-controlled, (two-phase study design consisted of a single-blindwashout period)	20 or 60 mg/ dayduring 6 cycles	**Fluoxetine** (20 mg)102 women[18-45 years old](96 included in analysis)	**Fluoxetine** (60 mg)106 women[18-45 years old](86 included in analysis)	**Placebo**105 women[18-45 years old](95 included in analysis)	–

Author, year of publication	Method of data collection	Outcomes	Adverse events/ side effects	Limitations	Overall effect
Maranho et al. 2023 (152)	Daily Record of Severity Problems Scale (DRSP)	All fluoxetine groups showed greater improvement.Scores decreased in all treatment groups, but most significantly in the Fluoxetine (10 mg) group.Participants in the 10mg/day group reported a reduction in symptoms exceeding 40%.	-headache (4 women in fluoxetine groups and 2 in placebo),-increased sleep duration (1 woman in fluoxetine group and 1 in placebo),-somnolence/sedation (2 women in fluoxetine group)-nauseas and decreased sleep duration (1 woman in fluoxetine group for each AE)	-small sample size-the order of natural cycle versus intervention cycle was not counterbalanced-markers of the GABAergic system or progesterone and its metabolites in plasma not included-diagnosis of emotional PMS over single cycle not two-short duration of the study	positive
Yonkers et al. 2013 (153)	Daily Record of Severity Problems Scale (DRSP), The Inventory of Depressive, Symptomatology, Premenstrual Tension Scale,Clinical Global Impression- Severity and Improvement scales,last-observation-carried forward method	In IDS-LOCF and PMTS-LOCF women in the fluoxetine group showed improvement in symptoms compared to the placebo group.	-nausea (1 woman in fluoxetine group, 4 in calcium group and 2 in placebo),-headache (1 woman in fluoxetine group, 3 in calcium group and 2 in placebo),-dry mouth (2 woman in fluoxetine group),-feeling spacy (2 woman in calcium group),-dizziness (1 woman in fluoxetine group and 2 in calcium),-fatigue (1 woman in calcium group),-irritability (1 woman in placebo group) and more*	-fluoxetine group had greater baseline severity on the DRSP-small sample size-recruitment via media advertisements-short duration of the study-single dosing regimen	positive
Nazari et al. 2013 (154)	The PMS diary,a self-assessment symptom rating scale	Both fluoxetine and buspirone demonstrated significant effectiveness in treating patients.	not investigated	-no placebo group-short duration of the study-single dosing regimen	positive
Hunter et al. 2002 (155)	The HADS,Causal attributions, The Coping Checklist, Ten-point Likert scales, Open-ended questions regarding the helpful and unhelpful aspects of the treatment, COPE measure	While both fluoxetine and the other treatment achieved similar overall effectiveness after 6 months, fluoxetine appeared to have a stronger effect on reducing anxiety symptoms.	gastrointestinal symptoms and loss of libido in fluoxetine group,more information not mentioned	-no placebo group-small sample size-recruitment via advertisements in newspapers and magazines-single dosing regimen	positive

Report (DSR), indicating that symptoms decreased by more than 50% in 65% of the women studied (161).

According to a 2015 study, which investigated the efficacy of sertraline, including a placebo, on 188 women, treatment with this SSRI drug is not universally effective when administered *ad hoc*. The study utilized doses of 50 mg/d and 100 mg/d of sertraline (162).

A 2006 randomized clinical trial involving 314 women suggests the effectiveness of sertraline in alleviating moderate to severe PMS symptoms. Patients received sertraline throughout the luteal phase for the first two cycles, followed by continuous administration for one cycle and initiation of treatment at the onset of symptoms for one cycle. The doses used were 25 mg/d and 50 mg/d. Each mode of administration exhibited comparable efficacy, with the lower dose of 25 mg/d showing a favorable outcome (163).

According to the study by Freeman et al., the recurrence rate of PMS symptoms was significantly higher after short-term treatment compared to long-term treatment with sertraline. However, it should be noted that prolonged treatment also exhibited a high rate of symptom recurrence. Patients experiencing severe symptoms at the beginning of medication indicated the highest risk of relapse, regardless of the treatment duration. This study suggests that the high severity of complaints (before the start of treatment) is a marker for a worse prognosis in patients. The dosage used in this study ranged from 50 mg/d to 100 mg/d of sertraline (164).

On the other hand, the Yonkers et al. study shows no evidence of sertraline withdrawal symptoms after sudden discontinuation after 2 weeks of treatment for 2 cycles. This correlates with the theory cited above that short-term administration of sertraline is less likely to be fraught with side effects. The dose used ranged from 50 mg/d to 150 mg/d of sertraline, but the researchers did not consider the severity of initial symptoms (165).

According to a 2004 study, a dosing regimen (either continuous or luteal phase only) using 50 mg/d to 100 mg/d of sertraline does not show differences in efficacy for treating PMS/PMDD (151).

Due to the risk of relapse documented in the studies discussed above, this drug appears to be slightly inferior to fluoxetine. It should be noted that sertraline, in most studies, demonstrated efficacy in selected patients even at doses as low as 25 mg, emphasizing the necessity of individualizing therapy. Initiating therapy with a lower dose could potentially reduce symptoms and the risk of withdrawal syndrome, consequently lowering the risk of relapse, assuming its efficacy (Table 3). Moreover, sertraline has a shorter half-life than fluoxetine, which means it could be more convenient to use during luteal phase (166).

4.3 Paroxetine

A multicenter study using a placebo and paroxetine yielded a result indicating that paroxetine was effective in relieving PMDD symptoms. The study involved 327 women. Paroxetine was administered at doses of 12.5 mg/d or 25 mg/d or placebo once daily for three treatment cycles. The method for evaluating efficacy was the VAS-Mood score (focusing on symptoms such as irritability, tension, affective lability, and depressed mood) during the luteal phase. Both doses of paroxetine were found to be effective according to the VAS-Mood scale (167).

A clinical trial conducted by Landen et al. in 2006 demonstrated that continuous treatment of PMDD with paroxetine effectively reduced symptoms such as irritability, achieving a response rate of 85% compared to the placebo. Luteal-phase-only treatment showed comparable effectiveness to continuous administration for symptoms like irritability, affect lability, and mood swings. A modest effect on reducing the severity of symptoms was observed for depressed mood and somatic symptoms. Dosages ranging from 10 mg/d to 20 mg/d were utilized (168).

A 2008 study demonstrated the effectiveness of treating PMDD with paroxetine at a dose of 20 mg/d. The continuous treatment group achieved a response rate ranging from 50% to 78.6%, while the intermittent treatment group achieved a response rate ranging from 37.5% to 93.8%. The study was subject to limitations, including a small sample size of 36 participants and the absence of a placebo group (169).

In the Steiner et al., 2005 study, within the group using paroxetine during the luteal phase at a dose of 25 mg, at least one side effect was observed in 76.7% of patients. At a dose of 12.5 mg, it was observed in 67.7% of subjects. In the placebo trial, this percentage was 56.7%. The most commonly observed side effects associated with taking paroxetine were nausea, asthenia, headaches, and decreased libido (170).

According to the Landén et al., 2008 study, paroxetine demonstrates a rapid reduction in symptoms, which is uncommon for a serotonin-dependent antidepressant. Such a swift response to treatment has not been observed previously (146).

Paroxetine has shown high efficacy in treating premenstrual symptoms, although its use is associated with the frequent occurrence of at least one side effect (Table 4). It may emerge as an alternative to classical treatments for some patients due to its notably rapid action and very high efficacy.

4.4 Escitalopram

A study by Eriksson on the efficacy of escitalopram suggests a higher effectiveness of this drug than a placebo. The study involved 151 women, and the drug was administered intermittently for 3 months, only during the luteal phase. The doses used were 10 mg/d and 20 mg/d. The use of the 20 mg/d dose showed a symptom-reducing effect of up to 90%. The primary measurements focused on the sum of symptoms such as irritability, depressed mood, tension, and affective lability. Irritability alone, considered the main symptom of PMDD in this study, was reduced by 80% compared to the placebo group — a reduction of 30%. Side effects, such as nausea and reduced libido, were not observed more frequently in patients receiving escitalopram at 20 mg/d than in those receiving a lower dose (46, 171).

The Freeman et al., 2005 study also demonstrated the efficacy of treating PMDD with escitalopram at doses ranging from 10 mg/d to 20 mg/d. However, the study was constrained by limiting factors, such as a low number of participants and the absence of a placebo trial (172).

Escitalopram, due to the limited number of available studies, cannot be conclusively evaluated as an effective drug for the treatment of PMS (Table 5).

TABLE 3 Collected research on sertraline treatment in PMS.

Author, year of publication	Drug, dosage form and total daily dose	Study design	Dosage, total duration of administration	First test group	Second test group	Third test group
Yonkers et al. 1997 (160)	**Sertraline hydrochloride** capsules 50 mg or 100 mg or 150 mg	1 cycle: single-blind, placebo-controlled3 cycles: randomized, double-blind, placebo-controlled	50 or 100 or 150 mg/day (If response was insufficient, dose was increased or matching placebo)during luteal phase	**Sertraline**121 women[24-45 years old](99 included in analysis)	**Placebo**122 women[24-45 years old](101 included in analysis)	–
Freeman et al. 1999 (161)	**Sertraline hydrochloride** capsules 50 mg or 100 mg or 150 mg	randomized, double-blind, placebo-controlled, parallel	50 or 100 or 150 mg/day (If response was insufficient, dose was increased) during 3 cycles	**Sertraline**62 women[18-45 years old]	**Desipramine hydrochloride** 50 women[18-45 years old]	**Placebo**55 women [18-45 years old]
Freeman et al. 2004 (151)	**Sertraline hydrochloride**tablets 50 mg or 100 mg	stratified, randomized, double-blind, placebo-controlled, parallel	50 or 100 mg/day (In the second or third cycle dose was increased to 100 mg) during 3 cycles (continuous or luteal phase dosing)	**Sertraline (Full- Cycle Dosing)** 56 women [18-45 years old](40 women included in analysis)	**Sertraline (Luteal- Phase Dosing)**56 women[18-45 years old](35 women included in analysis)	**Placebo**55 women [18-45 years old] (43 women included in analysis)
Yonkers et al. 2015 (162)	**Sertraline hydrochloride**capsules 50 mg or 100 mg	double-blind, placebo-controlled, multisite, parallel-group, randomized, clinical	50 or 100 mg/day (If response was insufficient, dose was increased to 100 mg) from symptom-onset until the first few days of menses dosingduring 6 cycles	**Sertraline**125 women[18-40 years old]	**Placebo**127 women[18-40 years old]	–
Kornstein et al. 2006 (163)	**Sertraline hydrochloride** 25 mg or 50 mg	double-blind, placebo-controlled, randomized	25 or 50 mg/dayduring 4 cycles (luteal-phase and/or continuous and/or symptom-onset dosing)	**Sertraline** (25 mg)98 women [18-40 years old](74 women completed)	**Sertraline** (50 mg)97 women [18-40 years old] (77 women completed)	**Placebo**101 women[18-40 years old](79 women completed)
Freeman et al. 2009 (164)	**Sertraline hydrochloride** 50 mg or 100 mg	randomized, stratified, double-blind, placebo-controlled	50 or 100 mg/dayluteal-phase starting on day 14 before expected day of menses to menstrual day dosingduring 4 or 12 months (treatment group were studied for 18 months)	**Sertraline short-term** (drug for 4 months, placebo for 14 months) 87 women[18-45 years old](76 women were included in the analysis)	**Sertraline long-term** (drug for 12 months, placebo for 6 months) 87 women[18-45 years old](84 women were included in the analysis)	–
Yonkers et al. 2005 (165)	**Sertraline hydrochloride** pill 50 mg or 100 mg or 150 mg	randomized, double-blind, placebo-controlled	50-150 mg/day (continuous dosing) or50-100 mg/day (luteal-phase starting on day 14 before expected day of menses dosing)during 3 cycles	**Sertraline (luteal- phase)** and placebo 281 women[24-45 years old]	**Sertraline (continuous)**and placebo 251 women[24-45 years old]	–

(Continued)

TABLE 3 Continued

Author, year of publication	Method of data collection	Outcomes	Adverse events/ side effects	Limitations	Overall effect
Yonkers et al. 1997 (160)	The Daily Record of Severity of Problems,Hamilton Rating Scale for Depression, Clinical Global Impression Scale, Social Adjustment Scale	Participants taking sertraline experienced a significant decrease in their total daily symptom scores compared to those in the placebo group (depression, physical symptoms, and anger/irritability). The HDRS scores decrease in the sertraline group (44%) and in the placebo group (29%).	-adverse events occurred more frequently in the sertraline group than in the placebo group,-events occurring were: headache, nausea, insomnia, diarrhea, fatigue, and decreased libido	-the study cohort may not be generalizable to women with other psychiatric illnesses or to women with less severe PMS-regular monitoring through clinic visits and daily ratings could contribute to improved therapeutic response	positive
Freeman et al. 1999 (161)	Penn Daily Symptom Report (DSR), Hamilton Depression Rating Scale, Clinical Global Impressions–Severity Scale, Quality of Life Scale,Patient Global Ratings of Functioning and Improvement	Improvement were observed in all DSR factors with sertraline compared with desipramine and placebo, significantly for factors like mood and pain.DSR symptoms had decreased by more than 50% in 65% women in sertraline group, 36% in desipramine and 29% in placebo.	-adverse events occurred more frequently in the sertraline and desipramine group than in the placebo group,-sertraline resulted in a significantly higher incidence of nausea compared to the placebo group-conversely, dry mouth, dizziness, and constipation were significantly more frequent in the desipramine group compared to placebo.	-the study cohort may not be generalizable to women with other psychiatric illnesses or to women with less severe PMS	positive
Freeman et al. 2004 (151)	Daily Symptom Rating Form score and patient global ratings of functioning	Both groups of sertraline improved significantly more than the placebo group in DSRF scores (mood and physical symptoms were significantly more improved).Dosing with sertraline does not differ between continuous and premenstrual in PMS treatment.	-7 women from the full-cycle sertraline group, 5 women from the luteal-phase and 1 from placebo withdrawing from the study,-most frequent adverse events were gastrointestinal, decreased libido or orgasm, headache, insomnia, dry mouth, nausea, and nightmares	-the study cohort may not be generalizable to women with other psychiatric illnesses or to women with less severe PMS-small number of subjects with high postmenstrual symptom levels	positive

(Continued)

TABLE 3 Continued

Author, year of publication	Method of data collection	Outcomes	Adverse events/ side effects	Limitations	Overall effect
Yonkers et al. 2015 (162)	Premenstrual Tension Scale (PMTS) score,Inventory of Depressive Symptomatology–Clinician-Rated, Daily Record of Severity of Problems (DRSP), Clinical Global Impression (CGI) scales,Michelson SSRI (Selective SRI)Withdrawal Symptoms Scale scores	PMTS and CGI-S scores showed no significant differences.Symptom improvement was better with sertraline compared to placebo when measured by the IDS-C, CGI-I and DRSP	- nausea and difficulty sleeping occurred more frequently in the sertraline group	-maximum dose of 100 mg of sertraline hydrochloride-cohort size not meeting power estimates-attention and labor involved in charting symptoms may not be easily replicated in clinical settings	neutral/ po sitive
Kornstein et al. 2006 (163)	Daily Symptom Report (DSR), Clinical Global Impressions-Severity of Illness and -Improvement scales,Patient Global Evaluation scale, Quality of Life Enjoyment and Satisfaction Questionnaire, Social Adjustment Scale-Self Report	Improvement were observed in total DSR scores for Intermittent luteal-phase sertraline dosing (25 mg/d - 50 mg/d) compared with placebo (across 2 cycles). Continuous and symptom-onset dosing were also effective (25 mg/d)	-most common adverse effects in all groups were: insomnia, nausea, headache	-homogeneity of the sample in terms of absence of medical and psychiatric comorbidity-short duration of the study-sequential design	positive
Freeman et al. 2009 (164)	total premenstrual DSR scores, Structured Clinical Interview, Hamilton Depression Rating Scale score,demographic variables	There were no significant differences in discontinuation rates between the two sertraline groups.Improvement was observed in 72% of patients in sertraline group.Patients in the short-term group and with low symptom severity were more likely to experience improvement in their symptoms.	-most frequent adverse effects were insomnia, nausea, fatigue, headache, decreased libido or orgasm and changes in appetite,	-definition of relapse is conservative in requiring that symptoms return to the study eligibility level and may underestimate the rate of relapse-results maynot be generalizable to all women with premenstrualsymptoms-the study did not explore alternative dosing strategies or investigate other treatment options for patients who relapsed or showed no improvement	positive
Yonkers et al. 2005 (165)	Daily Record of Severity of Problems (DRSP)	Administration of active medication during the luteal phase effectively reduced total DRSP scores, regardless of whether participants continued taking the medication throughout their entire cycle or stopped at the beginning of their period.	not mentioned	-researchers did not consider the severity of initial symptoms- the nine-item withdrawal factor has not been validated, and several key withdrawal symptoms were not ratedin the DRSP-withdrawal factor	positive

TABLE 4 Collected research on paroxetine treatment in PMS.

Author, year of publication	Drug, dosage form and total daily dose	Study design	Dosage, total duration of administration	First test group	Second test group	Third test group
Cohen et al. 2004 (167)	Paroxetine CR12.5 mg or 25 mg	multicenter, randomized, double-blind, placebo-controlled, fixed-dose	12.5 or 25 mg/day, during 3 cycles (continuously)	**Paroxetine** (12.5 mg)103 women[18-45 years old](70 women completed)	**Paroxetine** (25 mg) 113 women[18-45 years old](72 women completed)	**Placebo**111 women [18-45 yearsold] (79 women completed)
Landén et al. 2007 (168)	Paroxetine capsules 10 mgor 20 mg	randomized, double-blind, placebo-controlled, 3 parallel groups	10 or 20 mg/day (firstand last 4 days was 10 mg)during 3 cycles (luteal- phase only or continuously)	**Paroxetine-continuous (PC)**60 women[≧18 years old](51 women completed)	**Paroxetine-intermittent (PI)**59 women[≧18 years old](55 women completed)	**Placebo (PBO)**59 women[≧18 years old] (51 women completed)

(Continued)

TABLE 4 Continued

Author, year of publication	Drug, dosage form and total daily dose	Study design	Dosage, total duration of administration	First test group	Second test group	Third test group
Wu et al. 2008 (169)	Paroxetine capsules 20 mg	randomized, controlled, open-label, parallel design, non-blinded, prospective	20 mg/dayfor 2 cycles(continuously), then during 4 cycles (luteal-phase only or continuously)	**Paroxetine-continuous** (first 2 cycles) 36 women[18-45 years old]	**Paroxetine-continuous** (4 cycles)14 women [18-45 years old]	**Paroxetine-intermittent**(4 cycles) 16 women[18-45 years old]
Steiner et al. 2005 (170)	Paroxetine CR12.5 mg or 25 mg	multicenter, randomized, double-blind, placebo-controlled, fixed-dose	12.5 or 25 mg/ dayfor up to 3 cycles (luteal- phase)	**Paroxetine** (12.5 mg)130 women[18-45 years old](104 women completed)	**Paroxetine** (25 mg) 116 women[18-45 years old](87 women completed)	**Placebo**120 women [18-45 years old] (101 completed)
Landén et al. 2009 (146)	Paroxetine capsules 20 mg	randomized, double-blind, placebo-controlled, crossover trial	20 mg/dayfrom date around ovulation to 3 day of menstruationduring 3 cycles (one of three cycles was alwaysplacebo)	**Placebo** -> **Paroxetine** -> **Paroxetine**8 women[≱18 years old](7 women completed)	**Paroxetine** -> **Placebo** -> **Paroxetine**7 women [≱18 years old](7 women completed)	**Paroxetine** -> **Paroxetine** -> **Placebo** 7 women[≱18 years old](7 women completed)

Author, year of publication	Method of data collection	Outcomes	Adverse events/ side effects	Limitations	Overall effect
Cohen et al. 2004 (167)	Visual Analogue Scale-Mood (irritability, tension, affective, CGI-I lability, depressed mood) score	Both groups of paroxetine showed significant improvement (also for physical symptoms and social functioning) in VAS-Mood scores compared to placebo group.	-adverse events occurred in all groups, but to the least extent in placebo,-most frequent adverse effects were asthenia, libido decreased and female genital disorders	-short duration of the study- the primary outcome measure was patient-rated	positive
Landén et al. 2007 (168)	VAS and PMTS-O scales, CGI-I and PGE scales	Both groups of paroxetine showed significant improvement (significantly in irritability, affect lability, mood swings, depressed mood and tension) in VAS-Mood scores compared to placebo group. Intermittent treatment was as effective as continuoustreatment for certain symptoms.	-nausea, headache, somnolence and more side effects occurred in all groups	- VAS-rated symptoms other than irritability were not defined as primary effect parameters-short duration of the study	positive
Wu et al. 2008 (169)	Prospective Record of the Impact and Severity of Menstrual Symptomatology (PRISM) calendar, HAMD, HAMA, Zung-SDS, STAI, and CGI-S	Paroxetine was effective in improving symptoms of PMDD in both treatment groups, with response rates varying between the two groups, and the effects lasting for six consecutive menstrual cycles.	not mentioned	-open-label design-lack of placebo group-small sample size	positive
Steiner et al. 2005 (170)	observer-rated PremenstrualTension Scale (PMTS-O), global assessment of disease severity (CGI-S, Severity of Illness item),global assessment of disease improvement (CGI-CI,	Paroxetine was effective in treating PMDD symptoms at both groups. Patients taking paroxetine CR showed significant improvement in both the main measure of effectiveness and in additional symptom measures compared to those taking a placebo.	-adverse event occured in all groups,-most frequent adverse effects were nausea, asthenia, headache and libido decreased	-lack of a direct comparison study between continuous and intermittent administration of paroxetine CR-short duration of the study-The study did not	positive

(Continued)

TABLE 4 Continued

Author, year of publication	Method of data collection	Outcomes	Adverse events/ side effects	Limitations	Overall effect
	Global Improvement item),patient global evaluation (PGE), patient-rated assessment of			explore the long-term effects or efficacy of luteal phase dosing with paroxetine CR	
Landén et al. 2009 (146)	self-rated irritability using a VAS,serum levels of paroxetine, patient-rated CGI-I	Paroxetine was found to be effective in reducing irritability.	- in the first paroxetine treatment cycle, 68.2% reported experiencing nausea at least once.-4 hours after taking medication/placebo the difference in the number of subjects experiencing nauseareached statistical significance	-small sample size-considerable number of nonresponders-short duration of the study-only one adverse effect studied-inability to draw conclusions about the feasibility of symptom-onset dosing for premenstrual symptomsother than irritability	positive

TABLE 5 Collected research on escitalopram treatment in PMS.

Author, year of publication	Drug, dosage form and total daily dose	Study design	Dosage, total duration of administration	First test group	Second test group	Third test group
Eriksson et al. 2008 (171)	Escitalopramtablet (as the oxalate salt) 10 mg or 20 mg	randomized, parallel-group, placebo-controlled, double-blind, single-center	10 or 20 mg/day,for 3 cycles (intermittently during luteal phases)	**Escitalopram 10 mg**(first 2 days with 5 mg)54 women[≧18 years old] (50 women wereincluded in analysis)	**Escitalopram 20 mg**(first day 5 mg, second day 10 mg)53 women[≧18 years old](51 women were included in analysis)	**Placebo**51 women[≧18 years old](50 women were included in analysis)
Freeman et al. 2005 (172)	Escitalopram 10 mg or 20 mg	randomized, double-blind, preliminary	11 or 20 mg/dayfor 3 cycles (during luteal phases or symptom-onset)	**Escitalopram** luteal- phase13 women[≧18 years old]	**Escitalopram** symptom-onset (first 2 days with 5 mg)14 women[≧18 years old]	–

Author, year of publication	Method of data collection	Outcomes	Adverse events/ side effects	Limitations	Overall effect
Eriksson et al. 2008 (171)	self-assessed VAS,10-item Premenstrual Tension Syndrome Scale– Observer Rating (PMTS-O), Sheehan Disability Scale,Clinical Global Impression–Severity (CGI-S) scale, Clinical Global Impression–Improvement (CGI-I) scale, Patient Global Evaluation (PGE)(SDS)	reduction of irritability, depressed mood, tension, and affective lability with 20 mg/day dose	the most frequent adverse effects were nausea, fatigue, dry mouth and decrease in sexual interest in all groups	-high placebo response rate-short duration of the study-lack of comparison with continuous treatment-no exploration of long-term effects or relapse rates	positive
Freeman et al. 2005 (172)	17-item Penn Daily Symptom Report (DSR), Clinical Global Impressions-Improvement scale, Hamilton Rating Scale for Depression, Sheehan Disability Scale	a significant improvement of DSR score in both groups,a significant clinical improvement in both groups	Escitalopram was associated with good tolerability. Side effects were minor and short- lived, with only two participants discontinuing treatment due to medication-relatedadverse events	-small sample size-short duration of the study-lack of placebo group	positive

4.5 Citalopram

In a 1998 study by Wikander et al., examining how the use of citalopram affects the treatment of premenstrual dysphoria with severe irritability, pharmacological medication was shown to be more effective than placebo. The drugs were administered either continuously or during the luteal phase only. The study revealed that the administration of the 20 mg drug during the luteal phase alone led to better control of irritability and improvement in well-being compared to continuous use of the drug (173).

Another study, in turn, demonstrated that citalopram administered as needed, in doses ranging from 10 mg/d to 20 mg/d, also showed efficacy in relieving PMDD symptoms (174).

On the other hand, Freeman et al. suggest that the treatment of PMS with citalopram is effective for patients in whom prior treatment with SSRIs has failed, whether used throughout the entire menstrual cycle or only during the luteal phase (175).

Studies on the treatment of PMS or PMDD with citalopram are riddled with limitations, including small subject numbers and insufficient independent research, hindering a comprehensive evaluation of citalopram's efficacy in PMS treatment (Table 6). Most studies underscore the effectiveness of citalopram when used intermittently—specifically, during the luteal phase of the monthly cycle.

4.6 Venlafaxine

A randomized controlled double-blind clinical trial evaluating the efficacy of venlafaxine as a representative of the SNRI group demonstrated its significant superiority over placebo in reducing PMDD symptoms. The study included 143 women who were administered venlafaxine for four menstrual cycles at doses ranging from 50 to 200 mg/d. In the group receiving the drug,

TABLE 6 Collected research on citalopram treatment in PMS.

Author, year of publication	Drug, dosage form and total daily dose	Study design	Dosage, total duration of administration	First test group	Second test group	Third test group	Fourth test group
Wikander et al. 1998 (173)	Citalopramcapsule 10 mg or 20 mg or 30 mg	randomized, double-blind, placebo-controlledwith 4 parallel groups	10mg or 20mg or 30 mg/day (based on side effects and symptom improvement, base dose-20 mg)during 3 cycles (continuous or semi-intermittent or intermittent)	**Citalopram continuous (CC)**19 women [≧18 years old](17 women included in analysis)	**Citalopram semi-intermittent (CS)**20 women [≧18 years old] (17 women included in analysis)	**Citalopram Intermittent (CI)**19 women [≧18 years old] (18 women included in analysis)	**Placebo (PL)**20 women [≧18 years old] (17 women included in analysis)
Ravindran et al. 2007 (174)	Citalopram10 mg or 20 mg	single-center open naturalistic flexible-dose	10 or 20 mg/dayduring 2 cycles	**Citalopram** symptom-onset7 women [18-45 years old](6 women completed)	–	–	–
Freeman et al. 2002 (175)	Citalopram20 mg or 40 mg	randomized naturalistic open-label	20 or 40 mg/dayduring 3 cycles (half or full)	**Citalopram** (half-cycle, 20-40 mg)11 women[18-45 years old]	**Citalopram** (full-cycle 10-20 mg)6 women [18-45 years old]	–	–

Author, year of publication	Method of data collection	Outcomes	Adverse events/ side effects	Limitations	Overall effect
Wikander et al. 1998 (173)	Daily symptom self-ratings using VAS,measurement of serum concentrations of citalopram, intent-to-treat analysis	significant improvement in the CC and CI groups over the PL group,the global self-rating seemed better in the CI group than in the CI and the CS groups	Few participants stopped treatment due to side effects: headache (1 in CC, 1 in CI), sedation (2 in CS, 1 each in CC, PL), and anxiety/tension (1 in CC, 1 in PL), side effects being uncommon, mild, and short-lived.Reduced sex drive, dry mouth, and sweating were the most frequently reported issues.	-small sample size-short duration of the study-flexibility in dosage may impact the expected relationship between dose intake and serum levels	positive
Ravindran et al. 2007 (174)	Premenstrual tension scale	symptoms improved significantly compared to before treatment,significant improvement	3 participants taking the 20 mg dose experienced restlessness,	-small sample size-relatively brief duration	positive

(Continued)

TABLE 6 Continued

Author, year of publication	Method of data collection	Outcomes	Adverse events/ side effects	Limitations	Overall effect
	(PMTS-O),Clinical Global Impression of Improvement (CGI)	in the CGI scale and PMTS-O scores in both cycles	dizziness, nausea, and diarrhea.1 person on the 10 mg dose reported mild anxiety and restlessness.	of follow-up-short duration of the study-lack of placebo group	
Freeman et al. 2002 (175)	Total premenstrual Daily Symptom Report (DSR) scores, Hamilton Depression Rating Scale (HAM-D-29)	significant improvement in total DSR scores and HAM-D-29 scores in both (half-cycle and full-cycle) treatment groups	12 participants during the first cycle reported nausea, insomnia, dry mouth, and general digestive issues (each reported by 4 participants),the occurrence of side effects did not differbetween the half-cycle (64%) and full-cycle (63%) dosing groups.	-small study group-uncontrolled and unblinded trial design-previous SSRI failure determined in uncontrolledconditions	positive

60% of patients experienced symptom relief, compared to 35% in the placebo group (176).

A study by Cohen et al. suggests that venlafaxine is effective and well-tolerated in the treatment of PMDD at doses ranging from 75 mg/d to 112.5 mg/d. However, this open-label study is significantly limited by a small sample size (177).

The study by Hsiao et al. also indicates the efficacy of venlafaxine in the treatment of PMDD. Patients reported relief from symptoms such as anxiety and depression. Doses ranging from 18.25 mg/d to 150 mg/d were used. However, the study was limited by a small number of participants and excessive variability in the doses administered, which were modified by the patients themselves (178).

Venlafaxine appears to be effective in treating premenstrual symptoms such as anxiety and depression, but the limited number of studies is a significant drawback, preventing a comprehensive evaluation of the drug's effectiveness. It should be noted that the effect of venlafaxine at the doses used in the studies primarily corresponds to an enhancement of serotonergic rather than noradrenergic conduction. It is plausible to consider the use of this drug in cases of high intolerance to SSRI drugs as an alternative in the treatment of PMS/PMDD.

4.7 Duloxetine

Duloxetine is a medication that is not only used in the treatment of psychiatric disorders but is also indicated for alleviating painful physical symptoms that may accompany depression (179). This suggests, in combination with its serotonergic component, that the drug could be effective for PMS associated with increased pain.

Ramos et al. present two female patients suffering from PMDD. In the case of one patient who had an isolated premenstrual disorder, there was an improvement of up to 94% in the premenstrual DRSP score with a daily dose of 60 mg. On the other hand, the second patient, being treated for Major Depressive Disorder (MDD), continued to experience severe mental symptoms despite previous psychiatric treatment, including venlafaxine 375 mg/d and clomipramine 150 mg/d. After the administration of 120 mg/d duloxetine, not only was there a satisfactory control of depression observed but, notably, the patient did not manifest premenstrual symptoms for the first time (180).

In contrast, a study by Mazza et al. indicated that duloxetine at a dose of 60 mg caused a significant improvement in symptoms (50% improvement) in almost 80% of patients. However, this study did not include a placebo group. Significantly notable was the elevated rate of improvement within a brief timeframe—following the initial two cycles during which the patients underwent drug administration (181). Another single-blind study demonstrated a swift clinical response in female patients, manifesting as early as the first cycle when duloxetine was administered at a dosage of 60 mg (182).

Duloxetine is a drug characterized by a dual mechanism of action that is particularly beneficial in the context of heightened physical pain. It is feasible to administer a relatively low dose of 60 mg/d. Adverse effects were observed in a small percentage of subjects, encompassing symptoms such as nausea, insomnia, decreased libido, and reduced appetite. However, it is crucial to acknowledge that studies evaluating this substance are hampered by significant limitations, including the absence of double-blinding, a limited cohort of female patients, or the complete absence of a placebo group. Further investigations employing double-blind, placebo-controlled trials are imperative to advance our understanding.

4.8 Buspirone

Buspirone affects serotonergic conduction through the 5HT1A receptor and also has properties that affect dopaminergic pathways (183). Both of these actions suggest a potential use of the drug in the treatment of PMS and PMDD.

In a single-blind study, Nazari et al. compared buspirone 10 mg/d with fluoxetine 20 mg/d, demonstrating that both formulations were effective with no advantage for either of them. However, it is conceivable that buspirone, due to its lower rate of side effects, may be the preferred drug to fluoxetine (154). Nevertheless, the study lacked a control group and had a short duration of 2 months. Conversely, another study comparing buspirone and nefazodone found that buspirone showed a better treatment effect than placebo, in contrast to nefazodone (184).

The limited number of studies and the absence of double-blind trials constrain the robustness of utilizing this substance. However, it appears to be effective and may be considered an option for certain patients.

4.9 Conclusion

In conclusion, SSRI drugs are highly effective in treating PMS and PMDD, particularly the irritability associated with the syndrome. Their use is linked to relatively mild side effects, which can be mitigated by employing the drugs intermittently. These characteristics justify their use as first-line drugs in the treatment of PMS. Fluoxetine demonstrates significant therapeutic efficacy and induces relatively few side effects at therapeutic doses in a luteal-phase-only regimen. Moreover, fluoxetine has undergone extensive study for PMS treatment, making it the most suitable drug for managing the disorder. Paroxetine also exhibits high efficacy in treating PMS, though its elevated rate of side effects renders it less preferable compared to fluoxetine.

Sertraline, due to its high rate of symptom recurrence, does not appear to be the best drug for treating premenstrual symptoms. Assessing the actual effectiveness of escitalopram, citalopram, and venlafaxine in the treatment of PMS is challenging due to the small number of studies and the limited number of participants. However, the selection of a particular SSRI drug should be based on individual patient preference and adjusted for efficacy and tolerability, as mentioned by the authors of the 2013 Marjoribanks et al. review (46). The treatment regimen should also be based on the patient's needs. While it can be assumed that other SSRI drugs are also effective, they may differ in the occurrence of side effects. It is presumed that all doses used in the cited studies are effective in treating PMS. However, there is a correlation indicating that the incidence of SSRI side effects increases with dosage, making high doses potentially intolerable for patients. It is noteworthy that a significant number of patients with PMS were administered doses that were akin to those utilized in the treatment of affective disorders. Doses developed theoretically for a more severe disorder and on groups, typically not including women, can often be too high. This is worth bearing in mind, as individual studies using lower doses in selected cases have proven effective and reduced the risk of side effects.

5 Herbal treatment

Most of the herbal research is fraught with significant limitations, constraining the ability to arrive at conclusive evaluations (Table 7). The predominant focus in existing studies centers around VAC, saffron, and curcumin.

TABLE 7 Collected research on selected herbs in PMS.

Author, year of publication	Herb, dosageform and total daily dose	Study design	Dosage,total duration of administration	First test group	Second test group
Ozgoli et al.2009 (185)	***Ginkgo biloba L.***coated tablets, 120 mg	randomized, single-blind, placebo-controlled	3 x 40 mg/dayfrom day 16 of the cycle to day 5 of the next cycle, during 2 menstrual cycles	**Ginkgo tablets**45 women [18-30 years old](43 women were included in the analysis)	**Placebo**45 women [18-30 years old](42 women were included in the analysis)
Sharifi et al.2014 (186)	**Chamomile *(Matricaria chamomila)*** capsules, 300 mg	prospective, randomized, double blind	3 x 100 mg/dayfor 7 days,during 2 menstrual cycles	**Chamomile capsules**59 women [18-35 years old](45 women were included in the analysis)	**Mefenamic acid capsules (MA), 250 mg**59 women [18-35 years old](45 women were included in the analysis)
Yamada and Kanba 2007 (187)	**Tsumura kampo medicine, kamishoyosan (TJ- 24)**extract granules 7,5 g	open-labeled pilot study	3 x 2.5 g/day during 6 menstrual cycles	30 women [18-48 years old](26 women were included in the analysis)	–
Jung-Gum et al.2010 (188)	**St. John's wort (SJW) (Hypericum perforatum)** tablets 600 mg	randomized double-blind placebo-controlled	2 x 300 mg/day during 2 menstrual cycles(6 weeks)	**SJW**25 women [20-30 years old]	**placebo**26 women [20-30 years old]

(Continued)

TABLE 7 Continued

Author, year of publication	Herb, dosageform and total daily dose	Study design	Dosage,total duration of administration	First test group	Second test group
Canning et al.2010 (189)	**St John's Wort (Hypericum perforatum)**coated tablets 900 mg	randomized, double-blind, placebo-controlled, crossover	2 x 450 mg/day during 2 menstrual cycles	**Hypericum perforatum (2 cykle) → washout (1 cykl) → placebo (2 cykle)** 19 women [18-45 years old](17 women were included in the analysis)	**placebo (2 cykle) → washout (1 cykl) → Hypericum perforatum (2 cykle)**17 women [18-45 years old](15 women were included in the analysis)
Stevinson and Ernst 2000 (190)	**St John's Wort *(Hypericum perforatum)*** tablets 300 mg (standardised to 900µg hypericin)	prospective, open, uncontrolled, observational pilot study	1 x 300 mg/day during 2 menstrual cycles	25 women [18-50 years old](19 women were included in the analysis)	–
Farahmand et al.2020 (191)	**Anise (*Pimpinella Anisum*)** capsules 330 mg	randomized double-blind placebo, controlled	3 x 110mg/dayfrom day 21 of the cycle to day 3 of the next cycle (10 days in total) during 2 menstrual cycles	**Anise capsules**42 women [18-35 years old] (35 women were included in the analysis)	**placebo**42 women [18-35 years old] (32 women were included in the analysis)
Farahmand et al.2020 (192)	**Echium amoenum (EA)** capsules 450 mg	randomized double-blind placebo, controlled	3 x 150mg/dayfrom day 21 of the cycle to day 3 of the next cycle (10 days in total) during 2 menstrual cycles	**EA capsules**42 women [18-35 years old] (37 women were included in the analysis)	**placebo**42 women [18-35 years old] (32 women were included in the analysis)
Khayat et al.2014 (193)	**Ginger (Zingiber officinale)** capsules 500 mg	randomized double-blind placebo-controlled	2 x 250mg/dayfrom day 21 of the cycle to day 3 of the next cycleduring 3 menstrual cycles	**Ginger**35 women [18-35 years old] (33 women were included in the analysis)	**placebo**35 women [18-35 years old] (33 women were included in the analysis)
Akbarzadeh et al.2015 (194)	**Melissa (Melissa officinalis)** capsules 1200 mg	randomized double-blind placebo-controlled	2 x 600mg/day during 3 menstrual cycles	**melissa**50 women [average age - 16 years] (50 women were included in the analysis)	**placebo**50 women [average age - 16 years] (50 women were included in the analysis)
Tjandrawinata et al.2011 (195)	**bioactive extract of Phaleria macrocarpa (DLBS1442)** capsules 200-300 mg	open study	2 or 3 x 100 mg/ dayfrom the 3rd last day of the cycle to the first 3rd day of the following cycle	**placebo (2 cykle) → DLBS1442 (2 cykle)**23 women [20-40 years old]	–

(Continued)

TABLE 7 Continued

Author, year of publication	Herb, dosageform and total daily dose	Study design	Dosage,total duration of administration	First test group	Second test group
			(average 6 days) during 4 menstrual cycles		
Sodouri et al.2013 (196)	**Zataria Multiflora (ZM)** pearls 80 mg	randomized double-blinded prospective	4 x 20mg/day7 days before first day of cycle during 2 menstrual cycles	**ZM**44 women [18-35 years old] (38 women were included in theanalysis)	**placebo**44 women [18-35 years old] (37 women were included in theanalysis)

Author, year of publication	Method of data collection	Outcomes	Adverse events/ side effects	Limitations	Overall effect
Ozgoli et al.2009 (185)	a self-administered questionnaire about daily symptom rating	Reduced severity of sleep disturbances, fatigue, bloating and palpitations only in the Ginkgo group. Reduce the severity of most other physical and psychiatric symptoms to a greater extent in the Ginkgo group than in the placebo group.	-nausea (1 person in the Ginkgo group and 4 in the placebo group)-increased desire for sleep (2 people in the Ginkgo group)	-small sample size-participants in the study were only female students, which does not reflect the general population of women with PMS-women were only observed for 2 menstrual cycless while taking Ginkgo/placebo, making it impossible to assess the long-term effects of Ginkgo on PMS symptoms-not very objective method of data collection through self- completion of questionnaires by participants-the placebo tablets were made of starch, which may have affected some PMS symptoms	positive
Sharifi et al.2014 (186)	the questionnaires on the efficacy, side effect of the capsules and satisfaction with treatment	Chamomile capsules reduced the overall intensity of PMS symptoms, mainly psychological symptoms (anger and irritability) from MA	-more severe menstrual bleeding (in the Chamomile group)-more severe GI complications (in the MA group)	-small sample size-participants in the study were only female students, which does not reflect the general population of women with PMS-women were only observed for 2 menstrual cycles while taking Chamomile/MA, making it impossible to assess the long-term effects of Chamomile on PMS symptoms-not very objective method of data collection through self-completion of questionnaires by participants	positive
Yamada and Kanba 2007 (187)	The scores of the Global Assessment of Functioning (GAF) Scale and Hamilton Depression Rating (HAM- D) Scale in the late luteal phase	GAF and HAM-D total scores improved significantly after the treatment.14 patients (46.7%) hadremission, 5 (16.7%) showed improvement.	-hot flushes (1 person who could not continue TJ-24, not included in the analysis)	-small sample size-no placebo group-need to conduct a larger, well-controlled, double-blind, placebo-controlled study to confirm results-whether PMS symptoms can be improved after a shorter time of use of SJW (e.g. after 2 menstrual cycles) has not been tested	propably positive
Jung-Gum et al.2010 (188)	The questionnaire, which contained Beck Depression Inventory (BDI), Visual Analogue Scale (VAS, and Premenstrual Assessment Form (PAF) filled before and after treatmentThe menstrual daily diary for PMS (supplemented the PAF) to record daily symptoms by	No significant changes in total BDI, VAS or PAF scores were observed.Improved score in the SJW group regarding emotional lability, hostility/anger and impulsivity compared to the placebo group.	-nausea (four women, but only on the first day)	-small sample size-women were only observed for 2 menstrual cycles while taking St. John's wort/placebo, making it impossible to assess the long- term effects of St. John's wort on PMS symptoms-narrow age range of women (20-30 years), which does not reflect the general population of women with PMS	neutral/ positive

(Continued)

TABLE 7 Continued

Author, year of publication	Method of data collection	Outcomes	Adverse events/ side effects	Limitations	Overall effect
	participants (during the experiment,around 3 or 4 months)				
Canning et al.2010 (189)	the Diary booklets which include:-the Daily Symptom Report (DSR), a checklist-the State scale of the State-Trait Anxiety Inventory (STAIS), BDI, Aggression Questionnaire (BPAQ) and Barratt Impulsiveness Scale version 11 (BIS-11) Biochemical Measures: the hormone (estradiol, progesterone, testosterone, LH, FSH and prolactin) and cytokine (IL-1b, IL-6, IL-8, IFNg and TNFa)	Significant impact on physical (appetite, swelling) and behavioural (poor coordination, insomnia, confusion, headaches, crying, fatigue) symptoms of PMS in the Hypericum group in both goups. No significant changes in PMS symptoms related to pain or mood were noticed (pain symptoms only seemed to decrease towards the end of the treatment period).no significant differences in biochemical measures	-digestive and respiratory symptoms (almost equally distributed between both groups)	-small sample size-not very objective method of data collection through self-completion of questionnaires by participants	positive
Stevinson and Ernst 2000 (190)	The Daily Symptom Ratings (DSR), a checklistthe modified, self-report Social Adjustment Scale (SAS-M), the Hospital Anxiety and Depression scale (HAD)	improving the total score of SAS-M and HAD scale	nausea, constipation, flatulence, dizziness, heavy menstrual flow (5 women, at the beggining of study)	-small sample size-no placebo group-women were only observed for 2 menstrual cycles while taking St. John's wort, making it impossible to assess the long-term effects of St. John's wort on PMS symptoms-a randomised, placebo-controlled, double- blind study should be conducted to confirm the results	propably positive
Farahmand et al.2020 (191)	Premenstrual Symptoms Screening Tools (PSST) questionnaire	Significantly reduce PMS symptoms and improved PSST total score in the Anise group.	-nausea (1 case) and menorrhagia (1 case) in the Anise group-nausea (2 cases) and diarrhea (1 case) in the placebo group	-small sample size-participants in the study were only collage students, which does not reflect the general population of women with PMS-not very objective method of data collection through self-completion of questionnaires by participants-Anise was just prescribed for 2 menstruation cycles, making it impossible to assess the long- term effects	positive
Farahmand et al.2020 (192)	Premenstrual Symptoms Screening Tools (PSST) questionnaire	effective reduce of PMS symptoms, mainly anxiety/ tension and crying symptoms and improved Premenstrual Symptoms Screening Tool (PSST) total score in the EA group.	-nausea (3 cases) in the placebo group	-small sample size-participants in the study were only female students, which does not reflect the general population of women with PMS-EA was just prescribed for two menstruation cycles, making it impossible to assess the long- term effects-not very objective method of data collectionthrough self-completion of questionnaires by	positive
Khayat et al.2014 (193)	the daily record questionnaire	reduction in the severity of mood and physical and behavioural symptoms in the ginger group	-nausea in the group of ginger	-small sample size-participants in the study were only female students, which does not reflect the general population of women with PMS-ginger was just prescribed for three menstruation cycles, making it impossible to assess the long-term effects-not very objective method of data collection through self-completion of questionnaires by participants	positive
Akbarzadeh et al.2015 (194)	Premenstrual Symptoms Screening Tools (PSST) questionnaire	reduction in physical, psychological and social PMS symptoms and improvement in total PSST scores in the melissa group	not mentioned	-small sample size-participants in the study were only high school girls, who were at different stages of puberty, which does not reflect the general population of women with PMS-not	positive

(Continued)

TABLE 7 Continued

Author, year of publication	Method of data collection	Outcomes	Adverse events/ side effects	Limitations	Overall effect
				very objective method of data collection through self-completion of questionnaires by participants-high placebo effect	
Tjandrawinata et al.2011 (195)	Daily self-assessment using a visual analog scale (VAS) in a symptom diary	noticeable relief of PMS pain symptoms, including but not limited to abdominal pain, back pain and fatigue and improvement of VAS total score	few adverse events reported, mostly mild in severity, the most commonly reported adverse events were:- diarrhea (6 reports)	-small sample size-no comparison group-need to conduct a larger, additionally randomised with placebo group study to confirm results	propably positive
Sodouri et al.2013 (196)	prospective record of the impact and severity of menstrual symptoms (PRISM) in the form of a calendar.	No change in severity or incidence of symptoms was noted between the ZM group and placebo.	not mentioned	-small sample size-participants in the study were only collage students, which does not reflect the general population of women with PMS-ZM was just prescribed for 2 menstruation cycles, making it impossible to assess the long-term effects-high placebo effect-the effects of other dosages need furtherinvestigation, cause this dosage might could not control the symptoms of PMS	neutral

5.1 Chasteberry's extract (Vitex Agnus-Castus, VAC)

VAC is a herbal preparation, and its mechanism of action primarily involves enhancing dopaminergic conduction (197). An empirical argument supporting the use of a drug with this affinity is the frequent occurrence of hyperprolactinemia in women experiencing some symptoms of PMS (198).

In his study, Schellenberg demonstrated that, over time, the number of patients responding to VAC treatment increased. By the study's conclusion, which encompassed three cycles, more than half of the women taking VAC experienced a symptom reduction of over 50%. In contrast, the placebo group exhibited a reduction of only 24%. Another study by Schellenberg et al. revealed that the most optimal therapeutic effects were achieved with a 20 mg dose taken once daily, with no additional benefits observed when increasing the dose to 30 mg (199).

Furthermore, according to Cerqueira et al., VAC demonstrated improvements in both physical and psychological symptoms of PMS and PMDD (200). Another study also underscored the efficacy of VAC extract, indicating enhancements in all PMS symptom domains as measured by PMSD, except for abdominal cramping (201). It is worth noting, however, that abdominal cramping may be inherent to the nature of PMS.

In contrast, Van Die et al. suggested the potential use of VAC in combination with St. John's wort for premenopausal women with PMS. The results showed promise, especially in addressing mood swings. Despite the observation of improvements in anxiety and hyperhydration levels, the degree of enchantment was not significantly different from that observed with a placebo. It is essential to note that this study was conducted with a small group (14 people) (202).

Moreover, Ma et al. highlighted the efficacy of the substance in controlling symptoms related to water retention in a study with a larger participant pool (203). A noteworthy concurrence with this study is the observed progressive improvements over time, which align with findings in the earlier mentioned Schellenberg study. Interestingly, the study also reported a relatively high percentage of placebo results, potentially attributed to the subjective measurement methods employed. This methodology may explain the results in the He et al. study, where VAC demonstrated improvement but placebo results were as high as 50% (204).

Ambrosini et al. supported the effectiveness of VAC in controlling PMS-related headaches (205). Presumably, the herb's impact on headaches is linked to its high affinity for μ and κ subtype opioid receptors (197). However, it is essential to note that the study lacked a control sample. Additionally, the Bergel et al. study observed that persistent headaches associated with VAC led one patient to discontinue treatment. Interestingly, in this study, VAC did not demonstrate an impact on prolactin levels (206).

This raises questions about the credibility of the previously mentioned study, particularly since this study, revealing headaches as a side effect despite high limitations, provides more qualitative data than the research discussed earlier. On the other hand, He et al. whose study also identified headaches after VAC administration, suggested that many reported side effects might be attributed to the inherent nature of PMS (204).

Most of the cited studies face significant limitations, a point emphasized by Verkaik et al. In their meta-analysis on VAC studies in PMS, they highlighted the high risk of bias, heterogeneity, subjective methods, and underpowered inclusion criteria, collectively diminishing the quality of evidence regarding the effectiveness of VAC (207). More discerning and selective studies

are imperative. Furthermore, many herbal studies exhibit notable methodological flaws, such as the absence of a placebo group.

In conclusion, while VAC appears to be an effective formulation, further research is essential to conclusively demonstrate its benefits. It is important to keep in mind that herbal therapies are frequently associated with various unpredictable interactions, potentially contributing to the high number of side effects, as seen in the Berg et al. study where the group was allowed to take other drugs in addition to VAC (206).

5.2 Saffron

The argument in favor of using saffron finds support in studies on the substance conducted in affective disorders (208). In rat studies, saffron has been shown to increase BDNF expression (209) in the hippocampus. The suspected mechanism of action involves the safranal and crocin compounds, which impact serotonergic conduction (210). Additionally, this preparation contains flavonoids and carotenoids, which exhibit antioxidant effects and prevent the formation of prostaglandins, potentially explaining its analgesic effect (211).

Conversely, a study by Fukui et al. discovered that a 20-minute exposure to the scent of the preparation lowered cortisol levels and elevated estrogen levels, irrespective of the menstrual cycle timing. This exposure was associated with symptom relief, as measured by the STAI (State-Trait Anxiety Inventory). It is worth noting that the rapid decrease in cortisol levels may indicate a beneficial short-term effect of saffron exposure in situations of heightened tension and stress (212).

In the study by Beiranvand et al., saffron was administered once a day for two menstrual cycles at a dose of 30 mg, revealing a significant decrease in PMS severity in the saffron group compared to the placebo group (213). This finding aligns with an earlier study by Agha-Hosseini et al., where saffron, at a total dose of 30 mg divided into two doses of 15 mg each, demonstrated a notable reduction in PMS symptoms for up to 76% of women after two monthly cycles of administration (214).

Rajabi et al. explored the impact of saffron on PMDD symptoms by comparing it with an antidepressant and a placebo, similar to previous studies on depression. Both preparations were administered twice a day. The dosage was limited to the luteal phase based on the mechanism of action. The results indicated comparable efficacy between fluoxetine and saffron (215). Notably, side effects were less frequently observed with saffron, potentially favoring the herbal preparation.

Saffron appears to offer an alternative to SSRI drug treatment for PMS. However, further studies are warranted to both indicate and confirm its effectiveness.

5.3 Curcumin

Curcumin, a member of the ginger family, is a curcuminoid derived from turmeric. Its suspected mechanism of action in addressing PMS is linked to the modulation of neurotransmitter levels, including serotonin (216). Additionally, a study by Fanaei et al. demonstrated an increase in BDNF levels in women with PMS following curcumin supplementation, which correlated with clinical improvement in patients (217). Another pivotal aspect of curcumin's action involves the inhibition of prostaglandin synthesis by suppressing COX-2 (218, 219).

Khayat et al. demonstrated that administering curcumin for 10 days starting 7 days before menstruation is an effective method for relieving PMS symptoms compared to a placebo (220). They utilized a dose of 100 mg twice daily. On the contrary, Bahrami et al. used a higher dose of 500 mg once a day with the same dosing schedule but found no clear advantage of curcumin over placebo (221). However, both studies are limited by the relatively small number of subjects and the short study duration of 3 cycles.

Another aspect of curcumin's impact on women with PMS was explored by Arabnezhad et al., who studied vitamin D levels using a 500 mg dose of curcuminoid and 5 mg of piperine following the same schedule. They reported a slight improvement in vitamin D levels relative to the placebo. On the contrary, the markers of liver and kidney function measured in this study did not exhibit differences between the study group and the placebo (222). Another study analyzed the effects of curcuminoid and piperine on inflammatory markers and iron metabolism in women with PMS. However, it failed to show changes indicative of a benefit from curcumin, except for a reduction in hsCRP. It is noteworthy that the baseline hsCRP value was already low (223).

5.4 Conclusion

In conclusion, despite the theoretically beneficial effects of curcumin, its conclusive efficacy for PMS symptoms has not been established. While a recent study by Bahrami et al. suggests improvements in cognitive function for women with PMS (224), isolated reports on its effectiveness are insufficient to draw concrete conclusions.

6 Alternative treatment

The most common treatment for PMS is pharmacotherapy. However, non-pharmacological methods, such as cognitive-behavioral therapy (CBT), regular aerobic exercise, yoga, vitamin supplementation, and leading a healthy lifestyle, are increasingly recommended as additional options (225).

6.1 Cognitive-behavioral therapy

Cognitive-behavioral therapy (CBT) is a psychotherapy that aims to identify negative, disturbing, or destructive thought patterns and develop coping strategies (10) to alleviate associated symptoms, such as depression, stress, and anxiety (226).

Ussher and Perz suggest that couples may benefit more from CBT than individual therapy. Women may feel symptoms such as depression, anger, and irritability during the premenstrual phase (226, 227), which can lead to increased conflict in the relationship with their partner (228, 229). Conversely, women may experience feelings of guilt or other negative thoughts during quiescence. The

study involved four 90-minute therapy sessions with a clinical psychologist over 5 months. The focus of the meetings was to challenge these negative thoughts and develop coping strategies. Women were encouraged to engage in self-care and make lifestyle changes, such as exercise and diet. Regardless of the treatment modality, both treatment groups showed improvements in women's well-being compared to the control group. The study found a sustained reduction in depression, anxiety, and stress over the following three months (226). The results emphasize the significance of receiving understanding and support from loved ones during PMS treatment, as well as the importance of informed education about PMS.

The authors of a separate study demonstrated that CBT can enhance the quality of life for young women with PMS. They highlighted that the knowledge gained during therapy sessions on problem-solving, stress management, and education about a healthy diet can significantly impact positive treatment outcomes (230).

6.2 Supplementation

Zinc (Zn) supplementation can provide antioxidant, anti-inflammatory, and antidepressant benefits as a micronutrient (231, 232). Several studies have found that women with PMS have lower levels of zinc (Zn) (233–236). Jafari et al. confirmed that zinc supplementation for 12 weeks reduced the severity of both physical and psychological symptoms of PMS. The study reported an increase in BDNF and TAC levels, which may have contributed to the positive effects of the treatment (232).

Vitamin D plays a crucial role in maintaining calcium homeostasis, sex hormone concentrations, and the normal functioning of neurotransmitters (237–240). In addition, it reduces the production of prostaglandins (241). Furthermore, it has significant effects on the female reproductive system (242). Bahrami et al. demonstrated that high doses of vitamin D (50,000 IU cholecalciferol/week for nine weeks) alleviate PMS symptoms and painful menstruation in adolescent females. The treatment also reduces the incidence of back pain, tendency to cry, and possibly nausea, as well as loss of concentration or lack of energy (243). However, the results of another study contradict this, as it found no significant effect of vitamin D supplementation on PMS symptoms despite administering a dose of 2000 IU every other day for 12 weeks (244).

One study found that calcium supplementation can reduce affective and behavioral symptoms of PMS, such as depression, changes in appetite, and early fatigue (245). Another research confirmed that taking 500mg of calcium daily for two months can reduce mood disturbances related to PMS (246). Earlier studies have also noted a reduction in PMS symptoms (247, 248).

B vitamins play a crucial role in the metabolic processes of many of our body's systems (19). In a comparative study by Chocano-Bedoya PO et al., it was demonstrated that vitamins B1 and B2 significantly reduce the risk of PMS (249). Abdollahifard et al. found that taking vitamin B1 during the luteal phase reduces both physical and psychological symptoms of PMS (250). Some studies have shown that vitamin B6 can alleviate and reduce the occurrence of PMS symptoms (251–253). B vitamins affect neurotransmitter metabolism through various mechanisms (249). Vitamin B1 is important in the metabolism of GABA precursors, which regulate conductance thought to be crucial in the pathogenesis of PMS (254, 255). Vitamin B2 is essential for the activation of vitamin B6. Vitamin B6 plays a crucial role as a cofactor in the production of serotonin. In contrast, several other studies have not found clear evidence of vitamin B6 effectively modifying PMS symptoms (256–258). However, despite the conflicting results, it is recommended that B vitamins be supplemented as they may help alleviate mild PMS symptoms through the mechanisms described above (259).

Magnesium (Mg) is a cofactor for many enzymes and influences many biochemical reactions. It is responsible for protein synthesis, proper muscle and nerve function, and maintaining blood osmoticity (260). According to Moslehi et al.'s meta-analysis, there is currently no significant relationship between serum or erythrocyte magnesium concentrations.

Additionally, there was no observed vitamin A deficiency in either the luteal or follicular phases. However, it is important to note that the study had a small sample size, consisting of only 10 PMS patients in the study group and 10 women in the control group (261).

6.3 Changing to a healthier lifestyle

In addition to the non-pharmacological treatments mentioned above, such as supplementation and physical activity, other factors can influence a healthy lifestyle and potentially improve quality of life.

Research has shown that diet can affect the likelihood of experiencing PMS symptoms. Two studies have confirmed that consuming high amounts of unhealthy foods, such as fast food, soft drinks, processed meat, salt, sugar, sweets, hydrogenated fats, mayonnaise, high-fat dairy products and red meat, can increase the risk of PMS (262, 263). In contrast, consuming meals that are rich in fruits, vegetables, dried fruits, nuts, legumes, garlic, and fish may decrease the likelihood of experiencing PMS (263).

Some studies have indicated that the consumption of caffeine and caffeinated beverages is linked to PMS symptoms, particularly increased breast pain. Therefore, it is recommended to avoid consuming caffeine (264–267). However, several studies have failed to find any correlation (268–270). Therefore, further research is required to determine conclusively whether caffeine has any impact on PMS.

In addition to consuming high-calorie, fatty, sugary, and salty foods, smoking (268, 271–273) and alcohol consumption (274) are also significant risk factors for PMS.

6.4 Aerobic exercise and yoga

Physical activity may alleviate some symptoms, such as depression or increased pain tolerance, by increasing the secretion of endorphins and reducing cortisol concentrations (275). Aerobic

exercise can also reduce feelings of fatigue, improve concentration, and reduce the intensity of other PMS symptoms. Regular physical activity has been shown to have a regulating effect on prolactin, oestradiol, and progesterone concentrations, as well as an increase in hemoglobin, erythrocytes, and thrombocytes (276).

It is important to note that regular exercise can alleviate PMS symptoms, while occasional physical activity may exacerbate them (277).

Mohebbi Dehnavi et al. confirmed that regular aerobic exercise has a positive effect on PMS symptoms. In their study, 35 female students performed high-intensity aerobic activity for 30 minutes, 3 times a week, for a total of 8 weeks. The completion of it resulted in a reduction in the severity of some physical symptoms of PMS (278).

However, the results of studies on this topic are contradictory. Several of them indicate that aerobic exercises, such as walking, running, or swimming, have a positive impact on PMS symptoms (279–281). Others have found no significant association between physical activity and physical symptoms of PMS (282, 283).

Yoga has been found to have a positive effect on reducing both physical and psychological symptoms of PMS, as evidenced by several studies (284–286). Yoga comprises three key elements: breath control (pranayama), postures (asana), and meditation (dhyana) (287). The breathing techniques employed during yoga have a significant impact on various bodily systems, including the nervous system. They regulate the function of the autonomic nervous system (ANS) and inhibit its sympathetic part. They also reduce heart rate and blood pressure (288, 289). Presumably, this helps relax the mind and body and can relieve feelings of tension, anxiety, or depression (284). Yoga poses involve limb positioning and muscle contraction, which stimulates pressure receptors under the skin. By increasing vagus nerve activity, cortisol production is reduced (290). Furthermore, yoga increases BDNF levels (291), a factor whose increase is one of the resultant effects of SSRI drugs. This effect can be linked both to the activation of the autonomic system during exercise and to the stimulation of prefrontal cortex activity during meditation (292) (293). This can have positive effects on pain, depression, and immune function (284). Meditation, also known as relaxation training or relaxation exercises, involves achieving calmness and inner tranquility by maintaining a continuous state of mindfulness. Furthermore, they stimulate the secretion of melatonin, which enhances the quality of sleep and aids in falling asleep (291).

According to a study conducted by Chang et al., yoga alleviates both physical and psychological symptoms associated with PMS. In a research conducted by Vaghel et al., 65 women performed yoga exercises at home using a 30-minute DVD program, at least three times a week for three menstrual cycles (284).

Both yoga and aerobic exercise were found to have a positive effect on reducing the intensity of pain and other somatic symptoms of PMS. However, the group of women who regularly practiced yoga had better results compared to the group who regularly did aerobic exercise. Yoga may alleviate psychological symptoms of PMS, such as stress and anxiety, due to its focus on breath control and meditation in addition to physical activity, unlike aerobic exercise (294). Yoga can support a focus on feelings, which correlates with some of the components of behavioral-cognitive therapy.

6.5 Conclusion

Non-pharmacological treatments can significantly alleviate physical symptoms of PMS. These include supplementation with vitamin B6, vitamin D, zinc, calcium. CBT therapy can positively reduce the severity of PMS symptoms related to the psyche. Regular aerobic exercise and yoga can relieve physical complaints such as headaches, fatigue, cramps, swelling, and breast pain. By using breathing techniques and meditation during yoga, it is possible to reduce feelings of tension, depression, or anxiety. Limiting the intake of unhealthy food, alcohol, and smoking can also reduce the risk of symptoms.

It is worth noting that the treatment methods listed are interrelated and, when used together, can produce positive results. CBT therapy is designed to provide patients with appropriate psychoeducation. Women experiencing PMS can acquire a fundamental understanding of the condition, its causes, and coping mechanisms. Therapy sessions often promote a healthier lifestyle, including regular exercise, and dietary changes, which can alleviate most physical symptoms. Overall, this may improve women's well-being and quality of life. However, there is a lack of research that considers most non-pharmacological treatments simultaneously.

7 Surgical treatment

It is believed that hysterectomy combined with bilateral removal of the ovaries and fallopian tubes (TAH/BSO) can be considered an effective treatment for severe PMS or PMDD. However, it is important to be aware of the consequences it carries - patients are at risk of premature menopause with this form of treatment (295). Ovarian failure after hysterectomy alone is estimated to occur in 15-50% of cases. Due to the risk of the consequences of premature menopause: osteoporosis, premature death, mood disorders, infertility, neurological and cardiovascular diseases, patients are recommended hormone therapy (HRT) (296).

A study by Cronje et al. showed the efficacy of (TAH/BSO) in 47 patients with severe PMS, who continued hormone therapy after surgery. Interestingly, 96% of the women were 'satisfied' or 'very satisfied' with TAH/BSO, and 93.6% reported complete resolution of cyclic symptoms. The study concluded that TAH/BSO, in combination with HRT, was an extremely effective treatment for PMS (297).

Another invasive treatment for PMS is thermal ablation of the endometrium. A study that tested the efficacy of this form of therapy involved 36 patients reporting heavy periods and PMS symptoms. The average age of the women undergoing treatment was 41.4 years and the average body mass index was 26.7. Most of them, as many as 75 percent, had not undergone effective hormone therapy. Virtually all the women, 97%, reported improvement in PMS after endometrial ablation, both in terms of the severity of symptoms and in terms of the symptoms themselves (298). At this point, it should be noted that symptom relief may be related to the

cessation of bleeding itself. In particular, a study involving 73 women showed that initially after treatment when patients did not experience monthly bleeding, they did not report PMS symptoms at the same time, whereas when bleeding recurred, PMS-related complaints also appeared (299).

Surgical methods of treating severe PMS or PMDD, are very effective, however, the complications they may entail should not be overlooked. TAH/BSO appears to be the riskiest, and the potential health risks associated with organ removal require the implementation of hormone replacement. It should also be borne in mind that the studies referred to included a small group and that ablation is not a recognized form of treatment for PMS and PMDD and the impression of a reduction in the severity of complaints may have been correlated with the non-occurrence of bleeding.

8 Discussion

Non-pharmacological treatments should be considered before introducing medications. However, in cases of severe symptoms, consider them complementary support for pharmacological treatment. Psychoeducation plays a pivotal role at every stage, helping patients prepare for the most challenging days of the cycle. It should cover elements such as diet and physical activity levels, while fostering awareness of the disorder's complexity. CBT remains a viable option at any stage of the treatment process.

We recommend that pharmacological treatment should be tailored to the individual clinical needs of the patient, taking into account the entire clinical picture. In the case of the predominance of psychological symptoms, SSRI drugs are preferred, while physical symptoms are treated with OC drugs. It is important to personalize the treatment not only based on the patient's predominant symptoms but also taking into consideration their preferences and individual circumstances. For instance, for patients who often forget to take their medication, SSRIs might be a better option as they are fast-acting in PMS. Similarly, it is crucial to consider the significant side effects of the drug. For example, paroxetine has a strong anticholinergic effect and can cause weight gain, making it necessary to use caution when considering its inclusion in cases of coexisting diabetes or obesity. On the other hand, escitalopram may cause QT prolongation at higher doses, making it better to choose another drug such as sertraline for patients who are in the habit of self-medication and increasing doses. In case a patient chooses venlafaxine, it is important to keep in mind that it may raise blood pressure.

The most effective approach to treatment with SSRIs appears to be their administration during the luteal phase. Continuous administration is feasible, but it should be reserved for severe cases of PMS (e.g., in patients burdened with other psychiatric disorders) due to the higher risk of side effects. Notably, comparable therapeutic effects can be achieved by administering the drug solely during the luteal phase, making non-continuous administration the preferred treatment method. A continuous treatment regimen may also be considered if there is no response to the intermittent method (only in the luteal phase).

Based on the information presented in our study, the optimal selection among SSRIs would be fluoxetine, which can be used at a maximum dose of 20 mg. Scientific reports suggest no significant differences in side effects between 20 mg and 10 mg doses due to the interval in administration. However, we recommend restricting the administration of the maximum dose to the most severe cases. For others, the preferred starting dose is 10 mg, as studies indicate noticeable improvements in patients' conditions even at low doses. A follow-up visit is recommended after 3 cycles, as this is when response rates are typically high.

In cases where physical symptoms and irregular cycles predominate, OC drugs appear to be a preferable choice. Among

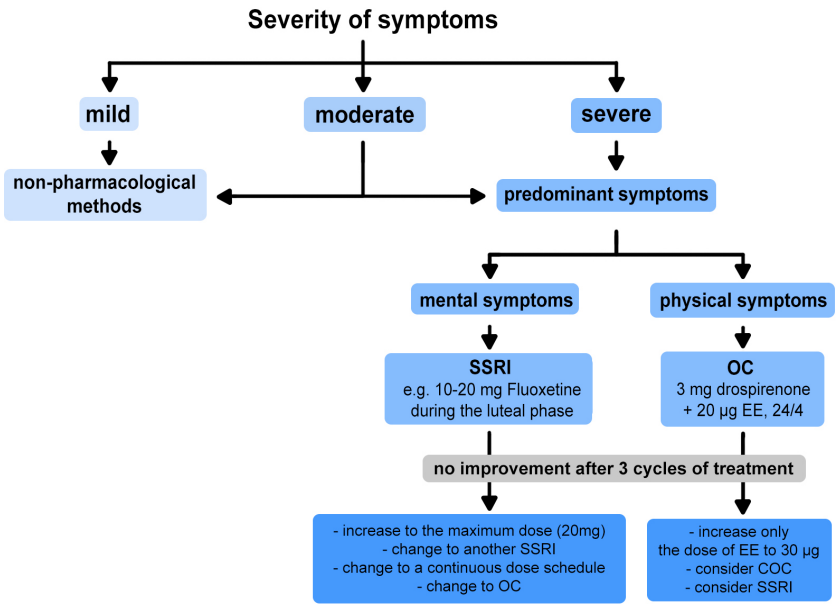

FIGURE 4
Sample treatment regimen for PMS; e.g. - for example; EE- ethinylestradiol.

the EE drugs, drospirenone has been extensively studied, with no demonstrated advantage of other preparations in the same group.

We recommend using a dosing schedule of 24/4 instead of 21/7, as supported by the studies we cited. These studies indicate that limiting placebo days has a beneficial effect on treatment. If the placebo regimen proves ineffective in symptom reduction, especially during the placebo phase, transitioning to a COC may be considered (Figure 4).

Considering the disorder's etiology, pain medications may offer a viable option. Additionally, research on neurosteroids suggests that they can be employed to alleviate PMS symptoms by inhibiting the action or synthesis of allopregnanolone. The use of isoallopregnanolone appears particularly promising, although further research is needed to conclusively demonstrate its therapeutic effectiveness.

Herbal treatment serves as an alternative to pharmacological drugs; however, due to significant limitations in the methodology of research on herbs, they should not be considered a therapeutic option in more severe cases. Moreover, numerous interactions restrict the possibility of their use, and while VAC or saffron seem to be the most promising, evidence of their efficacy is limited. Due to the widespread popularity of herbal supplements (300), it is advisable to ensure that patients do not concurrently use such preparations, as monotherapy is preferred to avoid potential interactions. When combining herbs with pharmacological drugs, there is a specific concern regarding their impact on hepatic drug metabolism. For example, St. John's wort (Hypericum perforatum) acts as an inducer of CYP3A4, CYP1A2, and CYP2C9, which may lead to decreased efficacy of several antidepressants, such as paroxetine, sertraline, and fluoxetine, due to increased liver metabolism. On the other hand, the use of Ginkgo biloba, by inhibiting cytochromes, may elevate plasma concentrations of drugs, potentially increasing side effects and exacerbating the antiplatelet effects of SSRI and SNRI drugs (301). Additionally, it is essential to note that patients using saffron are at a higher risk of developing serotonin syndrome when concurrently taking SSRI drugs.

It is essential to note that our review is not systematic, and despite attempts to cover all studies, one should keep in mind significant limitations.

Author contributions

SM: Conceptualization, Data curation, Methodology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. AO: Data curation, Investigation, Project administration, Resources, Writing – review & editing. XZ: Data curation, Methodology, Resources, Writing – original draft. KI: Data curation, Investigation, Resources, Visualization, Writing – original draft. ZS: Conceptualization, Visualization, Writing – original draft. NW: Funding acquisition, Project administration, Supervision, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Understanding premenstrual exacerbation: navigating the intersection of the menstrual cycle and psychiatric illnesses

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Premenstrual exacerbation of an existing psychiatric disorder refers to the worsening of symptoms inherent to the condition during the premenstrual phase. Research consistently indicates that hormonal fluctuations during the menstrual cycle present a unique period of vulnerability for the onset or exacerbation of psychiatric symptoms, impacting diagnosis, risk assessment, and treatment. This review sought to elucidate the phenomenon of premenstrual exacerbation and its impact across a spectrum of psychiatric illnesses, including mood, anxiety, psychotic, obsessive-compulsive, personality, and trauma-related disorders. Despite the expanded research in recent years on premenstrual dysphoric disorder and premenstrual syndrome, premenstrual exacerbation remains underexplored and poorly defined. This review offers significant contributions to the diagnosis and management of psychiatric conditions, advocating for heightened awareness and novel treatment approaches in the context of premenstrual exacerbation.

KEYWORDS

premenstrual exacerbation, premenstrual disorders, women's mental health, menstrual cycle, mood disorders, psychotic disorders, anxiety disorders, personality disorders

1 Introduction

There has been a growing recognition of premenstrual symptomatology and premenstrual disorders in recent years, particularly after premenstrual dysphoric disorder (PMDD) was added to the DSM-5 in 2013 (1). Premenstrual symptomatology includes emotional, behavioral, and physical symptoms during the luteal phase that resolve during the onset of menses (2). However, only a subset of these women fulfills the diagnostic criteria for premenstrual disorders, which include PMDD, Premenstrual Syndrome (PMS), and Premenstrual Exacerbation (PME) of underlying psychiatric disorders (1, 3, 4).

While research on PMDD and PMS has expanded, studies focusing on PME remain limited (5). PMDD and PMS are characterized by symptoms that emerge during the late luteal phase and abate following menstruation, with an absence of symptoms during the follicular phase. However, PME is characterized by the worsening of symptoms of another existing disorder during the premenstrual phase, and the symptoms of the existing disorder are still present throughout the entire menstrual cycle (3).

The prevalence of PME in psychiatric disorders remains poorly defined, likely due to the paucity of research and previous studies' reliance on retrospective assessments, which are prone to inaccuracies. The diagnosis of PME, similar to PMDD and PMS, necessitates prospective symptom tracking across at least two symptomatic menstrual cycles to distinguish it from other conditions and to overcome the limitations of retrospective recall (3).

This review aims to elucidate the relationship between the menstrual cycle and exacerbations of psychiatric illnesses, including mood, anxiety, psychotic, obsessive-compulsive and related disorders, personality disorders, and trauma and stressor-related disorders. Improved understanding of exacerbations of psychiatric illnesses across the menstrual cycle can ultimately improve the diagnosis, risk assessment, and treatment/management in affected individuals.

2 Mood disorders

2.1 Major depressive disorder

2.1.1 Prevalence

Analyses under the NIMH Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed that 64% of premenopausal women with major depressive disorder (MDD) seeking treatment in primary care and psychiatric settings reported premenstrual worsening of their depression (6). This significant figure, however, is derived from retrospective symptom reports, which are susceptible to recall bias, underscoring the necessity for prospective symptom evaluation across at least two symptomatic menstrual cycles for accurate diagnosis of PME. Notably, PME was linked to older age and a higher rate of familial history of depressive disorders and bipolar disorder (7). Aside from specifically PME of MDD, Payne et al. found that more women with MDD are more likely to experience premenstrual or menstrual mood changes compared to those without MDD, highlighting the complex interplay between menstrual cycle phases and mood disorders (8).

2.1.2 Course

Research studies have shown that PME of MDD leads to longer index episodes, more anxiety, and shorter time to relapse after remission (6, 7, 9). The STAR*D trial also showed that women reporting PME were more likely to report physical complaints such as leaden paralysis, gastrointestinal complaints, and psychomotor slowing (6), alongside a greater prevalence of comorbid medical conditions and diminished physical health (7). These women were also less likely to endorse blunted mood reactivity (6).

2.1.3 Treatment

Management of PME in MDD poses unique challenges, as standard antidepressant regimens may not adequately address premenstrual symptom flare-ups. In one small double-blind pilot study, variable dosing of sertraline was found to resolve PME of MDD, with an improvement in difference in scores in depression scales between the luteal and follicular phases when sertraline was increased premenstrually (10). However, the evidence base for this approach remains limited, with few studies supporting the efficacy of premenstrual dosage adjustments in antidepressant therapy (11).

Other studies have also evaluated the efficacy of treatments for PMDD in treating PME of MDD, such as augmentation of antidepressants with combined oral contraceptives or suppression of ovulation with gonadotropin hormone-releasing hormone (GnRH) agonists have had conflicting results (12–14).

2.2 Bipolar disorder

2.2.1 Prevalence

In retrospective studies, 64-68% of women reported menstrual cycle-related mood changes, while 44-65% of women in prospective studies reported menstrual cycle-related mood changes (15, 16).

2.2.2 Course

The mood changes associated with the menstrual cycle include depressive symptoms as well as hypomanic or manic symptoms (16). Notably, these fluctuations are not confined to the premenstrual phase but span various stages of the cycle, including ovulation and menstruation (16). Emerging data suggest that premenstrual exacerbation (PME) of bipolar disorder may signal a more challenging disease trajectory, characterized by heightened symptom intensity, reduced intervals to relapse, and increased disruption of daily functioning (16, 17).

There is some evidence to suggest that women are more likely to experience rapid-cycling bipolar disorder, and one hypothesis is that this is due to mood changes secondary to hormonal changes during the menstrual cycle. One study reported that women exhibited large mood fluctuations more frequently than men (15). Rasgon et al. found that a majority of women not taking hormonal contraception reported significant mood changes across the menstrual cycle, though not in any particular direction (17). However, other studies have found no significant change in mood scores across different phases of the menstrual cycle in women with rapid-cycling bipolar disorder (18, 19), or bipolar disorder (20), while others found differences in other phases such as the menstrual phase or follicular phase. These variations make it difficult to understand the pathophysiology behind PME of bipolar disorder.

2.2.3 Treatment

The therapeutic approach to managing PME in bipolar disorder remains underexplored, especially concerning the adjustment of psychotropic medication dosages in response to menstrual cycle phases. However, Robakis et al. found that women taking gamma-aminobutyric acid-A (GABA-A) receptor modulators such as the

mood stabilizer lamotrigine had less fluctuation in mood within and across menstrual cycle phases; when combined with hormonal contraception, these medications resulted in improved mood ratings in women with bipolar disorder (21). It is possible that GABA-A receptor modulators could act synergistically with hormonal contraceptives to further target mood symptoms in bipolar disorder (21). There is no empirical data supporting augmentation with an SSRI for treatment of PME in bipolar disorder.

2.3 Anxiety disorders

2.3.1 Prevalence

Nillni et al. (22) observed an increase in both the frequency and severity of panic attacks, as well as heightened anxiety and affective symptoms during the premenstrual phase among women with panic disorder (PD), based on retrospective assessments (22). However, when assessed prospectively with daily reports, results were mixed. Some studies reported increased panic attacks and anxiety symptoms during the premenstrual phase, as well as higher Social Avoidance and Distress (SADS) suicidality scores; however, other prospective PD studies found no differences in symptoms across menstrual phases (22–25). Likewise, one study found that women with PD exhibited greater skin conductance levels during anxiety-provoking trials, but no changes in self-reported anxiety when compared to women without PD during the premenstrual phase (26).

Similar mixed patterns have been noted among women with generalized anxiety disorder (GAD) and social anxiety disorder (SAD). Nillni et al. (22) found that approximately 45% of women with GAD retrospectively reported more severe social anxiety and avoidance symptoms during the premenstrual phase, as did women with comorbid GAD and premenstrual syndrome prospectively (24). In contrast, Li et al. (2020) found an increase in repetitive negative thinking (RNT), a key element in the development and maintenance of anxiety, in women with GAD during the mid-luteal phase, but no changes in other GAD symptoms (27). One study found that a subgroup of women with SAD reported more anxiety and avoidance in the premenstrual phase (27, 28). However, findings from prospective studies are more limited, and thus these conclusions are more consistently demonstrated in studies assessing anxiety symptomatology retrospectively (22, 25). Similarly, studies have demonstrated inconsistent findings in cortisol responses following administration of the Trier Social Stress Test (TSST) across menstrual cycle phases (22).

2.3.2 Course

Nillni et al. (22) reports results consistent with prior reviews which theorize that the rapid decline in ovarian hormones could lead to decreased levels of GABAergic neurosteroids, thus altering the anxiolytic function of GABA-A receptors and exacerbating anxiety symptoms premenstrually (22, 25, 27). Another proposed mechanism is that adrenal steroids, such as dehydroepiandrosterone (DHEA), which antagonize GABA-A receptors compete with low levels of allopregnanolone, a progesterone metabolite that normally acts as a positive modulator on the GABA-A receptor, to increase anxiety and post-traumatic stress disorder (PTSD) symptoms (22, 27).

2.3.3 Treatment

Heightened RNT in the luteal phase in women with GAD may correspond with increased susceptibility for the development of or relapse of anxiety disorders. Li et al. (2020) proposed therapy-based interventions to target RNT in women with GAD, such as rumination-focused CBT and traditional CBT. Otherwise, treatment options remain limited for PME of anxiety disorders.

2.4 Psychotic disorders

2.4.1 Prevalence

The exacerbation of psychotic disorders with reproductive events such as childbirth has been well-documented, while PME of psychotic disorders has been less well-studied. Gleeson et al. (29) found that 32.4% of women with a schizophrenia-spectrum disorder reported fluctuations of psychotic symptom severity across their cycle (29). Hsiao et al. (24) found that 20% of women fulfilled the definition of PME of schizophrenia (24).

2.4.2 Course

Emerging research suggests a potential role for estrogen in modulating the course of schizophrenia, highlighting gender differences in disease onset, symptomatology, and treatment response. Women tend to exhibit a later disease onset and a higher prevalence of affective symptoms compared to men (29, 30). One hypothesis for these gender differences includes a possible neuroprotective function of estrogen against psychotic symptoms (31), suggesting that low estrogen leads to increased vulnerability to psychosis. Bergemann et al. found that 60% of women with schizophrenia in their study had estradiol serum levels below 30 pg/mL in the follicular phase and below 100 pg/mL in the periovulatory phase (32). Other studies also report that women with schizophrenia have lower estrogen levels compared to normal reference range and also experience menstrual irregularities, though it is difficult to ascertain whether such menstrual irregularities are due to antipsychotic-induced hyperprolactinemia (33, 34).

This effect has been suggested in men as well, with one study demonstrating that estradiol concentrations were inversely correlated with negative symptoms in male patients (35). In addition to this, female schizophrenic patients often have worsening symptoms premenstrually, when estrogen levels are lower (36). Case reports for psychotic symptoms during the premenstrual phase with cessation of symptoms at the onset of menstruation could further support this hypothesis (37). However, this estrogen hypothesis of schizophrenia remains somewhat controversial.

One systematic review and meta-analysis showed that the rate of admissions for women with schizophrenia during the perimenstrual phase was 1.48 times higher than expected (95% CI: 1.31-1.67) (38), suggesting that psychotic symptoms worsen perimenstrually.

2.4.3 Treatment

The treatment of PME in psychotic disorders poses unique challenges. Unlike mood disorders where variable dosing of antidepressants may be beneficial, adjusting doses of antipsychotics, particularly those that raise prolactin levels and subsequently lower estrogen, may not be as straightforward due to the potential exacerbation of symptoms (39). Gattaz et al. (40) found that women who were admitted during phases of the menstrual cycle with low estrogen levels required lower effective doses of antipsychotic medications (40).

Adjunctive estrogen therapy has shown promise in improving outcomes for women with schizophrenia. A randomized, double-blind study comparing women treated with adjunctive transdermal estradiol for 28 days vs. placebo showed that those with adjunctive estradiol had significantly reduced positive and general psychopathological symptoms (41). Similar superiority has been shown with ethinyl estradiol as an adjunct to haloperidol for eight weeks in another double-blind, placebo-controlled trial (42). This effect has also been demonstrated in men, with a randomized placebo-controlled trial in 53 men showing a more rapid reduction in pathology when men with schizophrenia were treated with estradiol as an adjunct to atypical antipsychotic treatment for 14 days, with a reflected increase in serum estrogen levels (43). This effect in men suggests an effect of estrogen on psychopathology rather than an effect related to changes in ovulation. However, other studies have shown variable effects of estrogen supplementation for psychotic symptoms, possibly suggesting an individual variability for response to estrogen supplementation (34, 44, 45).

For women with PME of schizophrenia, adjunctive estradiol therapy premenstrually should be considered and further evaluated. In addition to this, further research should be conducted on the utility of selective estrogen receptor modulators in the treatment of PME of schizophrenia-spectrum disorders.

2.5 Personality disorders

2.5.1 Prevalence

Recent research underscores the heightened sensitivity of individuals with borderline personality disorder (BPD) to hormonal fluctuations. Eisenlohr-Moul et al. (46) reported that a significant majority (73%) of unmedicated women with BPD experienced clinically significant PME of emotional symptoms, including but not limited to depression, anxiety, and irritability (46, 47). Notably, the timing of symptom onset varies, with high-arousal symptoms such as irritability and anger intensifying during the luteal phase and peaking premenstrually, whereas low-arousal symptoms like depression emerge closer to menstruation and persist into the follicular phase (46–48). Similarly, a group of undergraduate females with elevated trait BPD features endorsed the most symptomatology during the mid-luteal and perimenstrual phases (46, 47, 49).

2.5.2 Course

Peters et al. (2019) proposes the most likely mechanism for onset of high-arousal symptoms during the luteal phase is an alteration of the GABA-A receptor which reverses the typical positive effects of GABAergic progesterone metabolites such as allopregnanolone, and mimics the onset of PMDD, likely sharing a similar pathophysiology (46, 47). However, low-arousal symptoms of BPD demonstrated PME with later onset in the menstrual cycle (MC) and more prolonged elevation, which is unlike the rapid resolution of PMDD symptoms in conjunction with the follicular phase, likely suggesting a different mechanism of action (46, 47). Another proposed theory for PME of low-arousal symptoms is that women with BPD may have greater serotonergic sensitivity to fluctuations in ovarian steroid hormones (47) In addition, studies have observed a greater proportion of and more lethal suicide attempts occurring in the early follicular phase, when ovarian steroids are at their lowest (47).

2.5.3 Treatment

To date, no pharmacological interventions have been specifically designed to target PME in BPD. However, the use of SSRIs during the luteal phase has demonstrated reduction of some PMDD symptoms, suggesting potential benefits for managing high-arousal symptoms in BPD (47, 48). Although studies have shown oral contraceptives to be beneficial for PMDD, they have been found to worsen symptoms in women with BPD and warrant further research (47, 48). Other studies have preliminarily demonstrated that stabilization of ovarian steroid hormones in a sample of women with suicidal ideation reduced PME of low-arousal symptoms (47, 48). Finally, non-pharmacological interventions can also be implemented such as cycle-tracking to increase awareness and develop appropriate coping strategies, ideally being combined with therapy modalities such as dialectical behavior therapy (DBT) (46–48).

2.6 Obsessive-compulsive disorder and related disorders

2.6.1 Prevalence

PME of obsessive-compulsive disorder (OCD) has been retrospectively reported in 20-42% of women (47, 50). One prospective study found that there was an increase in symptoms during the premenstrual phase compared to mid-cycle (50).

2.6.2 Course

The severity of OCD symptoms has been linked to reproductive cycle events characterized by low estrogen levels, such as the postpartum period and menarche (50). Forray et al. found that women who experienced OCD onset in the perinatal period and perinatal worsening of OCD were more likely to have PME of OCD symptoms compared to those who denied OCD onset related to pregnancy (65% vs. 39.3%, $p = 0.047$) (51). This phenomenon may be underpinned by serotonergic dysregulation, exacerbated by the hormonal shifts of the menstrual cycle (52, 53).

There is also limited evidence to suggest that OCD symptoms fluctuate throughout the menstrual cycle (54). Women with PME of obsessive-compulsive symptoms had a statistically higher frequency

of suicidal ideation, suicide attempts, and higher scores on the Beck Depression Inventory (55). These women were also more likely to have current use of selective serotonin reuptake inhibitors (SSRI), lifetime use of mood stabilizers, and sexual/religious obsessions (55).

2.6.3 Treatment

The limited evidence available underscores a significant gap in our understanding and management of menstrual cycle-related symptom fluctuations in OCD.

2.7 Trauma and stressor-related disorders

2.7.1 Prevalence

Research on PME of trauma and stressor-related disorders is limited. Preliminary reports suggest an increase in PTSD symptoms during the premenstrual and menstrual phases (56).

2.7.2 Course

Emerging research indicates that women with PTSD may experience heightened fear-related and avoidance symptoms premenstrually and during menstruation (56). Studies have also shown that intrusive flashbacks could be exacerbated during different phases of the menstrual cycle, though studies show differing phases where flashbacks were worse (56–58).

2.7.3 Treatment

Studies evaluating the treatment of possible PME of trauma-related disorders symptoms remain limited.

3 Discussion

This review has sought to elucidate the phenomenon of PME and its impact across a spectrum of psychiatric illnesses, including mood, anxiety, psychotic, obsessive-compulsive disorders, personality disorders, and trauma-related disorders. It emerges that a subset of women exhibits a heightened sensitivity to the normal fluctuations of ovarian steroid hormones, leading to PME of symptoms inherent to their psychiatric condition. Research consistently indicates that hormonal fluctuations during the MC present a unique period of vulnerability for the onset or exacerbation of psychiatric symptoms. Notably, PME appears to affect certain disorders more profoundly, suggesting the involvement of distinct neurological and psychological mechanisms (25, 46). Despite these findings, the impact of menstrual cycle-induced hormonal changes on the diagnosis and management of psychiatric disorders remains largely underappreciated (25).

3.1 Limitations

There are numerous limitations that hinder the ability to conduct robust research on the prevalence of PME of pre-existing psychiatric disorders (25). Many current studies rely on the use of retrospective assessment of PME which is limited by participants' memory and potential biased recall. The prospective assessment of symptoms is considered the gold standard, via data collection throughout the entirety of the MC (25, 27). In addition, there are potential effect modifiers that may be difficult to completely eliminate: the effect of psychotropic medication on hormonal fluctuations as well as the role of the MC on drug absorption and metabolization, usage of hormonal contraception, and inpatient treatment settings which may bias towards a treatment effect (25). Therefore, study results should be interpreted in light of these modifiers. Future studies should aim to implement standardized menstrual phase definitions, hormonal assays to verify cycle phase, a minimum observation period of three menstrual cycles, prospective symptom measurement, characterization of participants' reproductive status (naturally cycling, pregnant, menopausal), and larger sample sizes (25, 27). Future areas of study include the role of testosterone in premenstrual exacerbation of psychiatric disorders as well as randomized trials clarifying the efficacy of hormonal treatments and contraceptives for PME of psychiatric disorders.

3.2 Implications

Overall, there remains a lack of robust evidence into PME of known psychiatric disorders. Recognizing PME is crucial, as fluctuations in symptom severity related to the MC can significantly affect diagnosis, risk assessment, and treatment planning (25). The persistence of symptom exacerbation throughout the MC, despite pharmacological intervention, calls for a reevaluation of existing treatment paradigms (25). Preliminary findings suggest that certain disorders, particularly mood disorders and borderline personality disorder, exhibit a higher sensitivity to PME, warranting more frequent screening and tailored management strategies (25). Finally, psychopharmacologic and psychosocial treatment modalities to address PME are vastly understudied, but many existing interventions such as CBT and DBT may be used to target certain symptoms (47).

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The experiences and psychological impact of living with premenstrual disorders: a systematic review and thematic synthesis

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Introduction: As the psychological impact and decreased quality of life experienced by women living with a Premenstrual Disorder (PMD) has been reported in the literature, the aim of this systematic review and thematic synthesis was to explore a) their experiences and the psychological impact of PMDs, specifically Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD), and b) their perceived support needs.

Method: Six databases were searched for publications reporting on qualitative studies, since the database inception. The Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines were followed.

Results: Seventeen papers reporting on 479 women met the inclusion criteria: ten focused on PMS, six on PMDD and one on PMS and PMDD combined. Two main PMD themes were identified: 1) *controlled by PMDs*, which had three subthemes, and 2) *a women and life left broken*, with five subthemes.

Conclusion: Women's accounts revealed that experiences of PMDs were intense, life changing and life-controlling. Women were left holding the responsibility of understanding and managing their own condition, whilst advocating for themselves in a healthcare setting in which their condition has been little understood. Consequently, women developed coping strategies to lead a functional life, and experienced changes to their sense of self. Clinical recommendations included the need for professionals working with women in crisis, to assess for PMDs and signpost towards specialist services.

KEYWORDS

premenstrual syndrome, PMS, premenstrual dysphoric disorder, PMDD, women's health, menstrual cycle

1 Introduction

Premenstrual disorders (PMDs) are on a continuum of premenstrual symptoms ranging in severity from Premenstrual Syndrome (PMS) to the more debilitating Premenstrual Dysphoric Disorder (PMDD) (1), despite being diagnosed separately since 1987 (2). Given this continuum, both PMDD and PMS papers will be included within this review, under the term PMD. Up to 80% of women experience premenstrual symptoms each month (3), for approximately 20-40% of menstruating women these symptoms meet a clinically significant level, affecting their daily functioning, and are defined as PMS (2–4). Only 3-8% suffer symptoms severe enough to be classified as PMDD (2); however, prevalence rates vary depending on assessment method (5). At present, there is no clear understanding of the etiology of PMDs; however, theories include genetics, increased sensitivity of the central nervous system to menstrual cycle hormones and psychosocial factors [for a comprehensive overview, see Hantsoo and Epperson (6)].

Premenstrual Disorders are defined by the cyclical nature of their symptoms, occurring during the luteal phase and subsiding with menstruation, with a symptom-free period between menstruation and ovulation (2). Symptoms of PMDs include low mood, affective liability, and interpersonal conflicts, as well as physical discomfort, changes to appetite and sleep. According to the DSM-V (7), symptoms must cause an impairment to the individual's daily personal, professional, or social commitments during the luteal phase to meet the threshold for a PMDD diagnosis. PMDD is linked to co-morbidities with depression, anxiety and panic disorders, as well as social phobia, OCD (8) and suicidal ideation (9).

Treatment options for PMDs are limited, and a cure for PMDD specifically is only truly possible by removing the ovaries (2). However, an individual's day-to-day life can be improved through symptom management, such as prescribing antidepressants or hormone therapies, to reduce the fluctuation of hormone levels (2). For more mild symptoms, non-pharmacological treatment recommendations include cognitive behaviour therapy, dietary intervention, exercise, exposure to sunlight, stop smoking and not drinking alcohol (10).

In terms of interventions, Kancheva Landolt and Ivanov's (11) systematic review of 32 peer-reviewed papers found non-pharmacological interventions provided a significant reduction in PMS symptoms. In addition, Carlini et al.'s (12) scoping review of 113 studies highlighted that PMS and PMDD symptom reduction was possible with both pharmacological and non-pharmacological interventions, but the authors expressed concern about the quality and methods of some non-pharmacology studies.

The impact of PMDs on a woman's life has been documented by various quantitative studies (13), and although some women experienced their premenstrual changes positively (14), most literature recognises the negative impact. Experiencing PMDs placed a burden on women's occupation (15) and daily activities (16), and has been associated with depression, stress, sleep disturbances and a poor relationship with food (17). Prabhavathi et al. (18) found that as the severity of PMS symptoms increased, cognition and psychomotor execution decreased, highlighting the impact symptoms had on a woman's functional abilities. Given the vast impact of PMDs, it is unsurprising that data from 500 female students showed a direct association with PMS and decreased quality of life measures (19).

In Osborn et al.'s (20) review of ten quantitative studies, women with PMDD were noted to be a high-risk group for suicidal ideation; however, the authors did not find women with PMDD to be at a higher risk for suicide attempts. In contrast, Prasad et al.'s (9) review of 13 papers identified an almost sevenfold increase in risk of suicide attempts. Finally, in the only review of the qualitative literature to date, Moe and Karlsson (21) identified 12 papers reporting on the experiences of women with PMDD only. Two main themes identified the social, emotional, and professional limitations women experienced due to PMDD and their journey to a diagnosis and treatment options. Although the authors used a comprehensive approach to provide nursing specific clinical recommendations, they did not explore the psychological impact of this particular diagnosis, nor did they highlight how services could support these women.

There is a growing qualitative literature exploring women's experiences of PMDs. Changes to women's body dissatisfaction have been documented across the menstrual cycle, and many women chose to conceal their body during the premenstrual phase (22). Cosgrove and Riddle (23) interviewed 30 women with PMS and described the contrast between women's view of themselves with and without their symptoms, leading them to question which was their true identity. Uncertainty about one's own self could be connected to women's reported feelings of loneliness (24). These studies provide insight into the affect PMDD has on a woman's self-image and identity but lacked a comprehensive exploration of the wider psychological impact. As previously discussed, PMDs are considered to sit on a continuum of symptom severity (1), as recognised by Carlini et al. (12) in their review of interventions. As a synthesis of PMDs experiences could provide novel insights into their psychological impact on women. Therefore, the proposed review of qualitative studies aimed to a) explore women's lived experiences of a PMD's, such as PMS or PMDD, and b) explore their perceived support needs from healthcare services.

2 Method

2.1 Search strategy

The systematic search was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (25) and the protocol was registered with PROSPERO in January 2024 (CRD42024505284). The SPIDER tool (26) categories phenomenon of interest (PI), design (D), and research type (R) were used to create search terms (see Table 1). Medical Subject Heading (MeSH) terms identified synonyms, whilst search categories were combined with Boolean operator "AND". Due to diagnostic terminology changing from LLPDD to PMDD in the DSM-IV in 2000 (7, 27), the decision was made to include PMD,

TABLE 1 Search terms by category and search strategy.

	Search terms	
1	(PI) Phenomenon of interest	"Premenstrual dysphoric disorder*" OR PMDD OR "premenstrual syndrome*" OR PMS OR "late luteal phase dysphoric disorder*" OR LLPDD OR "premenstrual disorder*" OR PMD
2	(D) Design	Interview* OR "focus group*" OR questionnaire* OR survey* OR "case stud*"
3	(R) Research Type	Qualitative* OR "mixed method*"
4	2 OR 3	
5	1 AND 4	

PMS, PMDD and LLPDD within the search terms, to ensure no eligible papers were omitted. Six databases were searched from inception to March 2024, CINAHL (EBSCO), EMBASE (OVID), HMIC (OVID), Medline (OVID), PsycINFO (OVID) and Web of Science. Backwards searching of identified papers' reference lists and papers citing the included papers were also used.

2.2 Inclusion and exclusion criteria

Papers were included if 1) participants experienced PMS or PMDD, with a self-reported diagnosis or diagnosis confirmed by study or medical team, 2) studies aimed to understand the participants' experiences related to their condition, 3) studies which utilised qualitative research methods for data collection and analysis (e.g., interviews), including mixed method studies in which qualitative results were presented separately, and 4) studies written or translated into English. Papers were excluded if 1) participant eligibility was unclear or their diagnosis was vague, 2) participants with and without a diagnosis were recruited, and without findings reported separately, or 3) they reported on secondary research (e.g., conference posters or literature reviews).

2.3 Quality appraisal

The Critical Appraisal Skills Programme (28) tool is a validated checklist used to assess included papers, with ten domains including methodology, ethical issues and results. As the CASP does not offer a summary scoring system (29), a numerical system was also used for better comparison across reviews (yes=1, partially agree=0.5, no=0). Total CASP scores were used to categorise methodological quality as high (> 8-10), moderate (6-8) or low (<5) (30, 31). As no accepted guidelines for excluding studies based on quality exist (32, 33), all studies were included irrespective of quality appraisal.

2.4 Data extraction and data analysis

All eligible papers were transferred into NVivo software in preparation for analysis and relevant study characteristics (e.g., aims, sample size and recruitment strategy) were extracted and tabulated. Thematic synthesis (32) was used for data analysis and involved three stages: line-by-line coding of the individual papers' findings was completed independently by two of the authors (DB & DMS), codes were then grouped into descriptive themes across and between papers, with the reviewers looking for similarities and differences between the codes. All themes were discussed and finalised by the whole team, allowing different perspectives and judgements of the meaning behind each code.

2.5 Reflexivity statement

All authors were white women and mothers; however, they ranged in age and stage of their careers. The first author (DB) was a trainee clinical psychologist, with experience working with women in secure services and supporting children and families in community services. The second author (DMS) was a Health Psychologist and Senior Lecturer, specialising in exploring pregnancy and behaviour change. The third author (EO) was a Clinical Psychologist working in paediatric services and had an interest in premenstrual disorder research. The fourth author (AW) was a Clinical Psychologist and Senior Lecturer, with an interest in understanding mothers experiencing severe mental health difficulties. As a team, we acknowledged our similarities with the participants as females of reproductive age, whilst holding in mind the potential for power differentials between researchers without a premenstrual condition and participants with a diagnosis. The similarities and differences between the research team supported nuances in interpretation during the synthesis, whilst discussions and reflective diaries were utilised to minimise the risk of biased interpretations.

3 Results

3.1 Search outcome

Initial searches identified 7,496 references. Following the removal of duplicates, the title and abstract of 4,154 papers were screened for eligibility (see Figure 1). The full text of 79 studies was assessed, with 15 selected for inclusion. An additional two papers were included following backwards searches of the citations and references, resulting in 17 included papers. An independent researcher (SH) assessed 10% of the search results against the eligibility criteria: there was a 100% agreement based on the title and abstract and 100% agreement after reading the full papers (kappa=1).

3.2 Characteristics of included studies

Seventeen papers, published from 1993 to 2024 and conducted in ten countries, were identified and synthesised (see Table 2). Sample sizes ranged from four to 83, with a combined sample of 479. Six studies recruited women with a diagnosis of PMDD: four

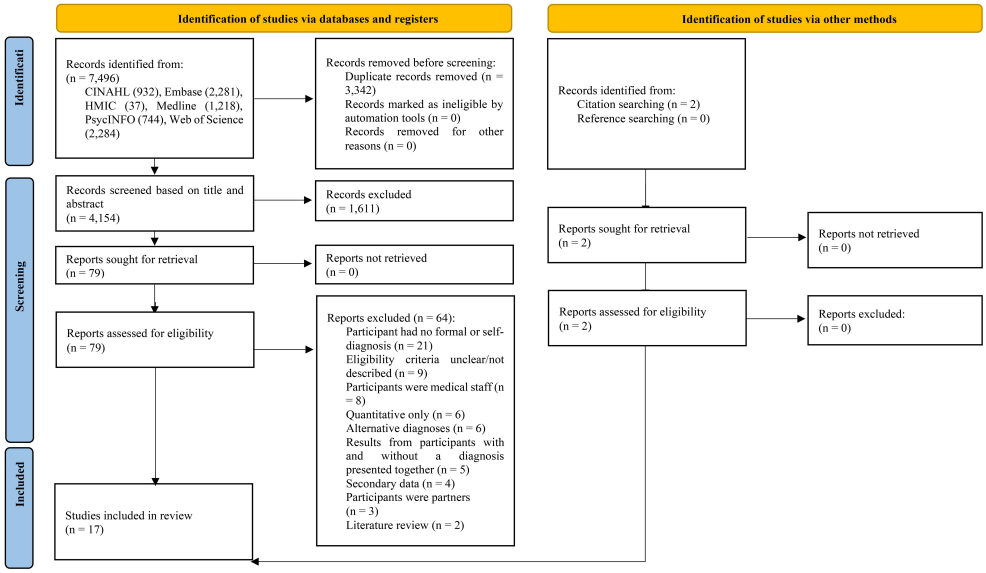

FIGURE 1
PRISMA diagram of the search strategy (25).

studies allowed participants to self-report their formal diagnosis, one study confirmed diagnosis using the *Premenstrual Symptoms Screening Tool* (PSST) (40) and the final study stated that the participants met the DSM-IV criteria for PMDD. One publication used the International Society for Premenstrual Disorders definition of Premenstrual Disorders (PMDs; which includes PMDD and PMS) as eligibility for participation. The other ten studies recruited women with PMS: six accepted self-report diagnosis, two used the PSST, and two stated that researchers confirmed PMS symptoms or diagnosis (see Table 2). Women were recruited from a range of settings, including social media, local newspapers, and radio adverts, as well as medical clinics and snowball sampling. Fifteen studies collected data via semi-structured interviews, the remaining two studies used interviews as well as open-ended surveys and a questionnaire followed by case studies. Thematic analysis was the most used analysis method (n=9), two studies used thematic decomposition and two described content analysis. Thematic coding, narrative analysis, the listening guide and a feminist phenomenological approach were each referenced once.

3.3 Methodological quality of included studies

The methodological quality of all 17 studies was assessed as high (n=14) or moderate (n=3), indicating the rigorous analysis and reporting of results presented. Only three studies had sufficiently considered the researcher-participant relationship (39, 45, 48); however, all papers provided a clear statement of findings and described the value provided by their results. The CASP quality appraisal ratings can be viewed in Table 3. An independent researcher (SH) independently assessed all papers, there was a substantial agreement (97.3%, kappa=0.74), any discrepancies were resolved through discussion.

3.4 Thematic synthesis

Two main themes were conceptualized to capture women's experiences. PMDs were described as life controlling, narratives indicated the psychological symptoms and maladaptive coping mechanisms left women feeling themselves and their lives were broken, and forever damaged. The two themes were 1) *controlled by PMDs* (with three subthemes) and 2) *a woman and a life left broken* (with five subthemes) (see Figure 2).

Themes are outlined below with their respective subthemes and quotes to support. Table 4 presents a matrix of these themes and their respective subthemes, highlighting which themes were endorsed by each of the 17 studies.

3.4.1 Theme 1: controlled by PMDs

This theme and its three subthemes captured the perceived control that PMDs exerted over women's lives, and the coping strategies women developed as a result, including active strategies and avoidance. The process of regaining control was framed as separately to coping strategies implemented, and therefore described as a separate subtheme.

3.4.1.1 Subtheme 1.1: life-controlling psychological symptoms

Psychological and behavioural symptoms of both PMS and PMDD were reported as negatively influencing quality of life more than any physical symptoms. The psychological impacts were defined as "*life-controlling*" [(52): p.5], with examples including emotional sensitivity, feeling overwhelmed and negatively towards

TABLE 2 Characteristics of included studies.

	Author (date) [ref] Location	Aims	Sample size and diagnosis	Participant characteristics	Recruitment and data collection	Methodology and analysis	Findings and themes
				PMDD only studies			
1	Buys (2024) (34) Australia	To explore the transition into recovery, management or transformation of PMDD and how participants understood those narratives	7 Self-diagnosed or reported a formal diagnosis of PMDD, but identified as in recovery, management, or transformation of PMDD	22-45 years old 57% Australian, 28% British, 15% Turkish 85% employed, 15% student Age at onset of symptoms, age at diagnosis and relationship status not reported	Social media adverts and online support groups. Narrative interviews	The Listening Guide) (35, 36)	Two narrative themes: 1) within abjection 2) beyond abjection
2	Chan et al. (2023) (37) USA	To explore the diagnostic and treatment experiences of PMDD patients in the U.S. healthcare system and identify barriers to diagnosis and treatment	32 Self-identified having PMDD (87% reported formal diagnosis)	21-50 years old Experienced PMDD symptoms for a mean of 17.43 years and mean of 5.6 years from symptom onset to diagnosis Age at diagnosis ranged from 16 to 45 94% white, 12% Hispanic, 3% Alaskan native, 3% mixed ethnicity 65% single, 29% married and 6% divorced 86% had attended collage	Online adverts (supported by IAPMD) Semi-structured interviews	Feminist phenomenological approach (38)	Study presents a PMDD Care Continuum that represents five themes as a timeline of participant experiences: 1) PMDD Symptoms 2) Patient delay 3) Diagnosis delay 4) Treatment delay 5) Condition management delay
3	Osborn et al. (2020) (39) England	To explore women's experiences of both having PMDD and of receiving this diagnosis	17 PMDD diagnosis confirmed by the *Premenstrual Symptoms Screening Tool* (PSST) (40) questionnaire	20-56 years old Average symptom onset of 15 years old Average diagnosis of 35 years old 83% white British 47% married, 47% single, 6% divorced 53% obtained undergraduate degree or higher 59% mothers	Recruited via two NHS gynaecology clinics. Semi-structured interviews	Reflexive thematic analysis (41, 42)	Four themes: 1) A broken woman 2) Misdiagnosis and the lost decades 3) A life transformed 4) Negotiating the aftermath
4	Marfuah and Barat (2018) (43) Indonesia	To understand the experiences of adolescents with PMDD	6 Met the diagnostic criteria for PMDD with DSM – IV	14-18 years old Age of first menstruation was between 10 and 15years old 100% Javaness 100% Students relationship status not reported	Purposive sampling from one collage Interviews	Thematic analysis (no reference within paper)	Four themes: ***3)*** Symptoms perceived as a change that affects the psychological, behavioural and physical teens 2) Symptoms of intermittent throughout the menstrual cycle

(Continued)

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TABLE 2 Continued

	Author (date) [ref] Location	Aims	Sample size and diagnosis	Participant characteristics	Recruitment and data collection	Methodology and analysis	Findings and themes
				PMDD only studies			
							3) Environmental factors and hormones play a role in the emergence of symptoms 4) The symptoms cause discomfort and interfere with social relationships
5	Hardy and Hardie (2017) (44) England	To explore women's experience of PMDD in the workplace	15 Self-reported a formal diagnosis of PMDD	25-49 years old 80% receiving treatment for PMDD Received a diagnosis 6months to 4years prior to the interview 53% British, 40% American, 13% did not disclose 87% employed, 13% unemployed relationship status not reported	Online adverts via social media Semi-structured interviews	Thematic analysis (41)	Two themes: 1) Phases of PMDD at work and 2) The role of the organisation
6	Jurvanen (2017) (45) Sweden	To understand the subjective experiences of private- and work life for people with PMDD	11 Self-reported a formal diagnosis of PMDD	55% worked full time, 18% worked part time, 27% were freelance Age range, age at onset of symptoms, age at diagnosis, ethnicity and relationship status not reported	Social media adverts Semi-structured interviews	Thematic analysis (41)	Five themes: 1) The impact of PMDD on work and occupational life 2) PMDD and social life 3) Psychological welfare and PMDD 4) Medical shortcomings 5) Participants' thoughts
				PMDD and PMS studies			
7	Labots-Vogelesang et al. (2023) (46) Netherlands	To improve understanding of the perspectives of women with PMD, their coping strategies and their expectations of the GP	20 Researchers confirmed symptoms met IAPMD definition of PMD	27-49 years old PMD symptoms started at 14 to 43 years old 95% Dutch, 5% Moroccan 75% married/partnership, 20% single, 5% widowed 80% employed, 15% unemployed, 5% student 60% mothers	Adverts in local newspapers and closed PMS/PMDD Facebook pages. Semi-structured interviews	Thematic analysis (The qualitative data analysis & research software) (47)	Three themes: 1) Separate female identities 2) A life-controlling condition 3) Differences in coping strategies

(Continued)

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TABLE 2 Continued

	Author (date) [ref] Location	Aims	Sample size and diagnosis	Participant characteristics	Recruitment and data collection	Methodology and analysis	Findings and themes
				PMS only studies			
8	Park et al. (2023) (48) England	What are the lived experiences of women with PMS? To what extent does PMS influence their daily occupations? What are the needs of women with PMS	4 Self-reported PMS symptoms	No participants details reported	Social media adverts. Semi-structured interviews	Inductive thematic analysis (41)	Three themes: 1) Occupational disturbance 2) Social impairment and occupational disengagement 3) The importance of self-awareness to engage in occupations
9	Tutty et al. (2022) (49) Canada	To explore the relationship between women's premenstrual symptoms and parenting stress	46 Mothers who self-reported PMS	23-47 years old 72.7% white, 16.4% Indigenous, 3.6% Vietnamese, 3.6% Filipino, 3.6% East Indian 65.5% married or living with a partner, 34.5% lived alone Mothers of between 1 and 6 children, with at least one child under 18 80% attended post-secondary schooling 51% employed outside of the home, 37.7% not employed outside of the home, 11.3% students 27.2% currently taking anti-depressants Age at onset of symptoms and age at diagnosis not reported	Adverts placed in local newspapers and public locations, including; libraries, hospitals and child welfare offices. Mixed methods, semi-structured interviews	Thematic analysis (41)	Three themes: 1) Effects of PMS on mothering 2) Parenting changes after bad premenstrual phases 3) Strategies to address negative mothering
10	Ussher and Perz (2020) (50) Australia	To examine the role of premenstrual embodiment in women's premenstrual distress	83 Self-reported PMS, symptoms assessed with the *PSST* (40) and daily diary measures	Average age 35 years old 100% in a relationship 98% were heterosexual, 2% lesbian Age at onset of symptoms, age at diagnosis and ethnicity not reported	Participants recruited from a larger scale project (51). Recruited via social media, local radio, newspapers and women's health centres. Open-ended survey responses and interviews	Theoretical thematic analysis (41)	Two themes: 1) Inhabiting the abject premenstrual body 2) Reframing premenstrual embodiment: resisting the self-objectification and dehumanization.
11	Labots-Vogelesang et al. (2019) (52) Netherlands	To explore which symptoms/ complaints are considered most disabling and why, what cognitions women have about the cause of PMS and how	20 Women who met DSM-5 criteria for PMS, confirmed by researcher	27-49 years old PMS symptoms started at 14 to 43 years old 95% Dutch, 5% Moroccan 75% married/partnership, 20% single, 5% widowed	Recruited via local newspapers and social media Semi-structured interviews	Thematic coding (no reference) Consolidated Criteria for Reporting Qualitative Studies (COREQ) (53)	Three themes: 1) The disturbance in preferred feminine roles of being a good mother and wife 2) PMS as a life-controlling condition

(Continued)

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TABLE 2 Continued

	Author (date) [ref] Location	Aims	Sample size and diagnosis	Participant characteristics	Recruitment and data collection	Methodology and analysis	Findings and themes
				PMS only studies			
		these affect their help-seeking behaviour		80% employed, 15% unemployed, 5% student 60% mothers			3) Differences in coping strategies
12	Siahbazi et al. (2018) (54) Iran	To discover the experiences of women with PMS, with a focus on quality of life	21 Moderate to severe PMS based on the *PSST* (40)	15-45 years old 48% married, 48% single, 4% divorced 43% mothers (between 1 and 3) 58% employed, 28%, housekeeper 14% students 67% attended higher education, 33% high school education Age at onset of symptoms, age at diagnosis and ethnicity not reported	Purposive sampling Semi-structured interviews	Content analysis (55)	Four themes: 1) Physical consequences 2) Psychological consequences 3) Behavioural consequences 4) Familial-social consequences
13	Ussher and Perz (2013) (56) Australia	To identify key themes in women's construction and experience of premenstrual change, and the ways in which women negotiate and cope with PMS, in the con- text of relationships	60 Self-reported to experience PMS	22-48 years old 98.5% Anglo-Australian, 1.5% Asian 80% in a relationship 66% heterosexual, 34% lesbian 47% mothers 82% employed Age at onset of symptoms and age at diagnosis not reported	Participants recruited from a larger scale project (50). Recruited via social media, local radio, newspapers and women's health centres. Semi-structured interviews	Thematic analysis (41, 57)	Three themes: 1) Self-monitoring and awareness 2) Recognition and acceptance of premenstrual change 3) Coping through self-regulation of premenstrual distress
14	Hoga et al. (2010) Brazil (58)	To describe the perceptions of women with PMS regarding the behaviour of their spouses in face of this event	20 Self-report PMS symptoms	19-44 years old 55% single, 35% married and 10% divorced 95% employed Years in education 10-16years Age at onset of symptoms, age at diagnosis and ethnicity not reported	Snowball sampling Semi-structured interviews	Narrative analysis (59)	Three themes: 1) Difficulties in identifying the syndrome and in adopting care practices 2) Lack of knowledge and sensitivity of men 3) Its impact on the couple relationship
15	Mooney-Somers et al. (2008) (60) Australia	To examine the development, experience and construction of premenstrual symptoms across a range of relationship types and contexts	60 Self-reported PMS	22-48 years old Majority Anglo-Australian 80% partnered 66% heterosexual, 33% homosexual	Mixed method Recruited via local media, women's health centres, community groups and	Thematic decomposition (61), a version of thematic analysis (41)	Three themes: 1) Naming to explain 2) 'PMS' becoming the only explanation for distress

(Continued)

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TABLE 2 Continued

	Author (date) [ref] Location	Aims	Sample size and diagnosis	Participant characteristics	Recruitment and data collection	Methodology and analysis	Findings and themes
PMS only studies							
				47% mothers Age at onset of symptoms and age at diagnosis not reported	social organizations. Semi-structured interviews		3) 'PMS' as not a legitimate explanation for distress
16	Perz and Ussher (2006) (62) Australia	To examine women's subjective experience of PMS, and the negotiation of PMS in the context of relationships	35 (interviews) 2 (case studies) Self-reported to experience PMS	17-49 years old 63% partnered 59.5% heterosexual 76.6% employed 44% mothers Age at onset of symptoms, age at diagnosis and ethnicity not reported	Mixed methods Recruited via local media and women's health centres Questionnaire, narrative interviews, followed by case studies	Thematic decomposition (61)	Women described PMS similarly, as being characterized by intolerance, irritation, emotional sensitivity, feeling more negative towards others, and feeling overwhelmed in the face of life's demands.
17	Burrage and Schomer (1993) (63) South Africa	To examine whether the daily coping processes of women suffering from PMS vary across the menstrual cycle and to investigate the effect that women's coping resources have on the severity of their premenstrual symptom	12 PMS symptoms confirmed by researcher	30-49 years old 83% married, 17% single 33% housewives, 25% secretaries, 8% nurse, 8% musician, 8% part-time worker 8% used oral contraception Age at onset of symptoms, age at diagnosis and ethnicity not reported	Recruited via advert in local newspaper Women completed 8 weeks of daily PMS symptom diaries Three formal semi-structured interviews	Content analysis (64)	Interview 1: common PMS experiences and feeling like two different people. Interview 2: difficulty in meeting daily demands and interpersonal conflict. Interview 3: hassles arising from family matters, role conflict and daily workload.

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TABLE 3 Overview of CASP scores.

	Author (year)	1. Clear Aims	2. Qual method appropriate	3. Research design appropriate	4. Recruit-ment strategy	5. Data collection	6. Researcher participant relationship	7. Ethical	8. Data analysis	9. Statement of findings	10. Value of research	Quality Score
PMDD only studies												
1	**Buys (2024)** (34)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	No (0)	No (1)	Yes (1)	Yes (1)	Yes (1)	High (9)
2	**Chan et al. (2023)** (37)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	High (9)
3	**Osborn et al. (2020)** (39)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	High (10)
4	**Marfuah and Barat (2018)** (43)	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)	No (0)	No (0)	No (1)	Yes (1)	Yes (1)	Moderate (6)
5	**Hardy and Hardie (2017)** (44)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	High (9)
6	**Jurvanen (2017)** (45)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	High (10)
PMDD and PMS studies												
7	**Labots-Vogelesang et al. (2023)** (46)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	High (9)
PMS only studies												
8	**Park et al. (2023)** (48)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	High (10)
9	**Tutty et al. (2022)** (49)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	High (9)
10	**Ussher and Perz (2020)** (50)	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)	No (0)	No (0)	Yes (1)	Yes (1)	Yes (1)	Moderate (7)
11	**Labots-Vogelesang et al. (2019)** (52)	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	High (8)
12	**Siahbazi et al. (2018)** (54)	Yes (1)	Yes (1)	Yes (1)	No (0)	Yes (1)	No (0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	High (8)
13	**Ussher and Perz (2013)** (56)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	High (9)
14	**Hoga et al. (2010)** (58)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	High (9)
15	**Mooney-Somers et al. (2008)** (60)	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	High (8)
16	**Perz and Ussher (2006)** (62)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	High (9)
17	**Burrage and Schomer (1993)** (63)	Yes (1)	Yes (1)	No (0)	Yes (1)	Yes (1)	No (0)	No (1)	Yes (1)	Yes (1)	Yes (1)	Moderate (7)
	Percentage of studies rated 'Yes' (1)	100%	100%	70%	94%	100%	18%	88%	94%	100%	100%	

Key

Yes (1)	Partially (0.5)	No (0)
High scores: > 8-10	moderate scores: 6-8	low scores: <5

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others. At their most extreme, women reported suicidal thoughts and attempts to end their life and "*monthly admissions to emergency department each time they reached crisis point*" [(39): p.7]. For some women, the time without symptoms was spent preparing for and worrying about their next premenstrual phase, highlighting the life-controlling nature of the condition.

> "*I'm actually always thinking about it. And when I feel good, I'm already preoccupied with it, like: 'Oh, I hope I won't feel bad again'*" [(6): p.5].

3.4.1.2 Subtheme 1.2: learning to cope

A wide variety of coping strategies to manage the symptoms and impacts of their undiagnosed PMDs were described, ranging from active approaches to avoidance. Although many papers referenced isolation, there was an interesting contrast in framing: some describing avoidance of "*emotional labour*" [(62): p.297], whilst others reported being alone as a form of self-care.

> "*I just want to lock myself in a room and hide under a duvet and not talk to or see anyone. And I'm completely disengaged and don't take initiatives*" [(45): p.25].

Many women had developed maladaptive coping strategies; for example, substance misuse, self-harm or disordered eating as a way to maintain control or as a form of self-harm. Secondary mental health difficulties were also described; eating disorders and suicidal thoughts or attempts to end their lives.

> "*And so at some point I […] would also feel the urge to end it all*" [(46): p.5].

Whilst some women lacked the energy to implement any coping strategies, others actively engaged with activities to look after their own body and prioritise themselves; "*taking the time-out to recognize my own needs has been very useful*" [(50): p.15].

3.4.1.3 Subtheme 1.3: taking back control of their lives

Shared amongst some participants was the sense of women taking back control of their lives, in contrast to feeling controlled by their PMDs, after receiving a diagnosis and/or treatment. This subtheme was more prevalent within the PMDD papers (see Table 4). Examples included women *"adjusting [their] lifestyle completely"* [(34): p.11] and the ability to plan their lives around their menstrual cycles, rather than work against it. Although some women struggled to accept their diagnosis and were reluctant to take medications, others described validation from finally being given a diagnosis and/or treatment. Participants described their treatment as "*life changing and life-saving*" [(39): p.8].

3.4.2 Theme 2: a woman and a life left broken

Women described the length of time between their first symptoms and their eventual diagnosis, and the responsibility they held to advocate for themselves throughout this process. Advocating for themselves across a significant length of time when feeling repeatedly dismissed by healthcare impacted women's sense of self, and other key life domains. Five subthemes were developed.

3.4.2.1 Subtheme 2.1: dismissed by healthcare professionals

On many occasions women visited healthcare professionals seeking advice and help, but they left feeling "*dismissed*" [(39): p.7], with one individual being told her symptoms were "*in their head*" [(37): p.4]. Professionals were deemed to have minimal knowledge regarding the symptoms or treatment options for PMDs, thus requiring women to be the expert and advocate for themselves.

> "*I realised that I basically have to treat myself*" [(48): p.643].

Women described spending months completing symptom diaries only to have doctors decline to read them, which they experienced as particularly frustrating because the DSM-V specifically highlights symptom diaries as a necessary part of the diagnostic process (7). If treatments were offered, these focused solely on physical symptoms, therefore not targeting most distressing psychological symptoms (as per theme 1, subtheme 1).

> "*You can no longer turn to a doctor because […] they had no answers either*" [(46): p.5].

3.4.2.2 Subtheme 2.2: fractured sense of self

Across the majority of studies, women used an array of terms to define and differentiate themselves with and without symptoms, as if they were two separate entities and described "*feeling like two different people*" [(63): p.113]. Examples included "*alter-ego*" [(39): p.5] and "*Jekyll and Hyde*" [(44): p.294]. This finding appeared to be in response to the guilt and fear women experienced regarding their "*out of character*" [(44): p.295] behaviours, whilst in the luteal phase. One consequence of a fractured self-image was a decline in self-esteem and self-confidence.

> "*I lost my confidence and I stopped saying what I really felt and what I really thought*" [(34): p.8].

Specifically, women described a self-objectification and annihilation of their "*sense of being attractive*" [(50): p.7] and used derogatory terminology to describe themselves: *"frumpy"*, "*disgusting*" and *"unattractive*" [(50): p.7]. Women chose to

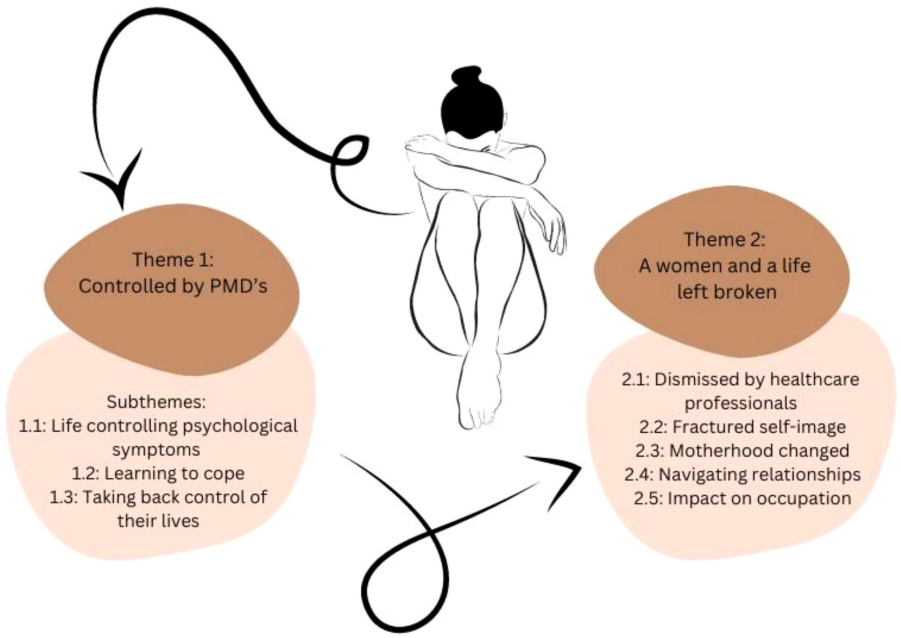

FIGURE 2
Overview of the two themes and subthemes.

conceal their body during their premenstrual phase by wearing looser fitting clothes, or by simply not leaving the house.

3.4.2.3 Subtheme 2.3: motherhood changed

For participants who had children, a majority spoke about the distress and impact of their symptoms on their children, and recognised being "*quite unreasonable with them*" [(49): p.90] during their luteal phase. Women described the difficulties fulfilling their role as a mother and the impact this had; "*I feel like I'm not being a good mom*" [(48): p.643]. Some women felt dominated by the needs of their family and described a feeling of resentment and internal conflict. Some women bravely shared their guilt of using physical chastisement with their children, such as spanking, when experiencing symptoms, something they would not typically do. Intense feelings of guilt then followed, and women overcompensated with their children afterwards or choose to isolate themselves during their luteal phase to avoid contact with their family to protect them.

> "*For women who were mothers, they talked about having felt unable to care for their children and their deep regret for not having been able to be the parent that they wished to have been*" [(39): p.7].

3.4.2.4 Subtheme 2.4: navigating relationships

Maintaining relationships through menstrual cycles was a common challenge, women spoke of volatile relationships and repeated conflicts with partners, and experienced guilt for not fulfilling their own role as a supportive partner. Many spoke about their difficulties in having to rely on someone else for support and recognised the responsibility of having to educate their partner. Some women had a perception that their male partners did not understand their intense symptoms and they had a "*perception that men did not understand the suffering of women*" [(58): p.375]. Relationships became fractured as partners told women that they "*cannot rely on you*" [(54): p.288], resulting in women having to apologise for their behaviour during their luteal phase. However, when partners did recognise the difficulties, women generally felt more understood and supported. This perceived lack of understanding resulted in some heterosexual women never choosing to tell their partner when they were experiencing symptoms related to their menstrual cycle.

> "*Very unfair that every month I have to say to my partner 'no I'm, it's the week that I'm getting my bad days so, you know, I'm just telling you now' it's a bit embarrassing*" [(60): p.6].

3.4.2.5 Subtheme 2.5: impact on occupation

As participants were working or were in education the term occupation was used to cover both activities. A common theme across studies was that maintaining an occupation whilst experiencing life-controlling symptoms was perceived to be a near impossible task. Women described regular absences, terminated employments and withdrawal from higher education: "*school was shattered*" [(43): p.223].

> "*I feel I can't do the 8 hours a day, 5 days a week job. I really don't think I could manage that mentally or physically. Because,*

> *if I look back at times I've been working, I have many days of absence. At least 2-3 days every month, and they always happen the days before menstruation*" [(45): p.23].

Some women described feeling less motivation to engage in occupations during their luteal phase, whilst others acknowledged their careers had been impacted by their symptoms of emotional dysregulation.

> "*Women often thought colleagues were talking about them and perceived them as being unable to do their job. Communications could often be misperceived as negative or a personal attack on them*" [(44): p.294].

Avoidance was used by some women to manage at work, as well as recognising they held a more negative view of colleagues; "*I find I get more annoyed by other people … especially at work*" [(50): p.915]. Although some individuals felt comfortable sharing their experiences with their employer, this came with its own complexities, including facing disciplinary action and justifying the chronic impact of PMDs.

4 Discussion

This systemic review of 17 studies was the first to explore and thereby report on the psychological impact of living with PMDs. Key themes highlighted PMS and PMDD were experienced as life controlling, women felt required to repeatedly advocate for themselves during appointments with medical professionals who failed to recognise their PMD, and they had to explain their condition to their family and work colleagues, who did not understand their symptoms' psychological impact. The weight of this responsibility was with women who already experienced debilitating symptoms each month, which reduced their psychological resilience. Women positioned themselves as the expert, researching and educating others, including medical professionals. As a result of these demands, combined with living with life-controlling symptoms and developing and learning coping strategies to lead a functional life, women viewed themselves and their lives as broken.

The current review expands upon the findings of Moe and Karlsson's PMDD review (21), the findings from both reviews support the impact PMD's had on a variety of life domains, including family, relationships, and occupation. However, novel insights were provided by the current review into the relationships women held with others. Themes described the difficulties women had fulfilling their roles as a mother and partner, and the subsequent guilt and regret experienced. Additionally, as Moe and Karlsson's review (21) included six papers in which the participants' diagnosis was not verified or was questionable, the current review provided a more diagnostically robust synthesis of qualitative studies relating to PMDD as well as PMS. Thus, only six studies from Moe and Karlsson's review of 12 studies were included in the current review.

To manage their enduring symptoms and maintain a functional life, women developed various maladaptive coping strategies, including disordered eating (16, 65). A strong association between suicidal ideation and PMDD was previously seen in Osborn et al.'s (20) and Prasad et al.'s (9) reviews, and reflected in the current review, in which a monthly crisis point was reached by many women. Given the level of risk highlighted, further research should focus specifically on understanding the relationship between PMDs and thoughts and attempts of suicide.

Whilst the contrast between women's self-image with and without PMS symptoms has been documented (23), the current review noted that women's sense of self appeared to be fractured with women describing themselves as two separate entities. Changes to identity in response to a physical health illness draw on narrative identity theory to understand the mismatch perceived identity (66). Current themes connected this fracture in identity to the guilt women felt for their behaviour during their luteal phase, and the self-objectification which followed.

Although the psychological impact PMD symptoms had on women's quality of life has been quantified in the literature (13, 19), the current review extends these observations by recognising that even during non-symptomatic periods, women were still worrying about their next menstrual cycle. Despite the combination of PMS and PMDD diagnoses in this review, these findings were seen across all studies.

Of the eight individual sub-themes, seven were equally representative of both PMS and PMDD focused papers, highlighting that there are a number of shared experiences. However, the subtheme "taking back control" was only endorsed by papers recruiting women with PMDD. Although PMDD sits at the more severe end of the continuum, the findings of this subtheme may reflect the potentially curing treatment options for PMDD as opposed to the ongoing symptom management for women with PMS (2).

4.1 Strengths and limitations of synthesised papers

This review recognised the omission of relevant demographic information within the synthesised papers; 11% failed to document the participants' age and 41% did not report their ethnicity. This omission limits the transferability of results to other groups and settings. Only five papers reported on the length of time women had experienced symptoms, or their age at onset of symptoms or diagnosis, meaning nuances within the data and psychological impact could not be explored in depth. During analysis, the authors noted that no information regarding participants' sexuality or the gender of participants' partners was reported in the included studies. In addition, Park et al. (48) provided no participant demographic information, and two papers did not

reference the author of the chosen method of analysis. Similarly, the CASP rating scores (see Table 3) highlighted a notable trend of authors failing to reflect on the researcher-participant relationship (item 6), and how their own position could impact the analysis.

Whilst conducting scoping searches, the authors noted published titles which referenced a PMD; however, the methodology indicated that women without a formal diagnosis were recruited. As documented in Figure 1, a total of 21 papers were removed because they focused on non-clinical levels of premenstrual symptoms, and a further nine were removed due to unclear or undefined participant eligibility criteria. It is argued that this practice continues to blur the lines of what are typical premenstrual symptoms versus the severity of diagnosable PMDs. Transparency and clarity of participants' symptoms and/or diagnosis are needed in future research.

4.2 Strengths and limitations of review process

This review of 17 papers was conducted in a systematic, transparent way, using an established analysis approach and synthesised the voices of 479 women across 31 years of research. Searches were independently analysed for eligibility; assessment of each paper was conducted using the validated CASP (28) checklist and initial coding was conducted separately by the two authors independently to increase credibility and minimise risk of bias. However, the decision to only include academic papers written in English raised the possibility of language, location and publication biases.

As PMS and PMDD sit within a continuum (1), studies were combined under the term PMD to develop a comprehensive picture of women's experiences. Although it was a strength to combine qualitative PMD studies, it could also be argued that nuances of symptom severity could not be drawn out appropriately. At present PMS and PMDD are diagnosed independently; however, PMDD has only been a separate entity since 2013 (2), and hence more qualitative studies are emerging only since then. The matrix of theme representation (see Table 4) strengthened the decision to combine PMS and PMDD studies, as only one of eight subthemes was solely represented by both diagnoses. All seven remaining subthemes represented the experiences of women with both PMS and PMDD, highlighting the similarities of their psychological impact.

Another strength of this review was the clear specification of PMS and PMDD symptoms/diagnosis within included papers, ensuring that the synthesised data captured the experiences of women with clinical levels of symptoms, as opposed to the general population of menstruating women. Papers excluded for this reason were unlikely to represent the experiences of women with a clinically diagnosable level of symptoms. The optimum strategy to ensure formal PMS and PMDD diagnoses is debated by the research community (67). Whilst there are challenges with allowing participants to self-report their diagnosis, the validity of retrospective questionnaires has also been challenged (67). Therefore, ten papers in which participants self-reported their diagnosis were included for analysis.

TABLE 4 Matrix of theme representation within the included 17 studies.

	Author (year)	Theme 1: Controlled by PMS/PMDD			Theme 2: A woman left broken				
		Life controlling psychological symptoms	Learning to cope	Taking back control	Dismissed by healthcare professionals	Fractured self-image	Motherhood changed	Navigating relationships	Impact on occupation
	PMDD only studies								
1	Buys (2024) (34)	✓	✓	✓	✓	✓	✓	✓	✓
2	Chan et al. (2023) (37)	✓	✓	✓	✓	–	–	–	–
3	Osborn et al. (2020) (39)	✓	✓	✓	✓	✓	✓	✓	✓
4	Marfuah and Barat (2018) (43)	✓	✓	–	–	–	–	✓	✓
5	Hardy and Hardie (2017) (44)	✓	✓	✓	✓	✓	–	–	✓
6	Jurvanen (2017) (45)	✓	–	–	–	✓	✓	–	✓

(*Continued*)

TABLE 4 Continued

	Author (year)	Theme 1: Controlled by PMS/PMDD			Theme 2: A woman left broken				
		Life controlling psychological symptoms	Learning to cope	Taking back control	Dismissed by healthcare professionals	Fractured self-image	Motherhood changed	Navigating relationships	Impact on occupation
PMDD and PMS studies									
7	Labots-Vogelesang et al. (2023) (46)	✓	✓	✓	✓	✓	✓	✓	✓
PMS only studies									
8	Park et al. (2023) (48)	✓	✓	–	✓	✓	✓	✓	✓
9	Tutty et al. (2022) (49)	✓	✓	–	✓	–	✓	✓	–
10	Ussher and Perz (2020) (50)	✓	✓	–	–	✓	–	✓	–
11	Labots-Vogelesang et al. (2019) (52)	✓	✓	–	✓	✓	✓	✓	–
12	Siahbazi et al. (2018) (54)	✓	–	–	✓	✓	✓	✓	✓
13	Ussher and Perz (2013) (56)	✓	✓	–	–	✓	✓	✓	✓
14	Hoga et al. (2010) (58)	✓	✓	–	–	–	–	✓	–
15	Mooney-Somers et al. (2008) (60)	✓	✓	–	–	✓	–	✓	–
16	Perz and Ussher (2006) (62)	✓	✓	–	–	✓	–	✓	✓
17	Burrage and Schomer (1993) (63)	✓	✓	–	✓	✓	✓	–	✓

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4.3 Clinical implications

The difficult experiences women had seeking support from healthcare professionals were highlighted, adding to the concerning reality that healthcare professionals were less likely to take women's experiences seriously (68), especially when their symptoms were related to their reproductive health (39, 69). Consequently, women with a suspected or diagnosed PMD must continue to advocate for themselves and discuss their symptoms with their family and social support network. Clinicians should consider the psychological impact of PMDs and the associated impact on quality of life, recognising the potential need for referral to clinical psychology services for therapeutic support with processing of diagnosis and psychological impact, to reduce psychological distress.

Owing to the frequency of suicidal experiences described, additional training for healthcare staff to assess PMDs and signpost women to appropriate services is required. Increased understanding of PMDs would be beneficial in healthcare services where women in crisis may present, for example, emergency services, general practitioners, and mental health teams. Once diagnosed, many women described only being offered treatment for physical symptoms. Therefore, premenstrual training for healthcare professionals is needed to have an updated understanding of the growing research into the range of evidence-based treatment options [see Nevatte et al. (70) for further exploration of treatment options] and recognise the need for therapeutic interventions targeting the psychologically distressing symptoms.

5 Conclusion

For the first time, qualitative papers exploring the psychological impact of premenstrual disorders (PMS and PMDD) were synthesised in one systematic review. Women described PMDs as life-changing and life-controlling, they were often left holding the responsibility for understanding and managing their own symptoms, whilst advocating for themselves in a world which did not recognise their experiences. Key recommendations included the need for medical professionals working with women in crisis, to assess for PMDs and signpost towards specialist services, including psychological interventions.

Author contributions

DB: Conceptualization, Data curation, Formal analysis, Project administration, Validation, Writing – original draft, Writing – review & editing. DS: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – review & editing. EO: Conceptualization, Validation, Writing – review & editing. AW: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The link between childhood traumatic events and the continuum of premenstrual disorders

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Background: Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD), collectively known as Premenstrual Disorders (PMDs), cause significant distress and functional impairment, and premenstrual exacerbation (PME) affects a large proportion of women with psychiatric diagnoses. Childhood trauma is one factor that may contribute to PMD/PME risk. This study examines the relationship between childhood trauma and PMDs, PME, and non-PMD psychiatric illness.

Methods: This study is a secondary analysis of data from a prospective cohort. Participants completed self-assessments on childhood trauma using the Childhood Traumatic Event Scale (CTE-S) and on premenstrual symptoms using the Premenstrual Symptoms Screening Tool (PSST). Psychiatric diagnoses were assessed through structured clinical interviews. Participants were divided into four groups based on their PSST scores and psychiatric illness status: (1) Premenstrual Disorders (PMDs; moderate to severe PMS and PMDD), (2) PME, (3) psychiatric controls (PC; individuals with psychiatric illness but no significant premenstrual symptoms), and (4) healthy controls (HC; individuals with no psychiatric illness and no significant premenstrual symptoms). Statistical analyses, including ANOVA, Tukey's HSD test, Fisher's exact test, and logistic regression, were conducted to examine differences among the groups.

Results: Data from 391 participants were analyzed. Participants with PME and PC reported a higher quantity and severity of childhood traumatic events compared to HCs ($p < .05$). There was a weak but significant correlation between childhood trauma and premenstrual symptom burden across all groups ($R = .18$, $p < .001$). Within-group analysis revealed moderate correlations between childhood trauma and premenstrual symptoms driven by the PMD group ($R = .42$, $p = .01$).

Conclusions: The findings underscore the impact of childhood traumatic events on mental health and premenstrual symptoms and highlight the need for additional research to explore the underlying mechanisms linking childhood trauma to the continuum of premenstrual disorders, to improve the efficacy of trauma-focused interventions for affected individuals.

KEYWORDS

childhood trauma, premenstrual syndrome, premenstrual exacerbation (PME), Premenstrual Dysphoric Disorder (PMDD), adverse childhood experiences, menstrual cycle

Introduction

On average, women menstruate for 40 years of their lives, and approximately 80% experience physical and/or mood symptoms in the premenstrual week. While most women experience mild premenstrual symptoms that do not affect quality of life or functioning, an estimated 20-40% of women experience premenstrual syndrome (PMS) and 5-8% meet criteria for Premenstrual Dysphoric Disorder (PMDD). Premenstrual Syndrome (PMS) is characterized by recurrent physical and/or emotional symptoms occurring in the late luteal phase (roughly the week prior to the onset of menses); symptoms remit with the start of menstruation (1). Although these symptoms can affect daily functioning and quality of life, the affective symptoms that occur do not reach threshold for a depressive disorder, and some women have physical symptoms only. PMDD, on the other hand, is a mood disorder characterized by functional impairment secondary to affective changes in the late luteal phase. Collectively, these premenstrual syndromes (PMS and PMDD), often thought of as a continuum of Premenstrual Disorders (PMDs), contribute to significant physical and psychic burden across a woman's reproductive lifespan.

In addition to the PMDs, there is Premenstrual Exacerbation (PME) of psychiatric disorders. PME occurs in women with psychiatric disorders who experience a significant worsening in psychiatric symptoms during the week preceding their menses. PME of affective disorders is common. Recent retrospective and prospective studies have indicated PME prevalence rates ranging from 33.7% to 68.5% in women with major depressive disorder and 44-68% among those with bipolar depression (2–7). PME is associated with increased morbidity of psychiatric illness, including decreased general functioning, shorter remission times, more severe symptoms, and higher rates of treatment resistance. Like the PMDs, PME is thought to involve abnormal sensitivity to ovarian hormone fluctuations, although specific mechanisms remain unclear and could vary based on primary diagnosis (2).

Numerous biopsychosocial factors have been proposed as potential contributors to PMDs, including genetic predisposition, hormone sensitivity, neurotransmitter alterations, and inflammatory processes (8–14). Amidst these potential contributors, the influence of psychosocial stress, particularly trauma or adverse childhood experiences (ACEs), has emerged as a contributor to the risk for and severity of PMDs (2, 3, 15). ACEs refer to potentially traumatic events or experiences occurring in childhood or adolescence that fall into one of three general categories and can include one or many of the following: abuse (physical, emotional or sexual), neglect (physical or emotional) and household challenges (substance abuse, mental illness, domestic violence, parental separation or divorce, incarceration) (15). Several studies have found an association between the number of ACEs and the development and severity of PMDs. In a large cross-sectional analysis of nearly 12,000 participants, Yang et al. (2022) found a positive linear association between the number of ACEs experienced and probability of PMDs, with those experiencing >4 ACEs having a higher likelihood of having PMDD (7). Another study observed a similar correlation where the number and severity of premenstrual symptoms increased with increasing levels of childhood trauma (16). In a recent study, more childhood adversity was associated with increasing negative affect and greater stress response (as measured by cortisol) as patients progressed from the follicular to the luteal phase among women with PMDD (17).

Other research has focused on whether specific types of traumatic or adverse childhood experiences are associated with higher risk for or severity of PMDs. For example, some studies found a significant association between childhood emotional and physical abuse and later risk for PMDs (18–22). Yet other investigations pointed to sexual abuse during childhood and adolescence as posing the highest risk for PMDs, and particularly for PMDD (23). Conversely, others failed to find an association between sexual abuse and PMDs (24). Some studies found higher rates of PMDD among women with higher levels of childhood adversity independent of category (i.e. physical abuse, sexual abuse, emotional abuse, and neglect). Together, these conflicting results

may stem from differences in study methodology, varying definitions of PMDs (i.e., whether specifically studying PMDD versus PMS), limited sample sizes, and a scarcity of studies focused on the stressor timing (childhood versus lifetime adversity) in relation to the onset or severity of PMDs.

Despite the known connection between childhood trauma and increased risk for various mental health conditions (25, 26), including PMDs, only a few studies have explored the relationship between childhood trauma or adversity and PME. One such study by Koci et al. (2007) assessed the impact of childhood sexual and physical abuse on subsequent symptoms of PMS and mood symptoms throughout the menstrual cycle and discovered that both types of abuse were elevated among women experiencing "premenstrual magnification" of mood symptoms and among women with persistently heightened mood symptoms across the menstrual cycle, irrespective of premenstrual changes (23). Although this study underscores a connection between trauma and the development of *both* mood symptoms and PME, its applicability is constrained by the absence of formal psychiatric evaluations.

To date, significant gaps persist in our understanding of the correlations between PMDs (as well as PME) and the timing (e.g. childhood exposure), type, and severity of traumatic events; thus the present study aims to assess these relationships within a cohort of women who underwent thorough psychiatric assessment and premenstrual symptom evaluation. We defined participant groups by their primary diagnosis and premenstrual symptoms (1) PMDs (2), PME (3), psychiatric controls (PC) (4), healthy controls (HC), and evaluated associations with the frequency, nature, and timing of childhood traumatic events. We hypothesized that individuals with PMDs would have more childhood trauma (in both quantity and severity) compared to those with PME, psychiatric illness alone, and controls.

Methods

This is a secondary analysis of data from The Prospective Study of Pregnant Women, an observational cohort of pregnant individuals aged 18 and older with and without mood disorders at The Johns Hopkins University School of Medicine (27, 28). Exclusion criteria included current active suicidal ideation, medical instability, and active substance use disorders. Upon enrollment in the study, participants filled out a variety of study questionnaires, including demographic information, reproductive history including age of menarche, and self-assessments focusing on trauma and menstrual cycle symptoms: the Childhood Traumatic Event Scale (CTE-S), which gauges the history of childhood trauma, and the Premenstrual Symptoms Screening Tool (PSST), which collects retrospective assessments of mood and physical premenstrual symptoms. Past and current psychiatric diagnoses were determined with a Structured Clinical Interview for DSM-IV Disorders (SCID) (29) conducted by a trained research assistant and confirmed through clinical interview by a psychiatrist using DSM-IV criteria. Any discrepancy in diagnosis was reconciled through review by the study psychiatrists and research assistant. Data were collected and securely stored using the REDCap (Research Electronic Data Capture) tool hosted at Johns Hopkins University (30, 31). This study was approved by the Institutional Review Board of The Johns Hopkins University.

Study measures

Childhood Traumatic Events Scale (CTE-S): The Childhood Traumatic Events Scale (CTE-S) is a self-report questionnaire used to assess exposure to different types of trauma prior to the age of 17. This scale (32) assesses whether participants experienced six different types of trauma: 1) death of a close friend or family member, 2) major upheaval between parents (divorce, separation, etc.), 3) traumatic sexual experience, 4) physical violence, 5) extreme illness or injury, 6) "other major upheaval." For each type of trauma, participants are first asked whether they experienced it prior to the age of 17 or not. If they endorse experiencing it, they are asked further questions about their age at the time of trauma, the severity of how traumatic this event was (Likert scale 1 to 7), and how much they confided in others (Likert scale 1 to 7). For each participant, the sum of total number of traumatic events experienced and the total severity of traumatic events was calculated.

Premenstrual Symptoms Screening Tool (PSST): The Premenstrual Symptoms Screening Tool (PSST) is a questionnaire that translates DSM-IV criteria for Premenstrual Dysphoric Disorder (PMDD) into a rating scale with degrees of severity (33). The questionnaire assesses the severity of 14 different premenstrual symptoms and degree of interference in five areas of life using a Likert scale (1 to 4, "Not at All" to "Severe"). The PSST stratifies participants into those with no to mild premenstrual symptoms, moderate-to-severe premenstrual symptoms or PMS, and likely PMDD.

Structured Clinical Interview for DSM-IV Disorders (SCID): The Structured Clinical Interview for DSM-IV Disorders (SCID) is a semi-structured interview guide for making DSM-IV diagnoses. The SCID for Axis I assesses for current and lifetime mood disorders, psychotic disorders, substance use disorders, anxiety disorders, and eating disorders through questions that map onto DSM-IV diagnostic criteria (29).

Participants

Of the four-hundred and nine participants enrolled in the parent study as of June 2020, 18 participants were missing either PSST or CTE data, resulting in a final sample of N = 391 participants used for this analytic cohort. Participants were stratified into 4 groups based on their level of premenstrual distress (as measured by their PSST category) and their history of psychiatric illness as follows: 1) Premenstrual Exacerbation (PME) – those with moderate-to-severe premenstrual symptoms on PSST and either a current mood or anxiety disorder on the SCID or those on medication for a lifetime mood or anxiety disorder; 2) Premenstrual Disorders (PMDs) – those who met "moderate-to-severe PMS" or "PMDD" on the PSST, but did not have current

mood/anxiety disorder nor medication treatment for a lifetime mood/anxiety disorder; 3) Controls with psychiatric illness [Psychiatric Controls (PC)] – those with none to mild premenstrual symptoms on the PSST **and** either a current mood/anxiety disorder on the SCID or medication treatment for a lifetime mood/anxiety disorder and 4) Healthy Controls (HC) – those with none to mild premenstrual symptoms, no current mood/anxiety disorder and no medication treatment for a lifetime mood/anxiety disorder.

Data analysis

Demographics were summarized by group (HC, PC, PMD, PME). Categorical variables were summarized with N (%) and group-level differences were tested using Fisher's Exact Tests. Analysis of variance (ANOVA) was used to test for group-level differences in the CTE trauma measurements (number of events experienced, severity of events experienced). Adjusted models controlling for demographic variables were conducted to control for baseline differences. For *post-hoc* analysis of any significant ANOVA findings, Tukey's HSD test was used to test for pairwise comparisons between groups (34). Fisher's exact test was used to test for univariate differences in type of trauma experienced by group and to evaluate for differences in experience of prepubertal trauma, with prepubertal trauma being defined as trauma experienced before 2 years prior to menarche. Multinomial logistic regression with trauma type as the outcome was used to test for group level differences in types of trauma experienced, adjusting for relevant demographic covariates.

Exploratory correlation analyses assessed the relationship between the total PSST score (sum of all items) and CTE-S trauma measurements (number of events experienced, severity of events experienced) in order to explore the relationship between childhood trauma and premenstrual symptoms using continuous as opposed to categorical groupings.

Exploratory analyses assessed for differences in total PSST scores between the groups using ANOVA, to see if groups with the same categorical level of premenstrual distress (e.g. PME and PMD; PC and HC) experienced the same quantitative level of premenstrual symptoms.

Significance was evaluated at a level of $p < .05$. As this was largely an exploratory hypothesis-generating study, we did not correct for multiple comparisons in order to not miss associations worthy of future study in larger and more rigorous samples. Analyses were completed using R version 3.6.2 (35).

Results

Group differences in trauma

Sample characteristics

N=217 participants were classified as HC, 102 PC, 34 PMD, and 38 PME. Table 1 summarizes the participant demographics overall and by group. The groups differed in their distribution of race ($p = .040$), education level ($p < .001$), and income level ($p < .001$). The groups were otherwise similar in terms of age, ethnicity, and employment status.

Number of traumatic events

136 participants (62.7%) in the HC group, 74 participants (72.5%) in PC group, 26 participants (76.5%) in PMD, and 31 participants (81.6%) in PME experienced trauma prior to age 17.

One-way ANOVA revealed a significant difference in number of traumatic events reported between groups [$F(3,387) = 4.46$, $p = .004$]. Tukey's HSD test for multiple comparisons revealed that this was driven by a significant difference between HC and PC (adjusted difference = 0.37, 95% CI = 0.03 – 0.71, $p = .025$) and a significant difference between HC and PME (adjusted difference = 0.53, 95% CI = 0.03 – 1.02, $p = .033$), such that HCs reported fewer traumatic events compared to the PC and PME groups (Figure 1A). This difference between groups remained significant after controlling for medication use, race, income, and education [$F(3,353) = 5.27$, $p = .001$]. No other pairwise comparisons were significantly different (p's >.35).

Severity of traumatic events

There was a significant difference in the severity of reported traumatic events among groups ($F(3,387) = 7.67$, $p < .001$). Tukey's HSD test for multiple comparisons revealed that differences in severity scores were driven by a significant difference between HC and PC (adjusted difference = 2.25, 95% CI = 0.45 – 4.05, $p = .007$) and a significant difference between HC and PME (adjusted difference = 4.21, 95% CI = 1.58 – 6.84, $p = .003$), such that HCs reported a lower severity of traumatic events compared to the PC and PME groups (Figure 1B). This group difference remained significant after controlling for medication use, race, income, and education [$F(3,353) = 3.81$, $p = .010$]. No other pairwise comparisons were significantly different (p's >.23).

Trauma type

Table 2 depicts the frequency of types of traumas reported within each group. Fisher's exact test revealed a significant difference between groups, with more participants in the PC and PME groups reporting a history of sexual abuse ($p = .020$) and "other" trauma ($p = .008$), but no significant differences across other trauma types. However, multinomial logistic regression models revealed that there was no significant group difference in experience of sexual abuse once controlling for medication use, race, income, and education (ps >.15), but that those who earned higher income had lower odds of experiencing sexual abuse in childhood compared to those making $50,000 or less (Table 3). Participants who earned between $50,000 and $100,000 (OR = 0.39, 95% CI = 0.15 - 0.99, p = .047) and those making $100,000 or more (OR = 0.20, 95% CI = 0.07 - 0.57, p = .003) had lower odds of experiencing sexual abuse in comparison to those making $50,000 or less. Additionally, when controlling for medication use, race, income, and education, there was no longer a group-level difference or any significant demographic predictors of experiencing other types of trauma (Table 3).

TABLE 1 Participant characteristics overall and by group.

	Overall (N=391)	HC (N=217)	PC (N=102)	PMD (N=34)	PME (N=38)	P-value
Age						
Mean (SD)	32.7 (4.38)	32.8 (4.15)	32.9 (4.71)	32.6 (4.41)	31.6 (4.72)	.443
Race						
White	292 (74.7%)	169 (77.9%)	74 (72.5%)	24 (70.6%)	25 (65.8%)	**.040**
Black	52 (13.3%)	20 (9.2%)	22 (21.6%)	5 (14.7%)	5 (13.2%)	
Asian or Pacific Islander	25 (6.4%)	16 (7.4%)	2 (2.0%)	3 (8.8%)	4 (10.5%)	
Other	22 (5.6%)	12 (5.5%)	4 (3.9%)	2 (5.9%)	4 (10.5%)	
Ethnicity						
Not Hispanic	362 (92.6%)	201 (92.6%)	96 (94.1%)	33 (97.1%)	32 (84.2%)	.316
Hispanic	26 (6.6%)	15 (6.9%)	5 (4.9%)	1 (2.9%)	5 (13.2%)	
Missing	3 (0.8%)	1 (0.5%)	1 (1.0%)	0 (0%)	1 (2.6%)	
Education Level						
High School or less	17 (4.3%)	7 (3.2%)	8 (7.8%)	1 (2.9%)	1 (2.6%)	**<.001**
Some College or Associates	46 (11.8%)	12 (5.5%)	15 (14.7%)	5 (14.7%)	14 (36.8%)	
College Degree	98 (25.1%)	62 (28.6%)	17 (16.7%)	10 (29.4%)	9 (23.7%)	
At least Some Graduate	229 (58.6%)	135 (62.2%)	62 (60.8%)	18 (52.9%)	14 (36.8%)	
Missing	1 (0.3%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	
Income Level						
$50,000 or less	55 (14.1%)	16 (7.4%)	19 (18.6%)	9 (26.5%)	11 (28.9%)	**<.001**
$51,000 - 100,000	127 (32.5%)	77 (35.5%)	29 (28.4%)	8 (23.5%)	13 (34.2%)	
$100,000 or more	190 (48.6%)	116 (53.5%)	45 (44.1%)	16 (47.1%)	13 (34.2%)	
Missing	19 (4.9%)	8 (3.7%)	9 (8.8%)	1 (2.9%)	1 (2.6%)	
Currently Employed?						
No	66 (16.9%)	31 (14.3%)	23 (22.5%)	5 (14.7%)	7 (18.4%)	.329
Yes	320 (81.8%)	182 (83.9%)	78 (76.5%)	29 (85.3%)	31 (81.6%)	
Missing	5 (1.3%)	4 (1.8%)	1 (1.0%)	0 (0%)	0 (0%)	
Psychotropic Medication Use						
No	312 (79.8%)	217 (100%)	49 (48.0%)	34 (100%)	13 (36.8%)	**<.001**
Yes	72 (18.4%)	0 (0%)	49 (48.0%)	0 (0%)	23 (60.5%)	
Missing	7 (1.8%)	4 (1.8%)	4 (3.9%)	0 (0%)	1 (2.6%)	

Categorical data is represented by N (%) and P-values are for Fisher's exact test.
HC, Healthy Controls; PC, Psychiatric Controls (Controls with Psychiatric Illness); PMD, premenstrual disorder; PME, premenstrual exacerbation.
Bold values mean significant at a level of p <.05.

Prepubertal timing of trauma

61 participants (28.1%) in the HC group, 30 participants (29.4%) in PC group, 17 participants (50%) in PMD, and 16 participants (42.1%) in PME experienced prepubertal trauma. Fisher's Exact Test showed that there was not a significant difference between groups in number of individuals with prepubertal trauma exposure (p = .125).

Association between trauma measures and premenstrual symptoms in the total sample

Number of traumatic events

Across groups, there was a weak but significant positive correlation between number of childhood traumatic events and total PSST score

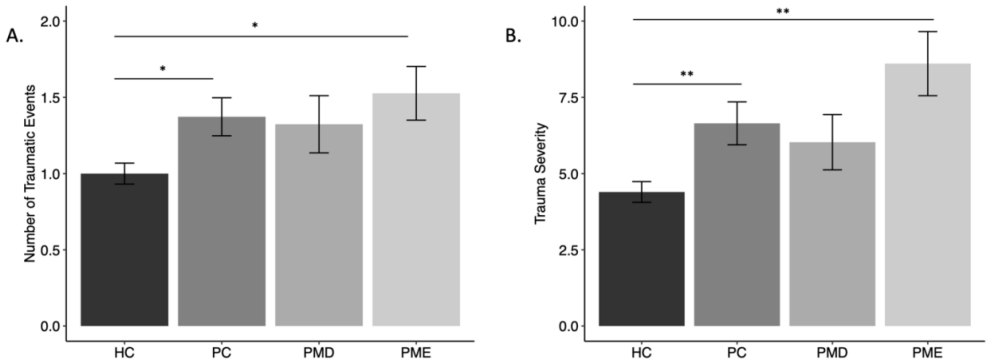

FIGURE 1
Mean measures of childhood trauma by group. [**(A)** number of traumatic events, **(B)** severity of events] by group. Error bars represent standard error. HC, Healthy Controls; PC, Psychiatric Controls (Controls with Psychiatric Illness); PMD, premenstrual disorder; PME, premenstrual exacerbation. * = p <.05; ** = p <.01.

TABLE 2 Types of childhood traumas experienced by group.

	HC (N=217)	PC (N=102)	PMD (N=34)	PME (N=38)	P-value
Trauma: Death					
No	142 (65.4%)	66 (64.7%)	21 (61.8%)	23 (60.5%)	.903
Yes	74 (34.1%)	36 (35.3%)	13 (38.2%)	15 (39.5%)	
Missing	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	
Trauma: Divorce					
No	164 (75.6%)	67 (65.7%)	22 (64.7%)	27 (71.1%)	.199
Yes	51 (23.5%)	34 (33.3%)	12 (35.3%)	11 (28.9%)	
Missing	2 (0.9%)	1 (1.0%)	0 (0%)	0 (0%)	
Trauma: Sexual Abuse					
No	195 (89.9%)	83 (81.4%)	28 (82.4%)	27 (71.1%)	**.020**
Yes	21 (9.7%)	18 (17.6%)	5 (14.7%)	10 (26.3%)	
Missing	1 (0.5%)	1 (1.0%)	1 (2.9%)	1 (2.6%)	
Trauma: Other Violence					
No	201 (92.6%)	94 (92.2%)	30 (88.2%)	32 (84.2%)	.266
Yes	16 (7.4%)	7 (6.9%)	4 (11.8%)	6 (15.8%)	
Missing	0 (0%)	1 (1.0%)	0 (0%)	0 (0%)	
Trauma: Severe Illness					
No	201 (92.6%)	91 (89.2%)	32 (94.1%)	35 (92.1%)	.755
Yes	16 (7.4%)	11 (10.8%)	2 (5.9%)	3 (7.9%)	
Trauma: Other					
No	178 (82.0%)	68 (66.7%)	25 (73.5%)	24 (63.2%)	**.008**
Yes	39 (18.0%)	34 (33.3%)	9 (26.5%)	13 (34.2%)	
Missing	0 (0%)	0 (0%)	0 (0%)	1 (2.6%)	

Categorical data is represented by N (%) and P-values are for Fisher's exact test.
HC, Healthy Controls; PC, Psychiatric Controls (Controls with Psychiatric Illness); PMD, premenstrual disorder; PME, premenstrual exacerbation.
Bold values mean significant at a level of p <.05.

TABLE 3 Multinomial logistic regression for trauma type outcomes (sexual abuse and other types of trauma).

	Odds Ratio	95% CI	p-value
Sexual Abuse			
Group			
HC	1.00 (ref)		
PC	1.05	0.39 – 2.62	.919
PMD	1.12	0.32 – 3.31	.845
PME	1.05	0.28 – 3.51	.939
Medication Use			
No	1.00 (ref)		
Yes	2.29	0.86 - 6.43	.103
Income			
$50,000 or less	1.00 (ref)		
$51,000 - 100,000	**0.39**	**0.15 – 0.99**	**.047**
$100,000 or more	**0.20**	**0.07 – 0.57**	**.003**
Education Level			
High School or less	1.00 (ref)		
Some College or Associates	1.48	0.40 – 5.98	.561
College Degree	0.81	0.19 – 3.61	.775
At least Some Graduate	0.63	0.17 – 2.59	.501
Race			
White	1.00 (ref)		
Black	0.83	0.29 – 2.19	.714
Asian or Pacific Islander	1.53	0.39 – 4.83	.497
Other	0.75	0.15 – 2.66	.683
Other Violence			
Group			
HC	1.00 (ref)		
PC	1.98	0.98 – 3.93	.054
PMD	1.64	0.66 – 3.81	.264
PME	2.13	0.77 – 5.63	.135
Medication Use			
No	1.00 (ref)		
Yes	1.14	0.53 - 2.49	.739
Income			
$50,000 or less	1.00 (ref)		
$51,000 - 100,000	0.74	0.32 – 1.76	.491
$100,000 or more	0.74	0.31 – 1.84	.501
Education Level			
High School or less	1.00 (ref)		
Some College or Associates	1.01	0.29 – 3.66	.986
College Degree	0.69	0.20 – 2.61	.579
At least Some Graduate	0.75	0.23 – 2.65	.645
Race			
White	1.00 (ref)		
Black	1.14	0.48 – 2.58	.762
Asian or Pacific Islander	0.99	0.31 – 2.70	.987
Other	1.60	0.55 – 4.26	.359

(Continued)

TABLE 3 Continued

Bold values mean significant at a level of p <.05.

(R = .18, p <.001), see Figure 2A. Upon testing for correlations within each group, the association was significant within the PMD group (R = .42, p = .013), but not the PME (R = .20, p = .234), HC (R = .05, p = .495), or PC groups (R = .13, p = .181).

Severity of traumatic events

Across groups, there was a weak but significant positive correlation between the severity of childhood traumatic events and total PSST score (R = .22, p <.001), see Figure 2B.

Correlation analyses within each group revealed a significant association within the PMD group (R = .41, p = .015), but not the PME (R = .30, p = .066), HC (R = .05, p = .422), or PC groups (R = .09, p = .348).

Group differences in premenstrual symptoms

Exploratory analyses were run to assess whether premenstrual symptoms (as measured by the total PSST score) differed between the PME and PMD groups (Table 4). ANOVA examining PSST scores revealed a significant difference by group (F(3,387) = 177.9, p <.001) *Post-hoc* analyses revealed a significant difference between the PME and PMD groups (adjusted difference = 4.85, 95% CI = 0.28 – 9.43, p = .033), such that those in the PME group experienced higher levels of premenstrual symptoms compared to the PMD group, but there was no difference between the HC and PC groups (adjusted difference = 1.95, 95% CI = - 0.38 – 4.27, p = .136). All other pairwise comparisons (PMD-HC, PMD-PC, PME-HC PME-PC) were significantly different from each other

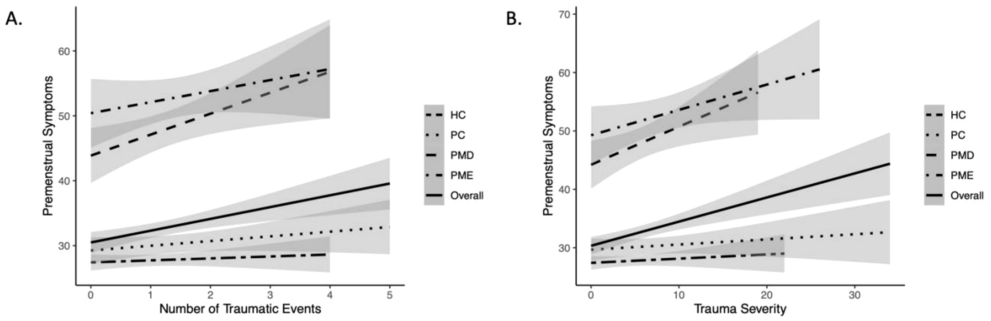

FIGURE 2
Association between measures of childhood trauma and premenstrual symptoms overall and within each group. [**(A)** number of traumatic events, **(B)** severity of events] and premenstrual symptoms (measured by PSST) by group. HC, Healthy Controls; PC, Psychiatric Controls (Controls with Psychiatric Illness); PMD, premenstrual disorder; PME, premenstrual exacerbation.

(p <.001). After controlling for medication use, race, income, and education level, there was a significant group effect (F(3,353) = 175.0, p <.001), but no longer a significant difference between the PME and PMD groups in *post-hoc* analyses (adjusted difference = 4.10, 95% CI = - 0.43 – 8.64, p = .092).

Discussion

The current study examined the relationships among PMDs, PME, psychiatric illness, and childhood trauma experiences. We found that the experience of childhood trauma (number of traumatic events and severity of traumatic events) differed by group; participants with PME, and participants with a current or lifetime mood/anxiety disorder (PC), had a significantly higher number of traumatic events and greater severity of trauma compared to HCs. It is notable, however, that our study did not find significant differences in exposure to specific types of traumatic events after confounding for variables. A childhood history of sexual abuse, for example, have been previously associated with PMDs (18, 36, 37). This discrepancy is likely a result of differences in the questionnaires used across studies. For example, most data evaluating early childhood trauma and adversity as it relates to PMDs have utilized the ACE Questionnaire (ACE-Q) (38) or the Childhood Trauma Questionnaire (CTQ) scales. Indeed, both the ACE-Q and CTQ specifically ask questions about emotional, physical, and sexual abuse and/or neglect. Physical and emotional abuse, as well as emotional neglect, have all been specifically associated with the development of PMDs (7, 39, 40). Since the CTE-S does not ask about emotional abuse or neglect, however, our results may have failed to show any differences in trauma type in the PMDs group for this reason. Additionally, sexual abuse has been associated with higher rates of developing PMDD, but due to the limited number of participants who met criteria for PMDD (n=6) in this study, we were underpowered to evaluate this difference. It is interesting, however, that the specific types of traumatic events measured by the CTE-S (e.g., divorce, death of family/friend, illness/injury, or being a victim of violence) were not associated with PMD status but do appear to be associated with the risk for psychiatric illness more generally. Regarding premenstrual symptom severity, we found a weak but significant correlation between childhood trauma (number of traumatic events and severity of trauma experience) and higher premenstrual symptom burden. Within-group analysis suggested that this association was driven by correlations within the PMD group but not the other groups. Indeed, this finding is supported by other studies, which also found a correlation between the frequency and intensity of traumatic experiences and the corresponding severity of premenstrual symptoms (16, 18, 23). Although we did not detect a significant pairwise difference between PMDs and HCs in premenstrual symptom severity, it is worth highlighting that the data (see Figure 1) show a similar pattern for both PMD and PME patients. In both cases the frequency and severity of trauma were higher relative to HCs. Future studies with larger sample sizes, particularly among those with PMD, may observe statistically significant effects. We also found that those with PME experienced quantitatively higher levels of premenstrual symptoms on the PSST compared to the PMD group, despite both groups scoring in the moderate to severe range on PSST. However, after controlling for medication use, race, income, and education level, the initial difference in PSST scores between the PME and PMD groups was no longer statistically significant in *post-hoc* analyses.

TABLE 4 Premenstrual symptom burden by group.

	HC (N=217)	PC (N=102)	PMD (N=34)	PME (N=38)	P-value
Premenstrual Symptoms Screening Tool Sum Mean (SD)	27.7 (6.68)	29.7 (8.12)	48.1 (8.35)	53.0 (9.32)	<.001

HC, Healthy Controls; PC, Psychiatric Controls (Controls with Psychiatric Illness); PMD, premenstrual disorder; PME, premenstrual exacerbation.

Together, this suggests that socioeconomic and demographic factors may partially account for the observed differences in elevated premenstrual symptom severity observed in the PME group. Another potential explanation is that the PME group may have represented a more psychiatrically ill population (as indicated by the increased presence of medication use). In this case those with PME may be experiencing ongoing symptoms of anxiety and depression throughout the month that (by definition) that worsen in the premenstrual period. Particularly, if the psychiatric symptoms experienced outside of the premenstrual time are already moderate to severe, it may be that the premenstrual worsening represents a time of additional suffering on an already stressed individual. Additionally, it is known that individuals experiencing depression have a subjectively enhanced experience of both physical and psychic suffering, which may further intensify the experience of physical and emotional premenstrual symptoms (41–43). To date, there are no known studies that have evaluated (qualitatively nor quantitatively) the symptom trajectory, characteristics, or severity of symptoms among individuals with PME across the menstrual cycle. Larger studies will be needed to determine whether there are differences in the subjective experience of premenstrual symptoms based on primary diagnosis and sociodemographic factors. It will be interesting to expand on the current findings to elucidate if higher PSST scores are associated with worse baseline mood or anxiety symptoms, or if PSST scores are independent of overall psychiatric severity outside of the premenstrual window.

Together, our results show that while PME and psychiatric diagnosis were associated with more frequent and more severe trauma exposure than in healthy controls, PMDs categorically were not associated with greater trauma exposure. Instead, within the PMD group, the number and severity of traumatic events was associated with greater premenstrual symptom load, which was not true in the other groups. Thus, it appears that trauma exposure increases risk for psychiatric diagnosis and PME generally, but among those with PMDs, it is the premenstrual symptoms that are more severe with greater exposure to childhood trauma. These results extend the expanding realm of research concerning the role of childhood adversity in reproductive affective disorders. Indeed, a history of trauma has been linked to most reproductive psychiatric illnesses, including PMDs, postpartum depression, and perimenopausal depression (44, 45). However, it is unknown the mechanisms by which childhood trauma would increase risk for reproductive affective disorders, which are characterized by sensitivity to gonadal hormone fluctuations. Recent data have suggested that the interplay between the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes, particularly the modulation of the HPA axis by gonadal hormones such as estrogen and progesterone and their neuroactive steroid metabolites, may underlie the elevated prevalence of mood disorders observed among women (45–48). Particularly relevant to women, who experience higher levels of childhood adversity than males, early life adversity may prime the HPA axis, resulting in more sensitivity to the natural gonadal hormone fluctuations across the reproductive life span. Intriguingly, recent research has demonstrated distinct profiles in cortisol function across the menstrual cycle among individuals with PMS and PMDD. In a study examining the intersection of childhood adversity and PMDs, women with PMDD and a history of abuse had greater premenstrual mood symptoms and higher cortisol levels than those with no abuse history, as they transitioned from the gonadal hormone milieu of the follicular phase to the luteal phase of the menstrual cycle (15). To date, there have been no specific investigation into HPA-HPG axis function in PME; future studies might discern whether the HPA axis profiles across the menstrual cycle among individuals with PME resemble those of individuals with PMS, PMDD, or MDD. In addition, gonadal hormone interaction with the serotonergic and GABAergic systems have been an important focus in exploring potential biological contributors to PMD risk (10, 15).

It's important to consider some important limitations when interpreting our findings. Firstly, our study assessed childhood trauma based on participants' retrospective self-reports, which naturally introduces a potential for recall bias. In addition to the challenge of recall bias, retrospective assessments limit the evaluation of any confounding variables that may have affected the outcome assessed. For example, the PSST asks retrospectively about premenstrual physical and mood symptoms, but we did not prospectively assess mood symptoms across the menstrual cycle. Additionally, while our study created groupings based on current PMD and psychiatric status to examine group differences in past ACEs, we acknowledge that the reverse approach could also be informative, i.e. grouping by ACE status (49, 50); however, we employed ANOVA evaluation to specifically observe differences across groups as we could not evaluate directionality in this retrospective analysis.

Although our study relied on validated measures to evaluate early life trauma, the CTE-S is not as widely used as the ACE-Q or CTQ, limiting generalizability of this study, and does not contain some of the key trauma domains (e.g. physical or emotional abuse/neglect) that have been previously associated with PMDs. The lack of information about emotional abuse and neglect may have limited our findings and ability to discern differences between our participant groups. Additionally, due to large differences in our sample sizes between groups and the relatively small number of participants with PMDD, our study may have been underpowered to recognize more subtle trends among groups. Further, the CTE-S only assesses trauma experienced in childhood and adolescence, and thus we were not able to account for the potential impact of stress or trauma experienced post-adolescence on PMD/PME risk.

Despite these limitations, our research contributes to an emerging field that confirms connections among childhood trauma, premenstrual symptoms, and psychiatric disorders. Our study uniquely focuses on evaluating the impact of trauma specifically on premenstrual symptoms and particularly among individuals with PME, a condition that has received insufficient attention in research and clinical practice. Our findings reveal that individuals with PME experience more severe premenstrual symptoms compared to those with PMD, underscoring the importance of further investigation, clinical assessment, and intervention for this specific patient group.

Future studies focused on exploring the link between trauma and PME may provide valuable insights into the underlying mechanisms connecting early life trauma or adversity to reproductive psychiatric disorders. Additionally, exploring the hormonal and neurobiological pathways involved in PME (particularly differences in the HPA and HPG axes), in comparison to those with mood disorders alone or in comparison to PMDs, may help elucidate the biological bases of these illnesses and fuel investigations to identify potential biological targets for intervention.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Johns Hopkins University Institutional review board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LS: Writing – original draft, Writing – review & editing. MB: Writing – original draft, Writing – review & editing, Formal analysis. KM: Writing – original draft, Writing – review & editing. KV: Formal analysis, Methodology, Supervision, Writing – review & editing. DS: Writing – review & editing, Conceptualization, Formal analysis. LO: Supervision, Writing – review & editing. JP: Supervision, Writing – review & editing, Project administration. LH: Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

JP has research funding from NIMH, Janssen Pharmaceuticals and Myriad. She has served as a consultant to SAGE Therapeutics, Biogen, Merck, Brii Biologics, Pure Tech, Dionysus Health, and Flo Health. She has founders stock in Dionysus Health. She has two patents: "Epigenetic Biomarkers of Postpartum Depression" and "Epigenetic Biomarkers of PMDD and SSRI Response."

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Menstrual management in transgender and gender diverse individuals: psychiatric and psychosocial considerations

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Transgender and gender-diverse (TGD) menstruators are individuals assigned female at birth (AFAB)*, who retain the capacity to menstruate and have a gender identity that differs from their natal sex. Reports indicate up to 1.6 million individuals in the US identify as TGD. Until recently, the mainstream menstrual discourse has failed to capture the experience of transmenstruators. However, a better understanding of the menstrual experiences of TGD-AFAB will allow for more individualized patient-centered care. In this review, we provide the relevant data necessary to inform the psychiatric management of menstruation in TGD-AFAB individuals, including experiences of menstruation, preferences for menstrual management, and the impact on mental health. Our review indicates that menstrual care in TGD patients must be tailored to the individual; clinicians should remain open-minded to the unique experience of transmenstruators; gender-affirming menstrual care is necessary to reduce psychological burden. It should not be assumed that TGD-AFAB menstruators are utilizing appropriate contraceptive methods and should receive contraceptive and fertility preservation counseling. We highlight the importance of having these conversations early in the reproductive arch, even before puberty onset. Keeping in mind the gender minority stress model, in the upcoming sections, we discuss the limited body of literature on mood disorders in TGD-AFAB individuals who menstruate, undergo menstrual suppression, or continue to ovulate. The psychological impact of hormonal therapies is also reviewed.

KEYWORDS

menstruation, transgender, transmen, mood disorder, gender diverse, menstruator, gender dysphoria

1 Introduction

Earlier estimates based on population-based surveys approximated that 0.3-0.6% of the United States population, or 1 million people, identify as transgender; however recent reports indicate that figure may be closer to 1.6 million (1, 2). Similarly, the DSM-V documents the prevalence of gender dysphoria as 0.005-0.014% for those assigned male at birth, and 0.002-0.003% for adults assigned female at birth, with recent reports indicating increasing numbers (3). Still, there is a lack of familiarity and competency around the medical and mental health needs of TGD individuals. According to the 2022 US Transgender Survey (USTS), amongst 92,329 respondents, 38% identified as nonbinary, 35% as transgender women (transwomen), and 25% as transgender men (transmen) (4). Of those respondents, 24% did not seek medical care, and 48% reported at least one negative experience due to their gender identity, including being misgendered; being refused care; being addressed with harsh or abusive language; or being subjected to physically rough treatment (4). Seelman et al., 2020 found that in the 2015 USTS, 54% of transmen found their routine healthcare providers knew very little ("nothing" or "some things") about trans-related care (5).

Although some TGD individuals undergo medical transition, many do not (6). A social transition is when an individual changes their appearance and pronouns. A legal transition involves legally changing one's name and documents to reflect this and their identified gender. Medical transition may involve gender-affirming hormone therapy (GAHT) and/or gender-affirming surgery. In TGD-AFAB individuals, common gender-affirming surgeries include masculinizing chest surgery (i.e., mastectomy), body contouring, and metoidioplasty, as well as non-surgical chest binding. Masculinizing GAHT in TGD-AFAB individuals is usually continued lifelong to maintain virilization independent of genital surgery. Testosterone is the mainstay of masculinization, which aims to induce secondary sex characteristics and suppress feminine physical features, and in most cases causes amenorrhea. At least 80% of TGD individuals have either taken, tried, or wanted to take GAHT at some point (7). Gender nonbinary or gender non-conforming individuals who do not identify as transgender may take hormones to develop more masculine sexual secondary characteristics. Although some gender-affirming treatments include a hysterectomy or oophorectomy, many TGD-AFAB menstruators wish to maintain their reproductive organs and childbearing potential (8–11).

Compared to other medical specialties, psychiatry has had a more fraught relationship with the TGD community. The Diagnostic and Statistical Manual of Mental Disorders (DSM) 3rd and 4th editions, for example, conceptualized gender identity disorder (GID) as pathologic. Although GID was subsequently reclassified as gender dysphoria (Supplementary Table 2) in DSM-V (3), literature continues to indicate a higher prevalence of mental health disorders among transgender individuals compared to the general population or cisgender individuals. TGD people experience a two-fold higher risk of receiving a psychiatric diagnosis compared to cisgender people and are diagnosed with a mood, anxiety, or psychotic disorder, with odd ratios of 1.5:1, 3.9:1, and 3.8:1 respectively (12). These disparities can be understood through the minority-stress framework, which describes the complex interaction between majority (cis-gender) and minoritized groups (transgender and nonbinary) communities.

Building on this, we aim to provide a comprehensive review of the experiential and clinical data necessary to inform the care of TGD-AFAB individuals. We review the gendered history of menstruation; the value of gender-inclusive menstrual dialogue; guidelines for transgender health around menstrual suppression, fertility preservation, and contraceptive counseling; and elucidate the interplay between gender dysphoria, menstruation, and hormone-related mood disorders in TGD-AFAB individuals.

2 Methods

We searched PubMed from March to July 2024 without date limitations for studies of TGD menstruators. We did not utilize any language restrictions and included historical and contemporary terms related to gender identity such as "transgender", "transgender diverse", "transmen", "menstruators", "assigned female at birth", "nonbinary", and "gender diverse". We utilized similar terms through Google to locate magazine articles, books, government announcements, and websites.

3 Historical and social considerations

Menstruation is a biological process that is steeped in historical significance. In Greek mythology, menstrual blood is referred to as "the supernatural red wine," conferring "miraculous power" to the gods (13). In Ancient Rome, menstruators were also thought to have "great powers," and menstrual blood was recommended as a treatment for illnesses of all kinds, including rabies, malaria, and epilepsy (13). Many indigenous tribes emphasize the strength of menstruators and menstruation itself. The Cherokee Nation of Oklahoma believes that menstruation is powerful, a source of feminine strength, and a destructive force against evil and enemies (14). In Cherokee mythology, *Stoneclad*, a cannibalistic monster was undefeated by warriors until he was in the presence of seven menstruating virgins who took his strength away (13). To channel the power of menstruators, Cherokee men would also practice bloodletting before games and battles (14).

Menstruation has also been invoked as evidence of women's inferiority, a notion that dates as far back as Aristotle (15). In biblical Jewish culture, menstruating women were required to remain separate from men for the duration of their menses. Orthodox Jewish women continue to use the ritual bath (mikvah) following menstruation and before engaging in intercourse after menses. The Roman Catholic Church of Thirteenth Century Europe perpetuated the "stigma of menstrual uncleanliness … [and] perceptions of menstrual blood as vile and polluting," encouraging women to refrain from taking Holy Communion while menstruating (16). In Islamic culture, menstruating women

are unable to pray, enter mosques, or touch the Quran; they are required to clean themselves through a spiritual bath (ghusl) each time menses concludes (17). Additionally, if menstruating, they are barred from completing the final ritual of Hajj, Tawaf-ul-Ziyarah, which involves circumnavigating the Kaaba to commemorate the end of the annual pilgrimage to Mecca (17).

By suggesting that menstruation was not a signifier of shame or weakness, but rather something that could be "managed," the feminist movement of the 20th challenged the historical menstrual and reproductive rhetoric and through the lens of women's empowerment, moved conversations around menstruation into the mainstream (18). More recently, conversations around menstruation have come to encompass an even wider range of perspectives, including those of transgender and non-binary menstruators. Kosher et al. (2023) refer to this as "the plurality of menstrual experiences," encapsulating the increasingly common viewpoint that "not all women menstruate, and not all menstruators are women" (19, 20). Said differently, menstruation is a deeply nuanced and subjective experience for TGD-AFAB individuals (21, 22).

While the experience of menstruation among TGD individuals is conventionally understood as "the individual who was AFAB; identifies with masculinity; experiences intense dysphoria around menstruation because it is gendered feminine; and is actively undergoing intervention to suppress or eliminate menstruation," the reality is much more complex (19). Fortunately, data examining TGD-AFAB individuals' attitudes toward menstruation, considerations around menstrual management, and decisions about menstrual suppression are emerging. Chrisler et al. (2016) surveyed 150 TGD-AFAB individuals to examine attitudes toward menstruation and menstrual suppression (21). While some respondents expressed a positive view of menstruation, the majority reported "mixed or ambivalent attitudes." Half of the participants reported that they would elect to suppress menstruation if suppression were possible without the use of testosterone. Fifty percent also agreed that "not menstruating would enhance their sense of their masculine identity" (21). More recently, Kosher et al. (2023) identified three major themes pertaining to menstruation in the TGD population: 1) dysphoria; 2) tensions between femininity and masculinity; and 3) transnormative pressures (19). A 2023 study by Schwartz et al. examined TGD adolescents' (N=129) experiences of menstruation and found that a majority (93%) experienced menstrual-related dysphoria (23). A substantial number (88%) were interested in menstrual suppression, with the primary reason being a desire for a complete cessation of menses (97%) and the second to improve menstrual-related dysphoria (63%) (23).

Beyond menstrual bleeding itself, the *management* of menstruation can be a source of distress for TGD menstruators (24). Although femininity is neither a predicate for menstruation nor an outcome of menstruation, terms like "feminine hygiene product" or "feminine care" abound in the marketing and sale of menstrual products. Furthermore, TDG-AFAB individuals may experience aversion to vaginal penetration (21), and many menstrual products are designed for insertion into the vaginal opening. In 2016, the Thinx period product brand released its Boyshort style underwear with a series of video and print advertisements featuring trans male model, Sawyer DeVuyst. According to Miki Agrawal, Thinx's Chief Executive Officer at the time, the Boyshort was "specifically designed with the trans male menstruating community in mind" and a deliberate step by Thinx to be part of "shifting [public] perspective" on the needs of the trans community (25). The introduction of the Boyshort to the period product market also came on the heels of a major shift in Thinx's marketing strategy. Moving away from its original *For Women with Periods* advertising campaign, Thinx opted for a revised *For People with Periods* tagline. The goal, Thinx says, was an acknowledgment that menstruation "is not a trait of, nor a defining factor of, a specific gender. It is something that can occur amongst all people" (26).

However, the lack of inclusive period products is just one way in which TGD-AFAB individuals have been impacted by a menstrual landscape designed almost exclusively for cis-gender women. The issue of period poverty for menstruators is an underrecognized public health issue. Broadly, period poverty refers to a lack of access to menstrual education, menstrual products, and facilities that allow for proper menstrual hygiene and disposal of menstrual products (27). It also refers to "the increased economic vulnerability menstruating people face due to the financial burden posed by menstrual supplies….[and] costs accrued from pain medication and underwear used during the menstrual cycle (28). " Period poverty also contributes to the cycle of generational poverty by adding to the marginalization of menstruators in the form of missed days of work, missed days of school, and diversion of monthly income to meet menstrual needs. TGD-AFAB communities are particularly vulnerable to the impact of period poverty. According to the University of Wisconsin-Madison Institute for Research on Poverty, nearly 34% of transmen and 24% of gender nonbinary individuals live in poverty, compared to 16% of cis-gendered individuals (29). In the 2022 USTS, TGD individuals reported facing substantially higher rates of housing instability compared to the general population (4).

To address issues of period poverty and menstrual inequity, at least 30 states and Washington D.C. have passed a combined total of 60 bills designed to improve access to menstrual health resources. While laws differ by state, they are generally aimed at improving access and affordability by eliminating sales tax for menstrual products and ensuring free menstrual products are available to individuals in public schools, correctional facilities, and homeless shelters (30). However, menstrual product availability in male-designated restrooms has become a topic of controversy in political and public discourse. Events that took place in a Connecticut (CT) High School made national headlines in 2024 after a tampon dispenser, affixed to the wall of a boys' restroom, was torn down. The tampon dispenser was placed in the boys' restroom in response to a relatively new CT state law that mandates public schools to provide free access to menstrual products for students. According to The Connecticut Department of Health "[t]he law was designed to affirm all genders in making empowered decisions about their health, including menstrual health. As a result, the law requires products to be provided in all-gender bathrooms, one men's restroom per school, and all women's restrooms in the building" (27).

However, such policies have not been applied uniformly across the United States. Nearly 47% of respondents in the 2022 USTS had thought of "moving to another state because their state government considered or passed laws that target transgender people for unequal treatment (such as banning access to bathrooms, health care, or sports), and 5% of respondents had moved out of state because of such state action" (4). In 2023, Florida signed House Bill 1521, barring TGD individuals from using locker rooms or public bathrooms consistent with their gender, highlighting continued barriers to menstrual management (31).

Unsurprisingly, research suggests that a majority of TGD-AFAB individuals feel "unsafe" or "very unsafe" managing menstruation in men's restrooms (21). The risk of being 'outed' by the use of individually wrapped menstrual products (tampons, pads) appears to contribute, in part, to the preferential use of extended-use period products like menstrual cups, adult diapers, or period underwear (21). A study by Lane et al. (2022) also identified public restroom design as a "significant barrier to menstrual management" (32). Participants described large gaps between stalls, the "reflective gaze" of the mirrored sinks, high urinal-to-stall ratios, and lack of disposal sites for menstrual products as being some of the most fraught aspects of queer menstruation.

4 Applying consensus guidelines in gender-affirming medical care

A professional body spanning disciplines and geographic regions, the World Professional Association for Transgender Health (WPATH) tasks itself with promoting evidence-based care, education, research, public policy, and respect for transgender health. WPATH is associated with 7 regional organizations: United States, European, Canadian, Asia, Australia, Aotearoa (New Zealand, and Southern Africa. Since the organization's formal inception in 1979, it has iteratively published standards of care (SOC). These documents have served as consensus guidelines and best practice recommendations for professionals caring for transgender and gender-diverse populations throughout the world (33). Within the last few years, there has been a shift in European countries with guideline implementation. The National Health Services England released the CASS Report in 2024, closed its Gender Identity Development Service, and recently banned puberty blockers for adolescents (34). Sweden, Finland, and Denmark continue to follow similar patterns.

While experiences of and feelings about menstruation among TGD-AFAB individuals are diverse, some may experience an exacerbation of incongruence between gender identity and perception of their bodies during menses. To address this, the most recent WPATH SOC-8 contains recommendations regarding the suppression of menstruation in adolescent and adult TGD-AFAB individuals (33). In most, GAHT with exogenous testosterone at adult physiologic doses will precipitate amenorrhea due to the sex steroid's effect on the endometrium, and resultant endometrial atrophy (35). However, menstrual suppression with GnRH agonists, combined estrogen-progestin, or progestin-only methods can be indicated, especially in adolescent populations.

WPATH recommends considering menstrual suppression agents in adolescents only once they have reached the early stages of puberty. The Endocrine Society Guidelines from 2017 also recommend against puberty-blocking and GAHT in pre-pubertal children (36). Adolescents may wish to halt puberty to further explore gender expression and identity, take time to consider GAHT initiation with testosterone, or use adjunctive agents for breakthrough bleeding during the early stages of initiation of GAHT. Furthermore, if there is a delay in consensus about GAHT among the individual, provider, and/or guardian, menstrual suppression should be considered as an initial step (33). Engaging TGD-AFB individuals in conversations about menstrual suppression can also provide a forum to explore readiness for gender-affirming treatment and any associated mental health needs (37).

The choice of menstrual suppression agent (between GnRH agonist and progestin-only or combined estrogen-progestin methods more commonly used as contraceptive agents) is dictated largely by the developmental status of the individual, consideration of individual medical risk factors (specifically venous thromboembolism in estrogen-containing methods), potential dysphoria caused by estrogen-containing agents, cost, and availability. While GnRH agonists can delay further progression of puberty and cause the regression of some early secondary sex characteristics, these agents are costly, and not always covered by insurance (33). In cases where GnRH agonists are not reasonably available, progestin agents (available as depot injection, oral pill, intrauterine device, subdermal implant) or combined estrogen-progestin agents (available as oral pill, transdermal patch, vaginal ring) can be used. Between 55-97% of transmasculine adults achieve amenorrhea within the first 6 months of testosterone therapy (38, 39). Lower rates of amenorrhea have been described in TGD-AFAB adolescents using testosterone (59% at 6 months) and higher success rates with NETA or DMPA monotherapy (40). Breakthrough bleeding requires clinical investigation to determine etiology and most commonly requires adjustment of testosterone dosage or additional hormonal intervention. Compared to individuals who initiated treatment with GnRHa at a later age, those who initiated at an earlier age (average age 11) had lower rates of depression, anxiety, suicidal ideation, and suicide attempts (41).

Ultimately, a third of TGD-AFAB individuals surveyed desired a hysterectomy, which would obviate the need for pelvic examinations and stop menses (5). TGD-AFAB individuals may seek a hysterectomy in response to pelvic pain (42). While pelvic pain has a prevalence of 25% among cis-gender women, higher rates have been reported in adult trans cohorts (43). In a 2020 cross-sectional survey of 486 AFAB trans participants, 72.2% reported pelvic pain after initiation of GAHT with testosterone, with most pain localizing to the suprapubic region and being characterized as "crampy" in nature (44). Additionally, this study found an association of pelvic pain after initiation of testosterone therapy with a personal history of PTSD, continued menstruation, and

experiences of pain with orgasm (44). In another survey conducted between 2015-2017, 69.4% of respondents reported abdominopelvic pain specifically onset since initiation of GAHT (45). All respondents who reported curative treatment of this pelvic pain identified hysterectomy as the treatment method (43, 45).

5 Contraception and fertility preservation

WPATH and the Ethics Committee of the American Society for Reproductive Medicine (ASRM) recommend discussing fertility preservation and family planning before initiation of GAHT (46). The impact of testosterone on fertility depends on duration and timing of use; if started before puberty and concurrently with puberty blockers, the individual may never develop reproductive function. If GAHT is initiated after puberty, reproductive function can be restored. The use of exogenous testosterone can have lasting effects on fertility (43). While testosterone does not affect ovarian reserve, testosterone can induce gonadal suppression through its action on the hypothalamic-pituitary axis, preventing ovulation and follicle development (44). Ovarian exposure to exogenous testosterone can cause ovarian capsule thickening, which can also impair fertility (45). While most TGD-AFAB individuals on testosterone will achieve amenorrhea and ovarian suppression, it is still possible to ovulate and become pregnant while amenorrheic (47). A study of TGD-AFAB individuals on testosterone found evidence of breakthrough ovulatory events by monitoring hormonal levels.

Studies have found that a majority of TGD-AFAB individuals express parental desire and that a quarter fear infertility (8, 10, 11). Fertility preservation options include embryo, oocyte cryopreservation, and experimental ovarian tissue banking, which can be used before gender-affirming surgery or the initiation of GAHT regardless of puberty status (43). Many TGD-AFAB individuals choose to forgo fertility preservation to avoid delaying GAHT. A majority also report fears that hormone injections and the pelvic procedures required for egg retrievals will worsen gender dysphoria (9, 23, 48). Overall, utilization of fertility preservation remains low in TGD communities. In a survey of TGD menstruators referred to a community health clinic in Tel Aviv, Alpern et al. found that while 61.9% wanted a child, only 5.8% accessed fertility preservation (9). There are many barriers to access to fertility preservation, including the high out-of-pocket expense of cryopreservation and assisted reproductive technologies and lack of adequate insurance coverage; provider discomfort in discussing fertility preservation with TGD-AFAB patients; fears of discrimination for the transgender parent as well as the child; and legislation barring gender-affirming care (9, 11, 35, 43).

Among TGD-AFAB individuals, 30% of pregnancies are unintended (47). Therefore, discussing contraception options is imperative, especially given the potential teratogenicity of testosterone. The teratogenic risks of testosterone in animal studies are well documented; however, the literature on human outcomes is sparse. *In utero* exposure to testosterone can result in abnormal development of genitalia including labial fusion and clitoromegaly, and several hypotheses that these exposures contribute to anorexia nervosa and autism in offspring (49). However, a longitudinal pregnancy cohort study failed to confirm this association (50). In a sample of 25 TGD-AFAB individuals who were on testosterone prior to pregnancy, 20% were on testosterone for at least some portion of their pregnancies. Among this sample size, rates of fetal anomalies, developmental disorders, or disorders of sexual development were equivalent to rates in TGD-AFAB individuals not on testosterone (47). More research is needed to identify long-term neurodevelopmental impacts of perinatal testosterone exposure.

Contraception in this specific population is inconsistently reported; however, estimates are between 20-60% (51). Contraceptive methods may be underutilized due to several factors, including the lack of education provided by medical providers, lack of access, as well as the frequent misconception by both transmen and providers that testosterone provides reliable contraception (51, 52). Furthermore, the irregular nature of ovulation while on GAHT may make pregnancy harder to anticipate; this places TGD-AFAB menstruators at high risk for unplanned pregnancy, especially coupled with limited access and inconsistent contraceptive use. And just as menstruation can worsen gender dysphoria by the repetitive reminder of natal sex, contraceptive methods, and fertility preservation may too (48). Oral Contraceptive Pills (OCPs) are marketed to women and can serve as daily reminders of anatomy; longer-term options, such as IUDs are invasive, painful, and require a pelvic exam and manipulation, exposing transmen to dysphoria-based discomfort. Other barriers to contraceptive use include concerns that hormones from OCPs can counteract the effects of testosterone by increasing sex hormone-binding globulin which binds to testosterone (51).

6 Psychiatric and psychosocial considerations

In understanding mood disorders among TGD-AFB individuals, we consider biological and psychosocial contributors. Biologically, GAHT with exogenous testosterone in TGD-AFAB individuals is known to increase total brain volume, total gray matter volume, thalamus volume, and cortical thickness, specifically in frontal and parietal brain areas (46, 47, 52). Kiyar et al. (2022) found that the neural profile of TGD individuals assigned male at birth (AMAB) shifted from natal sex to their gender identity after 6-10 months of GAHT on fMRI. This confirmed that total testosterone is involved with the neural processing of emotions (51). However, it remains unclear how testosterone-driven neural profiles change with menstrual-related mood disorders.

The gender minority stress model outlines psychological processes that ultimately lead to mental health conditions and mood disorders (49). Chronic exposure to gender-based rejection; gender victimization; lack of gender affirmation; violence targeting TGD individuals; and legislation barring gender expression leads to the internalization of negative self-concept, fosters negative

anticipation of upcoming experiences, and delays engagement in gender-affirming care. Internalization of negative self-concept may also contribute to gender dysphoria and a variety of mental health conditions (49).

6.1 Premenstrual disorder and premenstrual dysphoric disorder

There is limited data on premenstrual disorders amongst TGD-AFAB individuals as this population is often excluded from studies about menstruation (50). PMD symptoms are categorized as predominantly physical, emotional, or mixed (48). The prevalence rate of PMD among cisgender women is estimated at around 20-40 %, with around 5% of cisgender women experiencing PMDD, a severe form of PMD that was added to the DSM-V in 2013 (48, 53). An exclusion criterion of PMDD is an exacerbation of an underlying psychiatric disorder, which can include gender dysphoria. Undoubtedly, comorbid gender dysphoria and the inherent worsening of dysphoria for many TGD-AFAB individuals with the onset of menses complicates the diagnosis of underlying PMDD (50). Despite diagnostic challenges, anyone with a menstrual cycle, including a TGD-AFAB person, is susceptible to PMD and PMDD.

Treatment for PMDD, which often includes cycle suppression, can dovetail with gender-affirming care. Low-dose selective serotonin reuptake inhibitors (SSRIs), with either luteal or continuous dosing, remain a first-line treatment option (48, 54). Other treatments include herbal supplements, such as chasteberry which is supported by data from a systematic review, and vitamins, including Vitamin B6, Calcium, and Magnesium (48, 55).

People with PMDD are also at high risk for suicidality; a recent systematic literature review found that 7-16% of people with PMDD have attempted suicide (56) compared to 0.7% of the general population in the most recent CDC data. Given the high baseline rate of suicide attempts (between 32-50%) in transgender people (57), screening for PMDD and suicidality in TGD-AFAB menstruators merits increased clinical attention (58, 59). At the time of this writing, we could not find data on the prevalence rates of PMDD among TGD-AFAB menstruators.

6.2 Depression and anxiety

There is limited literature on depression and anxiety among transmen, as most studies combine transgender identities. In a review of the literature published between 2013-2018, Nguyen et al. (2018) found lower depressive symptoms in TGD-AFAB individuals receiving GAHT across all studies (60). They also found that transgender men and women over the age of 50 receiving GAHT experienced a reduction of anxiety symptoms, as well as decreased cortisol awakening response and perceived stress (60). Although they found ongoing self-reports of high stress, 70 TGD individuals had a decrease in cortisol awakening response, which has been linked to decreased anticipation of stress (61, 62).

6.3 Post-traumatic stress disorder, post-traumatic stress symptoms and discrimination

TGD individuals report higher rates of exposure to traumatic events, including abuse in childhood, physical assault, intimate partner violence, and sexual assault (63–65). They also experience pervasive discrimination, discrete traumatic events linked to discrimination, and anti-TGD bias (66). In a national sample, up to 63% of TGD individuals reported discriminatory events leading to eviction, job loss, losing stable housing, denial of medical care, or losing an intimate relationship (67). Despite this, the wide range of PTSD prevalence within the TGD community suggests that there may either be varying detection strategies for PTSD or an over-pathologizing of responses to trauma and discrimination. Studies linking symptoms to specific traumatic events found lower rates of PTSD diagnosis when compared to studies that assessed PTSD symptoms generally (64, 65, 68, 69). Given this, it is important to delineate trauma from discrimination in TGD individuals, as conflation of the two may result in over-pathologizing responses from discrimination-based psychological distress (66).

6.4 Bipolar disorder, mania

There is limited to no data to guide the management of bipolar affective disorder in patients undergoing GAHT. Studies that associate manic symptoms with exogenous testosterone are often reported in cisgender men with supraphysiologic levels of anabolic androgenic steroids (70, 71). This contrasts with GAHT in TGD-AFAB individuals, where the dosing of testosterone targets physiologic levels. There is limited data on the association of mania in transmen with exogenous testosterone administration (36). Thus far, there is no data to indicate that appropriate GAHT dosing of testosterone would lead to an induction of mania, but close monitoring during testosterone initiation in at-risk individuals is warranted.

6.5 Psychosis

Current literature indicates an increased prevalence of schizophrenia spectrum disorders and psychosis amongst TGD individuals (72). In a review of 254 million discharges in the United States National Inpatient Sample database in 2019, Hanna et al. (2019) found that 14.5% of TGD patients were diagnosed with psychosis, compared to 4.3% of cis-gendered patients, and 14.2% of TGD patients were diagnosed with schizophrenia, compared to 2.8% of cis-gendered patients (57). In their literature review, Barr et al. (2021) found variability in the reported rates of psychotic illness among TGD individuals, which they attributed to varying recruitment strategies, racial bias in diagnosis, and demographic differences, as TGD study participants were on average 17 years or younger (72). Through a cohort study examining birth certificates and national insurance data in the Netherlands from 2006-2020, Termorshuizen et al. (2023) found that of 5,564 TGD individuals,

the TGD-AFAB cohort was substantially more likely to be diagnosed with a non-affective psychotic disorder when compared to TGD-AMAB (73). They also found that up to 50% of TGD individuals were diagnosed with psychosis after the first registration of data indicative of TGD status, and up to 83.7% were documented at the same time (73). These results, coupled with the historical classification of gender dysphoria as symptomatology within the realm of psychotic spectrum illness, suggest a continued risk of diagnostic bias of psychosis amongst TGD individuals.

6.6 Aggression

Although WPATH SOC Version 7 listed destabilization of psychiatric disorders as a potential side effect of testosterone, this was removed in WPATH SOC Version 8 (33). There is no documented consistent association or correlation between anger and serum testosterone levels; however, if irritability, mood changes, or anger do occur, these symptoms are more likely during the first year of initiation of GAHT (74, 75). Of the literature linking anger expression with testosterone in TGD-AFAB individuals, there was no increased risk for psychiatric hospitalization or self-harm (76, 77). Self-report measures of irritability and aggression decreased after gender-affirming surgical intervention, perhaps reflecting a decrease in depressive symptom burden (78). If mood changes occur with testosterone treatment, then it may be helpful to consider dose adjustments; changing from short-acting to long-acting intramuscular injections, or changing to gel formulations (79).

6.7 Quality of life, body satisfaction, and self-esteem

Several studies indicate a statistically significant improvement in self-reported quality of life and self-esteem in TGD-AMAB and TGD-AFAB individuals receiving GAHT (80–82). Silve et al. (2021) interviewed 113 people (60 TGD-AMAB and 53 TGD-AFAB) using quality of life questionnaires and found that in transmen, improved quality of life was associated with employment, being in a stable relationship, physical activity, and increased body hair (83). However, in a systematic review of 32 articles looking at TGD individuals on GAHT, not all studies reported a consistent improvement in body satisfaction when cross-sectional data was analyzed. They also noted that the literature on quality of life was inconsistent, ranging from improved, neutral, and worsened quality of life (82).

6.8 Sexual desire

One year of GAHT treatment in TGD-AFAB individuals is associated with an improvement in sexual function, specifically masturbation frequency, arousal, sexual fantasies, and desire (78). Additionally, increased libido is also linked to the earlier treatment with GAHT (84). In a cross-sectional analysis of data from the PRIDE study in 2021-2023, TGD-AFAB individuals on GAHT reported increased sexual desire (85). They theorized that GAHT increases the quality of life and self-image, which in turn positively impacts other areas of their life, including sexual desire (85).

6.9 Gender dysphoria

Although the literature indicates a decrease in gender dysphoria with GAHT, long-term affirmation is also impacted by social gender recognition, discrimination, and other variables. In a cross-sectional survey of 359 TGD individuals (219 TGD-AMAB and 140 TGD-AFAB), higher levels of dysphoria were related to sociological indicators of identity (ex: legally changing sex on identification) in those utilizing masculinizing GAHT compared to those who were not, suggesting that gender dysphoria may be related to sociological indicators of identity rather than just the hormones themselves (86). In that same study, the AFAB individuals who ultimately initiated GAHT noted global gender dysphoria decreased at 3 months and subsequently increased at 6, 12, and 24 months (86). When delineated further, it seems that subjective dysphoria was decreased, but dysphoria impacted by social and sociolegal factors had increased (86). In another study from Australia, TGD-AFAB individuals undergoing GAHT were found to have a significant reduction in gender dysphoria within the first few months of treatment, however, over 2 years had an increase in dysphoria related to social and sociolegal factors (87).

7 Age-related considerations

Despite the expectation that the number of Americans aged 65 and older will surpass children in 2023 and an estimation of at least 700,000 senior TGD individuals, there is limited literature on older TGD individuals in the United States (88). Most data and knowledge about TGD individuals come from European cohorts, with a larger proportion documented as transgender women. Under-representation of TGD-AFAB seniors in the literature makes it difficult to determine the long-term impact of hormonal and GAHT interventions on TGD-AFAB menstruators (89, 90).

Studies on cis-gendered individuals with a prostate, and post-menopausal women on hormone replacement therapy (HRT) suggest that sex hormones can be neuroprotective and improve cognition (91, 92). Cognitive changes in menopause are believed to be related to decreased estrogen availability, and androgen receptors in the hippocampus and prefrontal cortex (93). However, it remains unclear if these studies can be extrapolated to TGD-AFAB menstruators.

Data drawn from health insurance companies and ICD codes indicates TGD individuals had a statistically significant elevated probability of being diagnosed with dementia when compared to

cis-gendered individuals (94). Furthermore, TGD-AFAB individuals aged 45+ who identified as ethnically minoritized reported more memory loss and confusion in the past year when compared to their cis-gender counterparts (95). It is important to note that these studies combine transgender men and women, and often do not ask further questions about non-binary and fluid identities.

When gender identity is parsed out, the findings change. Heesewijk et al. (2023) found that transgender men had an increased risk of dementia compared only to cis-gender women; later research in 2021 found that transgender men had a similar cognitive functioning profile when compared to cisgender men and cisgender women (96). It has been theorized that the reported increased rate of dementia may be associated with delayed gender affirmation, repeated dysphoric episodes when menstruating, as well as limited social support (97).

Currently, a link between GAHT and impaired cognition has not been consistently described in the literature (97). Although there is little to no published literature on lifestyle factors impacting cognitive decline in TGD-AFAB individuals, when compared to cis-gender people, there is an overall increased prevalence of known risk factors, including higher rates of cigarette and alcohol consumption and lower physical activity (97). A higher burden of depressive symptoms may also impact cognition; rates of clinically significant depressive symptoms in older transgender individuals have been reported as high as 48%, which is pointedly higher than the general population of 6-8% (98, 99).

8 Conclusions

The language of TGD healthcare continues to evolve towards improving inclusivity. Medical providers should engage patients in discussions about their gender identity, how they relate to it, and what it means to them, as it can vary greatly. An example is the variability of preferred pronouns- she/her/he/him/they/them. WPATH guidelines recommend providers use active listening to encourage exploration in those uncertain about their gender identity. Rather than impose their narratives or preconceptions, providers should assist people in determining their paths. These conversations should also include the changing legislation for TGD-affirming care. Supplementary Table 4 provides examples of how to address topics discussed in this review.

Limitations to our review include an emphasis on North American data and Euro-centric experiences. To extrapolate this to other cultures and ethnicities requires sensitivity to their specific identities and contexts. There are also significant limitations in the current global literature on TGD-AFAB individuals. Survey language often omits TGD-AFAB as a gender category or groups all TGD individuals into one category, which excludes the diversity and spectrum range of gender. This has led to limited literature on the impact of menstruation, menstrual-related disorders, pregnancies, fertility, and exogenous testosterone exposure among TGD-AFAB individuals.

Our review indicates that the WPATH SOC-8 has moved beyond a focus on surgery and hormones, now including sexual, reproductive, mental, and primary health care services. There remains a need for additional research on the reduction of barriers to OBGYN care, contraception, and fertility preservation in TGD-AFAB individuals. These barriers can be addressed through their inclusion in medical, psychiatric, and menstruation-related research, as well as in medical, graduate, and residency-level curricula. Doing so may allow more comfort in treating this increasingly prevalent patient population.

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Supplementary material

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The behavioral and physiological correlates of affective mood switching in premenstrual dysphoric disorder

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Premenstrual dysphoric disorder (PMDD), a more severe manifestation of premenstrual syndrome (PMS), is characterized by emotional, behavioral, and physical symptoms that begin in the mid-to-late luteal phase of the menstrual cycle, when estradiol and progesterone levels precipitously decline, and remit after the onset of menses. Remotely monitoring physiologic variables associated with PMDD depression symptoms, such as heart rate variability (HRV), sleep, and physical activity, holds promise for developing an affective state prediction model. Switching into and out of depressive states is associated with an increased risk of suicide, and therefore, monitoring periods of affective switching may help mitigate risk. Management of other chronic health conditions, including cardiovascular disease and diabetes, has benefited from remote digital monitoring paradigms that enable patients and physicians to monitor symptoms in real-time and make behavioral and medication adjustments. PMDD is a chronic condition that may benefit from real-time, remote monitoring. However, clinical practice has not advanced to monitoring affective states in real-time. Identifying remote monitoring paradigms that can detect within-person affective state change may help facilitate later research on timely and efficacious interventions for individuals with PMDD. This narrative review synthesizes the current literature on behavioral and physiological correlates of PMDD suitable for remote monitoring during the menstrual cycle. The reliable measurement of heart rate variability (HRV), sleep, and physical activity, with existing wearable technology, suggests the potential of a remote monitoring paradigm in PMDD and other depressive disorders.

KEYWORDS

PMDD, PMS, remote monitoring, sleep, HRV, physical activity

1 Introduction

Premenstrual dysphoric disorder (PMDD) is characterized by emotional, behavioral, and physical symptoms that begin in the mid-to-late luteal phase of the menstrual cycle, when estradiol and progesterone levels precipitously decline, and remit after the onset of menses (Figure 1) (1–3). Research suggests that the withdrawal of the neuroactive steroid allopregnanolone (ALLO), a metabolite of progesterone, during the luteal phase may diminish the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) among those with PMDD, leading to a heightened stress response and reduced parasympathetic nervous system activity (3, 4).

PMDD may be thought of as a more impairing and severe manifestation of premenstrual syndrome (PMS), which is also characterized by a combination of physical and emotional symptoms that commonly include anger, depression, irritability, mood swings, breast tenderness, headache, and bloating (5). A recent meta-analysis found a 3.2% global prevalence estimate of confirmed PMDD, whereas PMS has global prevalence estimates of nearly 50% (6, 7). Like other mood disorders, the precipitous onset and remission of symptoms, which can be severe and impairing, often leaves individuals with PMDD uncertain about when symptoms will begin and the degree of impact they will have each menstrual cycle.

Management of other chronic health conditions, including cardiovascular disease and diabetes, has benefited from remote digital monitoring paradigms that enable patients and physicians to monitor symptoms in real-time and make behavioral and medication adjustments (8–12). Although digital health has not been widely adopted in mental healthcare, preliminary evidence suggests it may help individuals with depression and their healthcare providers better identify personalized patterns of risk and enable just-in-time interventions (13). PMDD is an ideal mood disorder to begin building within-person algorithms to detect mood changes, given the frequent cadence of affective switching (i.e., switching from euthymia to depression and back again each month) and the clear benefit of detecting an impending affective switch early enough to prevent or reduce its severity.

In mood disorders generally, the transition into and out of depression (i.e., "affective switching") is characterized by increased rates of suicide (14–16). Thus, PMDD presents a unique risk due to the frequency of affective switching. Indeed, those with PMDD are seven times more likely to attempt suicide than individuals without PMDD (Prasad et al., 2021).

Despite the high mortality rate in PMDD and the associated importance of monitoring risk, PMDD is difficult to diagnose correctly and monitor over time. Specifically, both the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and the International Classification of Diseases, Eleventh Revision (ICD-11) require prospective daily assessment during two menstrual cycles (17–19). To meet the criteria for PMDD, symptoms must be present for the week before menstruation (i.e., the luteal phase), and symptoms must clear out within the first couple of days of menstruation. Per the DSM-5, at least five symptoms must be endorsed, including at least one symptom from criterion B (marked irritability or anger or increased interpersonal conflicts; markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts; marked anxiety, tension, and/or feelings of being keyed up or on edge) and at least one symptoms from criterion C (decreased interested in usual activity; subjective difficulty concentrating; lethargy, easy fatigability, or marked lack of energy; marked change in appetite, overeating or specific cravings; hypersomnia or insomnia; a sense of being overwhelmed or out of control; physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of "bloating" or weight gain) (18).

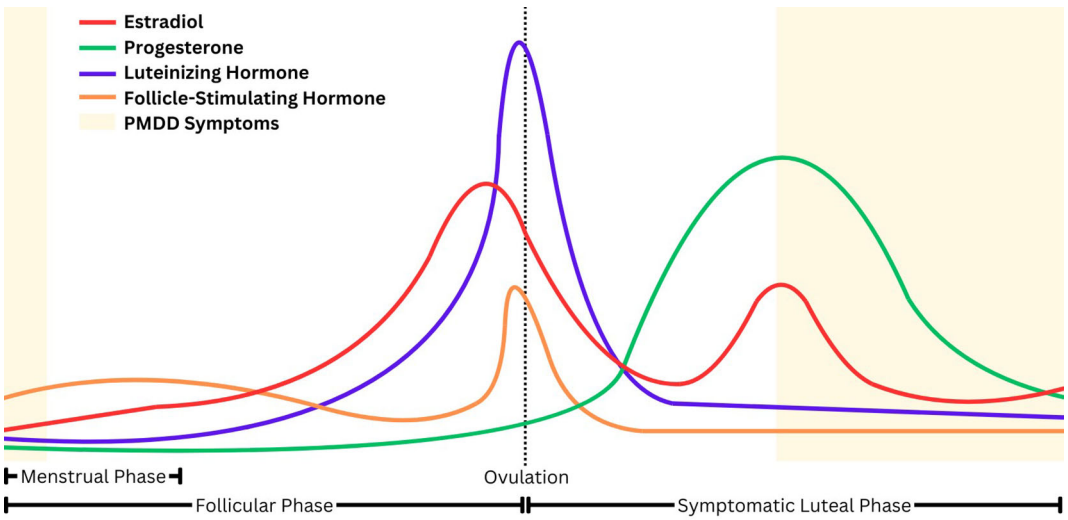

FIGURE 1
Hormones and PMDD symptom timing throughout the menstrual cycle.

At present, there are no commercially available apps or trackers to assist with PMDD diagnosis. The gold standard method of diagnosing PMDD calls for clinicians to use paper and pencil to hand-score prospective symptom ratings (17). Moreover, for individuals with PMDD, the timing of affective state transitions into and out of depression is contingent on the menstrual cycle. However, not all individuals have a reliably consistent cycle length, making it difficult to predict the highest-risk period (20). Ideally, clinicians would monitor those with PMDD during the highest risk period and introduce just-in-time interventions to mitigate impairment and prevent suicidality. Yet, current practice generally precludes prediction of symptom onset and timely intervention.

Other chronic conditions with heightened mortality rates have benefited from real-time remote monitoring. For example, the use of continuous glucose monitoring devices for diabetes mellitus reduces HbA1c by an additional 17-43% compared to usual care (8, 9). Similar impacts have been observed in cardiovascular disease. Compared with usual care, the use of combined remote monitoring and consultation decreases cardiovascular-related mortality and hospitalization by 17% and 28%, respectively (10). Encouragingly, 83% of adults with cardiovascular disease are willing to share wearable device data with their clinicians to improve their care (21).

Like diabetes mellitus and cardiovascular disease, PMDD is a chronic condition that may benefit from real-time, remote monitoring. However, clinical practice has not advanced to monitoring affective states in real-time (22, 23). Given that 29% of Americans already use fitness tracking devices, remote monitoring may be a feasible and affordable way to monitor affective switching (21). Consequently, using wearable devices for remote monitoring of mood disorder symptoms holds the potential for advancing population health in depressive disorders, as it has with cardiovascular disease and diabetes. However, since there is a lack of studies aimed at detecting affective switching through remote monitoring, reviewing the potential physiological biomarkers that could serve as endpoints for affective switching is warranted. PMDD, a relatively homogenous depression subtype with a known, frequent, and regularly occurring trigger of affective switching, holds promise for developing an affective state prediction model (24).

This review aims to synthesize the current literature on behavioral and physiological biomarkers of affective switching in PMDD and depressive disorders, with a focus on their suitability for remote monitoring. In particular, biomarkers were selected for review that are 1) able to be passively monitored with modern wearable technology 2) have an established association with mood and 3) have some literature supporting a relationship with the menstrual-cycle related changes. As a result, heart rate variability (HRV), sleep, and physical activity were selected for review. The review will also explore the predictive utility of passively monitoring smartphone behavior and social smartphone behavior. Finally, gaps in the existing literature will be identified and potential next steps toward applying remote digital monitoring to PMDD and other depressive disorders will be described.

2 Heart rate variability (HRV)

Heart rate variability (HRV), the variation in time between successive heartbeats, is a noninvasive measure of autonomic nervous system (ANS) activity, with higher HRV thought to reflect greater physiologic flexibility and ability to regulate emotional responses (25).

2.1 HRV measurement

HRV is measured using both time-domain measurements or frequency-domain measurements (26, 27), computed in several different ways: time-domain measurements look at the time between successive heartbeats; RR intervals refer to the time between all successive heartbeats; and NN intervals refer to the time between intervals from which artifacts, or abnormal beats, have been removed. Time-domain measures include the standard deviation of NN intervals (SDNN), the square root of the mean squared differences of NN intervals (rMSSD), and the standard deviation of the average NN intervals over a short time period (SDANN). SDNN provides an overall estimate of HRV, while rMSSD provides an overall estimate of short-term components of HRV, and SDANN provides an overall estimate of long-term components of HRV (26).

Frequency-domain measurements look at the relative power of a frequency band. Frequency domain measurements of HRV consist of very low frequency (VLF) power, low frequency (LF) power, high frequency (HF) power, and very high frequency (VHF) power. HF power represents parasympathetic nervous system (PNS) activity, while LF power can be produced by both sympathetic nervous system (SNS) and PNS activity. The LF/HF ratio is thought to represent the balance between the PNS and SNS (26, 27).

The gold standard for measuring HRV is electrocardiography (EKG), which involves measuring electric signals from the heart to measure heart activity (26, 28). HRV can also be measured with photoplethysmography (PPG) (29, 30). PPG uses LED light and a photodetector to measure the amount of light reflected by tissue, representing blood volume changes (31, 32). Thus, PPG measures pulse rate variability (PRV) as a proxy for RR intervals (29, 30). PPG devices are commonly worn on the wrist; however, newer PPG devices with increased accuracy can be worn on the finger (33).

2.2 Remote monitoring of HRV

Wearable devices with EKG or PPG capabilities enable remote monitoring of HRV. For example, the second-generation Oura ring, which uses PPG, demonstrated high agreement with EKG for nocturnal rMSSD (r^2 = 0.980) (34). A systematic review of 18 studies compared HRV derived from classic EKGs with HRV derived from commercially available wearable devices (30). Results indicated correlation ranges of r=0.98-0.99 and r=0.85-0.94 for time-domain and frequency-domain indices of HRV

respectively, when measured in a resting state. However, the correlations decreased when HRV was not measured in a resting state (30), indicating that wearable devices may be less accurate during activities. A separate review investigating the accuracy of PRV concluded a strong agreement between PRV and EKG when HRV is measured at rest. At the same time, the review noted that physical activity and mental stress may impair agreement. However, quantitative conclusions were precluded by heterogeneity across reviewed studies (29). Thus, currently available wearable devices are as accurate as EKG for measuring HRV and PRV during rest, though they may be less accurate during physical activity.

2.3 HRV and psychopathology

HRV is related to stress, including perceived stress, response to stressful life events, and adaptability to stress (35, 36). HRV has been shown to be significantly reduced in patients with major depressive disorder (MDD) and other psychiatric conditions, including schizophrenia, posttraumatic stress disorder, and bipolar disorder (37, 38). For example, two meta-analyses have demonstrated that individuals with depression have lower HRV, and lower HRV is associated with more severe depression symptoms (36, 39). However, emerging literature suggests that this association may not hold across all populations. Specifically, one study demonstrated that higher resting HRV was associated with more severe depression among Black Americans, especially among Black Americans who endorse the use of culturally compelled coping (40, 41). Thus, additional studies that investigate HRV functioning among diverse populations are needed.

2.4 HRV in PMDD and during the menstrual cycle

Evidence suggests that HRV changes throughout the menstrual cycle (42–45). However, this relationship may be particularly apparent for those with PMS/PMDD (46, 47). Obtaining a clear understanding of the interaction between PMDD, menstrual phase, and HRV presents challenges because 1) there are two domains of measuring HRV (i.e., frequency and time); 2) there are multiple components of HRV that can be analyzed within each domain (i.e., HF, LF, SSDN, RR intervals, SDAAN, etc.); and 3) there are multiple time points that can be compared (i.e., comparing HRV in a particular cycle phase versus comparing changes in HRV between cycle phases). Several studies have examined HRV in PMS and PMDD, both of which will be discussed to identify themes to guide future studies. Details regarding study samples, design, measurement devices, and findings of studies investigating HRV in PMS and PMDD can be found in Table 1.

2.4.1 Differences in HRV between PMDD, PMS, and asymptomatic control groups during the menstrual cycle

Individuals with PMS/PMDD have been shown to differ from those without PMS/PMDD in certain HRV metrics, regardless of cycle phase. While some studies indicate that those with PMS/PMDD experience lower HRV, on average, results are mixed across studies and thus may be driven by specific HRV components. For instance, while Matsumoto et al. (2007) found that individuals with PMDD have lower HF power throughout the menstrual cycle compared with individuals with PMS or no premenstrual symptoms, Baker et al. (2008) and Swami and Kumar (2023) found that overall HF power was not significantly different between groups (46–48). In contrast, Swami and Kumar found lower VHF power in those with PMS compared to controls throughout the menstrual cycle, and Baker et al. found smaller mean NN intervals in those with PMS compared with controls throughout the menstrual cycle (47, 48).

Results are similarly mixed with regard to LF power. Matsumoto et al. found that LF power was lower in those with PMDD compared with those with PMS and those without PMS/PMDD; Swami and Kumar did not find any group differences; and Baker et al. did not report LF power (46–48). A similar pattern emerged with the LF/HF ratio, where Swami and Kumar found an increased ratio in those with PMS overall; Baker et al. did not find any group differences; and Matsumoto et al. did not report the LF/HF ratio (46–48). Finally, Matsumoto et al. found decreased total power in the PMDD group compared with the PMS and control groups; while Baker et al. did not find any group differences; and Swami and Kumar did not report total power (46–48). Thus, the literature is mixed with regard to differences between PMDD, PMS, and control groups in HRV and its components when measured during the menstrual cycle rather than examining specific cycle phases.

2.4.2 Differences in HRV between PMS and asymptomatic control groups within specific cycle phases

Some studies have examined components of HRV between those with PMS and asymptomatic controls during the follicular phase, luteal phase, or both. For instance, two studies that implemented a social stress test in the luteal phase indicated a delay in HF power recovery after the stress task for the PMS group, compared with controls (49, 50). An additional study indicated lower SDNN and rMSSD in the luteal phase in those with PMS compared with controls (51). However, one study found a lower SDNN, rMSSD, and HF power in the follicular phase for the PMS group compared with controls and did not indicate any within or between-group differences within the luteal phase (52). Similarly, a study that investigated the relationship between PMS symptoms and HRV during the follicular phase found a positive association between PMS symptoms and SDNN and rMSSD for those not on hormonal contraceptives, which is the opposite direction of the effect one would expect based on Landén et al., 2004 (52). This effect did not remain among those on hormonal contraceptives, which could be because hormonal contraceptives have been shown to stabilize the hormonal shifts that occur during the menstrual cycle and reduce PMS symptoms (53, 54). Taken together, these studies suggest HRV and its components are lower in the symptomatic luteal phase in those with PMS compared with those without PMS.

TABLE 1 Characteristics of cited studies on HRV.

Author	Participants, n		Study Design	HRV Components	
	PMS/PMDD	Control		Time	Frequency
Baker et al. (2008) (47)	14; severe PMS (n=4) or PMDD (n=5)	15	EKG during overnight in-lab sleep study during follicular phase (6-12 days after menstrual bleeding) and late-luteal phase (9-10 days after luteinizing hormone surge)	NN[abe], SDNN[e], rMSSD, SDAAN	TP, HF[e], HFpf[a], LF/HF
Danel et al. (2019) (54)	177; PMS n=113 no hormonal contraceptive; n=64 on hormonal contraceptive		EKG continuously recorded for 10 minutes in follicular phase (4-8 days after menstruation).	SDNN[c], rMSSD[c]	–
de Zambotti et al. (2013) (55)	12; PMS	14	EKG during overnight in-lab sleep study during follicular phase (6-10 days after onset of menstruation), mid-luteal phase (5-9 days after luteinizing hormone surge), and late-luteal phase (10-14 days after luteinizing hormone surge)	–	TP, HFpf, LF/HF
Feula et al. (2022) (51)	20; PMS	20	EKG continuously recorded for five minutes during late-luteal phase (5 to 7 days before menstruation).	SDNN[b], rMSSD[b]	TP, HF[b], L, LF/HF[b]
Grrishma et al. (2015) (56)	60; mild PMS		EKG continuously recorded for 5 minutes during follicular phase (8-10 days after menstrual bleeding), late-luteal phase (1-5 days before menstruation)	SDNN, rMSSD[d]	TP[d], HF[d], LF[d], VLF[d]
Hamidovic et al. (2023) (50)	17; PMDD	18	Heart rate monitor during trier social stress test (TSST) during mid-luteal or late-luteal phase. HRV time points (baseline, instruction, TSST, recovery) were compared for PMS and control group	–	HF[b]
Landen et al. (2004) (52)	28; PMDD	11	EKG in both follicular phase (6-10 days after menstrual bleeding) and luteal phase (5 to 0 days before menstruation). Frequency domain HRV measured with EKG in lab for 10 minutes in standing-up position and 10 minutes in supine position. Time domain HRV measured with 24-h take-home EKG beginning on same day as frequency HRV EKG	RR, SDNN[c], rMSSD[c], SDANN	Supine HF[c], standing HF, supine HF/LF, standing HF/LF
Matsumoto et al. (2007) (46)	34; PMS (n=23) or PMDD (n=11)	28	EKG continuously recorded for five minutes during mid-follicular phase (5 days after menstrual bleeding) and late-luteal phase (within 7 days before menstruation)	RR[ae]	TP[ab], HF[ae], LF[a]
Meng et al. (2022) (49)	50; PMS	46	EKG recorded during stress test during late-luteal phase (not defined) and follicular phase (not defined). HRV time points (baseline, task, recovery) were compared for PMS and control group	–	HF[b], LF, LF/HF[b]
Swami & Kumar (2023) (48)	20; PMS	20	EKG continuously recorded for 15 minute during follicular phase (5 days after menstrual bleeding), late-luteal phase (7 days before menstruation)	RR[a], SDNN[b]	HF[d], LF, VHF[ad], VLF[ad], LF/HF[ad]

RR, regular intervals; NN, normal to normal intervals; SDNN, standard deviation of NN intervals; rMSSD, root of the mean square differences of NN intervals; SDANN, standard deviation of the average NN intervals over a short period of time; TP, total power; HF, high frequency power; HFpf, high frequency peak frequency; LF/HF, ratio of low frequency and high frequency power; LF, low frequency power; VHF, very high frequency power; VLF, very low frequency power; [a], PMS/PMDD and control group significantly different overall; [b], PMS/PMDD and control group significantly different within luteal phase; [c], PMS/PMDD and control group significantly different within follicular phase; [d], PMS/PMDD group significantly different in luteal phase compared to follicular phase, not considering control group; [e], PMS/PMDD significantly different in luteal phase compared to follicular phase for PMS/PMDD group, but not control group.

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2.4.3 Within-group changes in HRV during the menstrual cycle in PMDD

A considerable number of studies have indicated that the symptomatic luteal phase is characterized by reduced HRV in those with PMS/PMDD. Specifically, women with PMS/PMDD show decreased HF power in the luteal phase compared with the follicular phase (46–48, 55, 56). Additionally, individuals without PMS/PMDD do not show cycle phase differences in HF power, suggesting the luteal phase reduction in HRV is unique to those with PMS/PMDD (46, 47, 55). Time-domain measures such as SDNN and rMSSD are also lower in the luteal phase compared to the follicular phase for those with PMS/PMDD (47, 48, 56). Thus, studies have consistently shown certain aspects of HRV are lower in the luteal phase compared with the follicular phase in those with PMS/PMDD, but not in asymptomatic controls.

2.4.4 Methodological challenges and HRV summary

Across the three sets of studies reviewed, methodologic variation may account for important differences in findings. Of the studies reviewed, two measured HRV during sleep (47, 55), two measured HRV during a stress test (49, 50), and the remaining six measured HRV with a supine or standing EKG sample of varying lengths of time (46, 48, 51, 52, 54, 56). Additionally, as indicated in Table 1, different components of HRV are reported in each study, precluding a full comparison of study results. Finally, sample sizes are consistently small or moderate, and small sample sizes may obscure true findings and may also contribute to false discoveries. Adequately powered studies are needed to determine the extent to which HRV may be associated with the onset of mood symptoms, physiologic symptoms, or their combination during the menstrual cycle in those with PMDD, PMS, and asymptomatic controls.

Despite these methodologic differences, one clear and consistent pattern of results emerged. Across studies, some components of HRV were lower in individuals with PMS/PMDD during the luteal phase compared with the follicular phase, and this difference was unique to individuals with PMS/PMDD. This suggests that HRV variation may be a valid physiologic marker of within-person symptom variation in those with menstrually-related mood disorders (i.e., PMS or PMDD). In contrast, while some studies indicate PMDD is defined by lower HRV across the menstrual cycle compared with those with PMS and asymptomatic controls, these results have not been consistently replicated across studies and should be interpreted with caution. As such, HRV may not be a good diagnostic marker for PMDD.

3 Sleep

3.1 Sleep measurement

In the literature, sleep is typically assessed by examining the duration of sleep, sleep staging, or both using multi-modal physiologic assessment (Table 2). Polysomnography (PSG) uses a combination of electroencephalogram (EEG), electrooculogram, electromyogram, EKG, pulse oximetry, and airflow and respiratory effort to determine wakefulness and sleep as well as staging (57). PSG offers a comprehensive look at the structural organization of sleep, or sleep architecture, and is considered the gold standard for measuring sleep and diagnosing sleep disorders (58, 59).

Alternative ways to measure sleep physiology include actigraphy and photoplethysmography (PPG). Actigraphs are wearable devices, typically worn on the wrist, that measure sleep by detecting physical movements. Most modern actigraphs include accelerometers for movement detection (60). Additionally, PPG measures heart rate, HRV, blood oxygen saturation, and respiratory rate, which can be used to indicate sleep (32, 33, 61).

Subjective sleep measures, such as sleep diaries or questionnaires, prompt an individual to retrospectively report on sleep components (e.g., time in bed, sleep onset latency). While the most common subjective sleep measures demonstrate strong internal consistency and test-retest reliability, subjective sleep measures are not strongly correlated with objective sleep measures (62–64). In particular, the accuracy of self-reported sleep quality is vulnerable to being impacted by memory processes, personality, mood states, and subjective well-being (64–66). However, subjective sleep measures are low-cost and highly feasible while offering some insight into sleep habits and may help place physiological sleep assessments into context (e.g., knowing that an individual woke up several times in one night because of a thunderstorm can help with the interpretation of physiologic measures).

3.2 Remote monitoring of sleep

PSG typically involves an individual spending at least one night sleeping in a sleep laboratory setting and consists of a specialist observing and interpreting the gathered PSG sleep data. Despite PSG being the gold standard of sleep measurement, wearable devices therefore offer a more unobtrusive, affordable, and feasible way to monitor sleep on an ongoing basis. In determining the validity of remote sleep monitoring devices, attention is paid to sensitivity (i.e., ability to detect sleep), specificity (i.e., ability to detect wake), and staging (i.e., ability to detect sleep stage) (67, 68).

TABLE 2 Components of sleep architecture (59, 167, 168).

REM sleep	Rapid eye movement sleep
NREM sleep	Non rapid eye movement sleep
Stage 1 sleep	Brief period transitioning from wake to sleep, or "dozing off" period
Stage 2 sleep	Light sleep
Stages 3 and 4 sleep	Slow wave sleep or deep sleep
Total sleep time (TST)	Time spent in REM or NREM sleep
Sleep onset latency	Time it takes to fall asleep
Sleep efficiency	Ratio of total time asleep to time spent in bed intending to sleep
Wakefulness after sleep (WASO)	Time spent awake after sleep onset but before final awakening

Actigraphy can assess sleep-wake patterns in individuals with average or good sleep with reasonable reliability and validity compared to PSG (60, 69, 70). Additionally, the accuracy of consumer actigraphy devices is comparable to that of research-grade actigraphy devices (71–73). Actigraphy has strong sensitivity (ability to detect sleep) but tends to overestimate total sleep time. However, specificity (ability to detect wake) is consistently low (32, 74–77). Moreover, accuracy may diminish among people with lower sleep quality depending on the device being used (74, 78–80). Another disadvantage of actigraphy is its lack of validation for identifying sleep stages (68, 81). Taken together, these studies suggest that both actigraphy and commercial grade wearable devices can validly measure sleep initiation and duration.

Newer consumer devices include a combination of PPG, accelerometry, and body temperature to achieve increased sleep/wake scoring accuracy compared to actigraphy alone. Moreover, PPG can predict sleep staging with moderate accuracy compared to PSG (32, 68, 71, 82–84). With few exceptions, PPG-based devices that classify sleep into three or four stages have 65-75% staging accuracy (68). Despite this potential for remotely monitoring sleep staging, consumer wearable devices have distinct disadvantages in the research context: 1) the scoring algorithms used by the consumer devices are often proprietary and 2) ongoing improvements to these algorithms may impact within-person reliability during ongoing sleep studies (32).

Newer studies have begun to look at wearable and portable EEG devices, such as in-ear or headband EEG devices. Some wearable EEG devices, such as the Dreem headband or an in-ear EEG, may be more accurate than accelerometers and PPG and are capable of identifying all five sleep stages when used properly (32, 68, 82, 85, 86). Thus, portable and wearable EEG technologies hold promise for studying sleep/wake and sleep staging.

3.3 Sleep and psychopathology

Sleep disturbances are transdiagnostic precipitants and symptoms of MDD and other psychiatric disorders, including bipolar disorder and schizophrenia (87–89). Sleep disturbances are thought to indicate an underlying circadian dysfunction in MDD and mood disorders more generally (90), though circadian dysfunction has not been well studied in PMDD.

3.4 Sleep and the menstrual cycle

Sleep varies by menstrual phase among menstruating individuals, irrespective of PMS/PMDD status. The exact nature of this relationship, however, is not fully understood. Women generally report decreases in perceived sleep quality in the luteal phase compared with the follicular phase (91, 92). One study of 163 women used actigraphy to measure sleep and found that sleep efficiency declined gradually across the menstrual cycle, with a more apparent decline in the luteal phase. However, participants were not all regularly menstruating and were also in different stages of the reproductive life cycle (pre-, early-, and late-perimenopause) (92). Thus, the relationship between sleep efficiency and the menstrual cycle may be somewhat obscured by the inclusion of those who were not regularly menstruating.

Additional studies have directly examined the relationship between sleep and ovarian hormone changes during the menstrual cycle. Rising progesterone levels have been associated with objective sleep measures, including decreased sleep HRV (55) and increased PSG-measured sleep disturbances (93). A recent review found that endogenous progesterone has a sleep-promoting effect and that hormone-related sleep problems were more associated with the rate of change in reproductive hormones than the absolute levels of hormones (94). Taken together, progesterone may regulate sleep during the menstrual cycle in regularly menstruating individuals and may be responsible for cycle phase effects.

3.5 Sleep and PMDD

The menstrual cycle may have a greater impact on sleep among those with PMS or PMDD who report higher levels of insomnia and fatigue and perceive lower sleep quality throughout the entire menstrual cycle compared to those without PMS/PMDD, with the greatest differences occurring during the luteal phase (47, 92, 95–98). However, few studies have examined objective measures of sleep in this population (99).

Baker et al. (2012) compared objective and subjective sleep measures in 18 women with severe PMS and 18 women with minimal menstrual symptoms. The PMS group exhibited poorer subjective sleep quality in the luteal phase and increased levels of slow-wave sleep, as measured by PSG, throughout the menstrual cycle, compared with controls (100). Similar results were found by Shechter et al. (2012), where women with PMDD and luteal-phase insomnia (n=7) experienced more slow-wave sleep during the luteal phase compared with a control group (n=5). However, the sample size was small and the control selection criteria were not well defined (101). In a study done by de Zambotti et al. (2013) the PMS group (n=12) appeared to spend more time in slow-wave sleep in the luteal phase compared with controls (n=14) (17.4 vs 14.3% TST in mid-luteal; 16.2 vs 11.3% TST late-luteal), yet, these results did not reach significance (55).

In contrast, earlier studies indicated that individuals with PMS/PMDD display decreased slow-wave sleep compared to a control group during both the follicular and luteal phases although small sample sizes limit these findings (84, 95). A larger study (n=23 PMDD; n=18 controls) found no difference in slow-wave sleep during the mid-follicular phase or the late-luteal phase, however, results should be interpreted within the context of a clinical trial looking at sleep deprivation therapy (102).

The relevance of sleep in PMDD is further indicated by a series of studies that demonstrated a delayed reduction in endogenous melatonin levels in mornings during the luteal phase compared with the follicular phase in those with PMDD (102–106).

Overall, future studies should focus on delineating the relationship between PMDD and sleep at the within-person level

to determine if remote sleep monitoring devices can be used to predict or detect affective switching.

4 Physical activity

4.1 Physical activity measurement

Physical activity can be measured via self-report, accelerometers, pedometers, heart rate monitors, and sensors that combine different measurement modalities (108, 109). Aspects of physical activity that can be measured may include energy expenditure, step count, distance traveled, and time spent in different postures. The gold-standard method for measuring physical activity involves quantifying energy expenditure using the doubly labeled water method, which entails measuring elimination rates of specific isotypes following the ingestion of deuterium and heavy oxygen-labeled water (110). This method is expensive, burdensome, and time-intensive and is therefore not feasible for remote monitoring of physical activity (for a review, see Sylvia et al. (108).

4.2 Remote monitoring of physical activity

Wearable devices are overall an accurate and feasible way to track physical activity, although validity varies between brand. Fuller et al. (2020) conducted a systematic review of commercially available wearable devices for measuring steps, energy expenditure, and heart rate. The review indicated that criterion validity depends on the device, study type (controlled or naturalistic), and type of measurement. Validity for step count was best for Apple Watch and Garmin, while Fitbit, Samsung, and Withings were within +/-3 mean percentage error on average. Heart rate was also accurately measured; all brands fell within +/-3 mean percentage error on average, with a small tendency for underestimation. Wearable devices were found to be unreliable for measuring energy expenditure (111). However, this review did not include devices designed to be worn on the finger (e.g., Oura ring), which emerging studies demonstrate to be highly correlated with gold-standard measures of step counts, heart rate, and energy expenditure (112, 113).

4.3 Physical activity and psychopathology

Depressive symptoms and physical activity have a well-established link. A meta-analysis of 42 studies reported a significant inverse relationship between physical activity (i.e. actigraphy or pedometer) and rates of depression. However, these findings were based on cross-sectional studies, so the directionality of the effects cannot be inferred (114). Decreased physical activity has been consistently linked to risk for depression, although findings regarding the impact of depression on subsequent physical activity are mixed (115–119) Nevertheless, objective measures support a strong negative relationship between depressive symptom severity and daily step count (118, 119).

A wealth of research has been conducted on the effectiveness of physical activity as an intervention for depression. Hu et al. (2020) conducted a systematic review of eight meta-analyses across 134 studies concerning exercise as an intervention for depression symptoms. They concluded that exercise interventions have a moderate effect on reducing depressive symptoms (120). A separate systematic review of 13 studies reported that 10 studies showed a statistically significant reduction in depression symptoms following a randomized-controlled exercise intervention. The review concluded that any physical activity for 30-45 minutes at least three times a week, preferably performed under supervision, is recommended to treat MDD (121). Given both the naturalistic and experimental results linking depression and physical activity, physical activity may be a reliable physiologic indicator of depressed mood.

4.4 Physical activity, the menstrual cycle, and PMDD

To date, there is a lack of research on the relationship between physical activity, the menstrual cycle, and PMDD. A recent meta-analysis on the effects of the menstrual cycle phase on exercise indicated that there may be a trivial reduction in exercise during the early follicular phase (122). A separate study indicated no reduction in step count as a result of menstrual phase (123). Another review looked at the performance of athletes throughout the menstrual cycle and concluded mixed findings regarding levels of physical activity or athletic performance and the menstrual phase (124).

Studies investigating changes in physical activity throughout the menstrual cycle among individuals with PMS/PMDD are lacking. However, one study indicated that women with severe PMS walked 1,411 fewer steps during the luteal phase and menses compared with asymptomatic control women (125). Additionally, observational studies support a negative relationship between looking at PMS/PMDD symptoms and general exercise (126–128). Additionally, there is growing evidence supporting physical activity as an effective intervention for PMS (128, 129). A systematic review of five RCTs with 492 participants concluded that aerobic exercises effectively improve premenstrual symptoms (130).

Physical activity and depression symptom severity are likely bidirectionally related. As depression is a common feature of PMDD, more research is warranted to determine the extent to which objective measures of physical activity can be used to predict PMDD symptoms.

5 Social behaviors and smartphone use

5.1 Remote monitoring of social behavior with smartphones

Aspects of social behavior can be gleaned by tracking smartphone use. For instance, smartphone use for interpersonal connection is positively associated with a higher likelihood of participating in social activities (131), greater belonging support,

and greater tangible social support over time. Problematic smartphone use, involving an excessive psychological attachment to one's smartphone, is associated with less tangible social support over time (132). Thus, smartphone activity, and specific types of smartphone activity, may be a feasible proxy for social behavior.

5.2 Remote monitoring of mood with smartphones

Smartphone data may be associated with mood. Objectively monitored speech patterns from smartphone voice data can predict mood states with up to 97.4% accuracy (133, 134). Applying machine learning models to passively collected smartphone data has been shown to accurately detect fluctuations in mood states, including in those with MDD (135–138). Given the established predictive utility of passively collected smartphone-use data on mood fluctuations, applying these findings to affective switching among people with PMDD is a promising area for future investigation.

5.3 Social media use and mood

Research strongly supports a relationship between social impairments and depressive symptoms (139–141). Moreover, social interaction and support are known to influence clinical outcomes in depression (142–144). The emergence of smartphones and social media introduces new considerations when studying social impairment. While some social media interactions improve mood, most studies show that increased time spent engaging with cell phones and social media apps is associated with greater depression severity (145–149).

Studies of social media use and mood have produced mixed findings. A systematic review of 13 studies investigating adolescent social media use demonstrated a positive association between psychological distress and social media use across multiple measures (150). However, a separate review noted that research on social media use and adolescents has been mostly cross-sectional and has generated conflicting results and small effect sizes (151). Another review indicated a *positive* association between social media use and mood (152). Social media findings are thus hard to interpret. More detailed studies measuring how an individual uses social media will likely provide better information about the impact of social media on mood. So far, studies of the type of social medial interactions (i.e., active vs passive, private vs public) have yielded similarly mixed findings (153–155).

5.4 Social impairment, PMDD, and the menstrual cycle

PMDD is associated with social impairment during the luteal phase, including interference in relationships with friends, classmates, and coworkers (156–160). Rubinow and colleagues (2017) administered a Facial Discrimination Task in the luteal and follicular phases of women with PMDD and asymptomatic controls. They found that women with PMDD exhibited increased negative judgments and impaired specificity of judgments during the luteal phase compared with the follicular phase, while controls did not experience any menstrual effects (157). These findings suggest that facial recognition is impaired during the luteal phase in PMDD, which could have downstream effects on social behavior.

Women with PMDD also report higher levels of hostility regardless of menstrual phase (158) and more aggressive tactics to solve conflict during the luteal phase (161). Kaiser and colleagues found that among women with PMDD, pain and somatic dysphoria in the luteal phase is correlated with impairment in social activities, while premenstrual irritability in the luteal phase is correlated with impairment in relationships (159). These findings support previous research suggesting that those with PMDD suffer from increased irritability in the luteal phase, which could negatively impact social engagement (158, 162).

Overall, considering the feasibility of smartphone data collection, future research regarding the predictive utility of smartphone data both generally and as a proxy for social behavior among those with PMDD is warranted. However, current research methods of social media use are crude proxies for more nuanced social interactions that could be collected by monitoring social media and smartphone use.

6 Discussion

This review synthesized the current literature on behavioral and physiological correlates of PMDD suitable for remote monitoring during the menstrual cycle. PMDD is marked by the onset and offset of a depressive state provoked by hormonal fluctuations during the menstrual cycle. Switching into and out of depressive states is associated with an increased risk of suicide, therefore, periods of affective switching may be important to monitor to enable just-in-time interventions. Given the cyclical and chronic nature of affective switching in PMDD and attendant suicide risk, identifying remote monitoring paradigms that can detect within-person affective state change may help facilitate later research on timely and efficacious interventions. The reliable measurement of key physiologic variables associated with depression symptoms, HRV, sleep, and physical activity, with existing wearable technology, suggests the potential of a remote monitoring paradigm in PMDD.

6.1 HRV

HRV is an indicator of ANS activity that can be effectively monitored with remote wearable devices, particularly during rest period (29, 30, 34). HRV has been found to relate to stress and depression severity, and is significantly reduced in patients with mental illness (35–39). Although few studies have examined the relationship between PMDD and HRV, recent evidence suggests reduced HRV during the symptomatic luteal phase in those with PMS/PMDD (46–48, 55, 56). Findings consistently demonstrate decreased HF power during the luteal phase, which can be

interpreted as a reduction in overall PNS activity (26). These findings align with MDD literature that indicates lower HRV in individuals with symptomatic MDD, compared with controls (36, 39). Although existing studies demonstrated group-level reductions in HRV between the follicular and luteal phases in those with PMDD/PMS, additional research to establish within-person changes in HRV or HF power will be needed to establish the use of this variable as a correlate or predictor of symptom onset to guide clinical practice.

6.2 Sleep

Sleep disturbances are an established precipitant and symptom of psychiatric disorders that can be tracked easily and accurately with remote monitoring (68, 87, 88, 90). In particular, remote monitoring is an effective tool for capturing total sleep-wake time, and newer technology has begun to track sleep staging reliably (32, 68, 71, 82–86). Individuals with PMS/PMDD have more of a negative perception of sleep quality, particularly heightened during the luteal phase, compared to those without PMS/PMDD (47, 92, 95–98). Evidence suggests that the circadian rhythm may be disturbed in the luteal phase among those with PMS/PMDD, with some indications of altered melatonin secretion and slow-wave sleep (55, 100–107). However, because some studies indicate that sleep abnormalities persist throughout the menstrual cycle without showing phasic differences, sleep may be a less useful metric of affective switching in PMDD. Despite this, the prominent finding that perceived sleep quality diminishes in the luteal phase should not be disregarded. It is plausible that sleep quality perception is influenced by psychological state rather than actual sleep quality. However, it is also plausible that changes in perceived sleep quality can be attributed to changes in sleep architecture that are not detectable with between-person study designs. Future studies should focus on delineating the relationship between PMDD and sleep at the within-person level to determine if remote sleep monitoring devices can predict affective switching and help inform the implementation of effective sleep interventions.

6.3 Physical activity

Physical activity can be easily and accurately tracked with remote monitoring methods (111–113). Despite a well-established relationship between depression and physical activity, the bidirectional nature of this relationship has not been well articulated (114–119). In PMS/PMDD, there is not enough evidence that physical activity and exercise (both performance and amount) vary by menstrual phase. Research regarding physical activity/exercise as an intervention is more well-established. Evidence suggests that exercise can meaningfully reduce depression symptoms among those with a depressive disorder (120, 121). Further, growing evidence supports physical activity as an effective intervention for PMS/PMDD (128–130). Additional research is needed to determine whether objective measures of physical activity can be used to predict PMDD symptom onset.

6.4 Social behaviors and smartphone use

Machine learning models applied to passively collected smartphone data to predict mood and social behavior (133–138). Thus, the justification for studying PMDD and smartphone data is two-fold. First, PMDD is marked by social impairment during the symptomatic luteal phase (156, 157, 159, 160, 162). Thus, passively collected smartphone data may be a feasible and unobtrusive proxy for social behavior that can identify affective switching and inform effective social interventions. Second, smartphone data has been demonstrated to predict affective switching with reliable accuracy among individuals with psychiatric illnesses (133–138). Thus, studying the application of machine learning capabilities to model smartphone use in individuals with PMDD is a logical next step. Overall, smartphone data has the potential to reliably predict affective switching among those with PMDD and be used as a marker of social behavior. However, more granular data regarding social communication with smartphones and social media seem necessary, compared with rough metrics of smartphone and social media use.

6.5 Theoretical model of affective switching in PMDD

Based on prior research, withdrawal of the neuroactive steroid allopregnanolone (ALLO) during the luteal phase may diminish the inhibitory effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) among those with PMDD, leading to a heightened stress response and reduced parasympathetic nervous system activity (3, 4). Although not fully understood, in mammals, GABA activity may modulate the activity of neurons in the suprachiasmatic nucleus, which regulates melatonin secretion (163, 164). Thus, alterations in GABA functioning might have downstream effects on melatonin secretion and circadian rhythms, contributing to sleep disturbances. As a result, emotional regulation may become compromised by reduced GABA function and fatigue. Although the exact mechanisms of HRV are unclear, both depression symptoms and GABAergic activity may lead to decreased HRV, further impairing stress and emotion regulation abilities. The subsequent cycle of stress, fatigue, and depressive symptoms may yield social withdrawal and inactivity, creating a compounding effect on overall well-being. Importantly, the endpoints of sleep disturbances, HRV, physical activity, and social engagement can be unobtrusively monitored with widely used wearable devices and smartphones.

6.6 Limitations

Given that PMDD was not added to the DSM until 2013, there is less research on PMDD as a diagnostic entity, and earlier studies included those with PMDD in studies of PMS. Thus, the extent to which PMDD and PMS are distinct or overlapping entities concerning physiologic markers remains somewhat unclear. The research conducted since 2013 seems to indicate that PMDD is

distinct from asymptomatic controls with regard to certain physiologic markers, while those with PMS appear similar to those with PMDD in some studies and more similar to controls in others. Due to the relative lack of research focusing specifically on PMDD, PMS studies were included. However, PMS findings should be considered preliminary as they pertain to individuals with PMDD.

Moreover, existing studies on PMS or PMDD often included small sample sizes and had certain methodological issues. For example, PMDD diagnoses in the reviewed studies were not always based on the gold standard prospective reporting method. Additionally, existing studies did not always control for factors that may affect mood states and the menstrual cycle. For example, study results can be impacted by hormonal contraceptive use, comorbid diagnoses, cycle regularity, pregnancy status, and demographic factors such as age, race, or ethnicity (165). Although assessing and controlling for these factors can be challenging, future studies should measure and report such variables, and where appropriate, control for these confounding variables in statistical analyses.

Additionally, existing studies have predominately been conducted on cis-gendered women and neglect to consider the impact of alternate gender identities (transgender, non-binary, gender non-conforming, etc.). As such, those who do not identify as a cis-gendered woman are underrepresented in this area of research. Because people of alternate gender identities are at heightened risk for adverse mental health outcomes, excluding this population may perpetuate systemic barriers to accessing care (166). Considering gender identity in analyses, oversampling non-cisgender individuals, or not excluding people of non-cisgender identities is imperative.

7 Conclusion

PMDD is marked by frequent affective switching, with depressive symptoms beginning during the luteal phase and ending shortly after the onset of menses. Affective switching is a period of increased risk of suicide. Given the frequency of affective switching and the chronicity of PMDD, identifying an unobtrusive strategy for identifying periods of heightened risk could enable the delivery of just-in-time interventions. Additionally, given the frequency of affective switching, PMDD may serve as an ideal model for prospectively identifying physiologic markers of affective switching that could be applied to identifying depressive episodes in other depressive disorders that are more difficult to predict.

Remote monitoring is a promising, non-invasive, and passive mechanism for predicting affective switching and providing real-time intervention, as exemplified in chronic conditions such as diabetes and heart conditions. Prospectively identifying within-person physiological and behavioral correlates and predictors of affective switching suitable for remote monitoring is the first step in implementing such a strategy for PMDD. Whether phase-dependent variations in HRV, sleep, physical activity, social variations, and smartphone data that can be monitored remotely will be able to predict affective switching at the individual level will require additional research. If these physiologic variables predict within-person affective switching in those with PMDD, remote monitoring would hold tremendous promise for advancing population health by identifying personalized, scalable intervention strategies for those with PMDD.

Author contributions

RB: Writing – original draft, Writing – review & editing. EB: Writing – original draft, Writing – review & editing. GD: Writing – original draft, Writing – review & editing. JP: Writing – original draft, Writing – review & editing. CS: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Women with Premenstrual Dysphoric Disorder experiences of suicidal thoughts and behaviours: a mixed methods study

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Background: Women with Premenstrual Dysphoric Disorder (PMDD) experience debilitating psychological symptoms during each luteal phase of their menstrual cycle. Although women's increased risk of suicidal thoughts and attempts to end their lives has been highlighted, little is as yet known about women's own narratives. Therefore, this study aimed to explore the prevalence and the experiences of self-harm, suicidal thoughts and attempts in women with PMDD.

Method: In this mixed methods study, women's experiences of living with PMDD were captured via an online survey exploring risk and via semi-structured interviews with questions informed by survey results. Data were analysed using descriptive statistics and reflexive thematic analysis.

Results: Over 3,600 women completed the survey between January and March 2020 and 14 women were subsequently interviewed in 2022. The survey revealed that just under half of women had deliberately harmed themselves during a PMDD crisis, 82% had suicidal thoughts on one or more occasions during their luteal phase, and 26% of women had attempted to end their own life. Three main themes, which related to suicidal ideation in the context of PMDD, were generated from the interview data: 1) personal relationships and social connections affected by PMDD, 2) the increase in suicidal experiences caused by diagnosis delays and 3) self-worth damaged by PMDD.

Conclusion: Women living with PMDD are at high risk of self-harm, suicidal thoughts and attempts to end their lives each month, narratives highlighted the damaging impacts PMDD had on relationships. Risk was increased by delays in appropriate medical support and women reported internalising their experiences as their problem.

KEYWORDS

women's health, mental health, women, qualitative, quantitative

1 Introduction

Premenstrual Syndrome (PMS) is cyclical and characterised by psychiatric and somatic symptoms (1, 2), peaking in the luteal phase, and resolving after the onset of menstrual bleeding (2). Approximately 50-80% of women of reproductive age have mild PMS, and 30-40% report a severity of symptoms requiring treatment (3). In 1987, the DSM-III (4) categorised a severe form of PMS, originally titled Late Luteal Phase Dysphoric Disorder and later changed to Premenstrual Dysphoric Disorder (PMDD) (5). PMDD affects 5-8% of women of reproductive age (5, 6) and is a complex, disabling condition believed to be associated with the fluctuation of hormones during the luteal phase of the menstrual cycle (7). The treatments available for PMDD are limited, often focussing on symptom reduction (1). Women living with PMDD report various cognitive, psychological and somatic symptoms; some women experience increased stress, depression, anxiety and even psychotic episodes (8–11).

Suicide is a global problem, occurring throughout the lifespan and across diverse backgrounds (12). The relationship between self-harm, suicidal ideation and suicide attempts has been explored (13), with non-suicidal self-harm being the strongest predictor of suicidal thoughts which can lead to suicide attempts (14). Statistics show that within the general population women were three times more likely to attempt suicide than men (15). In addition, a significantly higher prevalence of PMDD has been found amongst women hospitalised for attempting to end their lives (16, 17). Three large cohort publications examining correlations found significant relationships between PMDD and suicidal ideation, suicide plans and attempts (18–20). In their systematic review of ten studies, Osborn et al. (21) also noted that PMDD was associated with suicidal thoughts, plans and attempts. Furthermore, survey data indicated that women with PMDD reported higher rates of self-injurious thoughts and behaviours, when compared to population averages for women without PMDD (22). This finding was based on 599 women with a prospectively confirmed diagnosis of PMDD. However, no association between suicide attempts and different phases of the menstrual cycle for women with PMDD was identified by Osborn et al. (21), as would have been anticipated. These discrepancies in studies may reflect differences in the severity of PMDD symptoms and diagnostic methods used for its identification (21). Osborn et al. (22) noted that it could take 20 years for a women's PMDD symptoms to be accurately diagnosed and treated, increasing the importance of further research to understand the psychological impacts that living with PMDD has on women's experiences of suicidal thoughts and behaviours (17) both before and after diagnosis.

There is a growing literature aiming to explore the experiences of women with a premenstrual diagnosis. In order to understand the psychological impact of living with a premenstrual disorder (PMD), Brown et al. (24) conducted a metasynthesis of 17 qualitative papers and identified two themes 1) "*controlled by PMD's*" and 2) "*a women and a life left broken*". In their review of 12 qualitative papers, Moe and Karlsson (25) focussed on PMDD only and identified two themes: 1) "*limitations due to PMDD*" and 2) "*attempts to manage life with PMDD*". However, Moe and Karlsson's review (25) presented recommendations for nursing. Despite insightful findings, neither review (24, 25) captured women's perspective of self-harm, suicidal thoughts or suicide attempts, in the context of their PMD. However, Osborn et al. (23) interviewed 17 women regarding their journey to receiving a PMDD diagnosis and identified that feeling hopeless in the context of their PMDD appeared to be linked to suicidal ideation and sometimes to women's attempts to end their lives.

To date, no study has focussed solely on women's experiences of self-harm and suicidal ideation in the context of their PMDD. Thus, the aims of this study were twofold: 1) to examine how many women with PMDD reported the experiences of self-harm, suicidal thoughts or attempted suicide and 2) to explore women's lived experiences of PMDD, with a focus on their experiences of self-harm, suicidal thoughts and behaviours.

2 Method

2.1 Design and ethical approvals

A mixed methods design was chosen to explore the above-mentioned aims. Utilising quantitative and qualitative methodologies (26) enabled the development of an enhanced understanding of the impact of PMDD on women.

The survey was granted ethical approval via the British Broadcasting Corporation (BBC) internal processes, including a review by the BBC data protection team who provided a privacy notice to be presented alongside the survey. A data sharing agreement was signed between the BBC and University of Manchester. Ethical approval for the interviews was granted by the University of Manchester in March 2022 (Ref: 2022-12850-22464). Due to risk concerns and the potential need to get medical or psychological support for an individual, ethics for the interviews was only granted for the additional recruitment of women currently living in the UK.

2.2 Survey overview

In 2020, BBC news aired a PMDD documentary called "*My periods made me suicidal*" (27). During the production of the show a survey was completed by thousands of women internationally. The survey was designed by the BBC to capture information regarding the wider impact of PMDD on a woman's life. The present study utilised sections of the BBC dataset.

2.3 Survey participant eligibility and recruitment

Participants were women aged ten years and over, who reported receiving a formal diagnosis of PMDD from a healthcare professional. As the survey was available online, it was accessible

worldwide. The survey was advertised via social media accounts managed by the BBC and the *International Association for Premenstrual Disorders* (IAPMD) (28).

2.4 Survey procedure

Potential participants were presented with an electronic information sheet followed by 14 multiple-choice questions, with consent implied by the completion of the survey. For the purpose of the current study, only data relating to demographic information (e.g., age and years since diagnosis) and questions relating to self-harm, suicidal thoughts and attempted suicide were selected for analysis.

2.5 Survey data analysis

Six multiple-choice questions were selected from the larger anonymous survey dataset: three questions gathered demographic information (e.g., age and years since diagnosis) and three questions related to self-harm, suicidal thoughts, and attempted suicide. Survey responses were made available within Microsoft Excell and descriptive statistics were used, with data tabulated.

2.6 Interview overview

In the qualitative part of this mixed methods study, women were interviewed to collect lived experience data, which were analysed using reflexive thematic analysis (29). This method allows for further exploration of participant experiences and perspectives, beyond the quantitative data available from the survey. The survey findings informed the development of the qualitative topic guide used in the subsequent interviews with British women.

2.7 Interview participant eligibility and recruitment

All participants were English speaking women, over 18 years old, living in the UK, who reported receiving a formal diagnosis of PMDD, their symptoms were tracked for a minimum of two months by their medical doctor. Participants were recruited via a social media advert shared online and within premenstrual disorders forum pages between April and September 2022. Potential participants, who contacted the research team to express interest, were emailed a copy of the information sheet and consent form.

2.8 Interview development and data collection

Although the survey captured the data from a large number of women with PMDD, it included pre-defined multiple-choice questions. To understand the wider ranging impact of PMDD on women, a topic guide was developed based on the survey results, which included questions and prompts related to experiences of self-harm, suicidal thoughts and suicide attempts. Additionally, a demographic questionnaire was developed to record their use of symptom trackers, estimated age of symptom onset and age of diagnosis.

2.9 Interview procedure

Interviews were completed via video call, once the participant had provided written informed consent and completed the short demographics questionnaire. A semi-structured topic guide was followed, and interviews were recorded, securely stored and transcribed verbatim.

As participants were not recruited through a medical team, all participants provided their GP details and consented to them being contacted, in case there were any risk or safeguarding concerns raised during the interviews. All participants were made aware they had two weeks after the interview date to withdraw, after this time all data would be anonymised and could not be identified. Due to the emotive topic, a distress management plan and debrief sheet were developed to protect their wellbeing.

2.10 Interview data analysis

The analysis of the qualitative data was guided by the six stages of Braun and Clark's reflexive thematic analysis (29, 30). This method was chosen to understand the participants' experiences with theoretical freedom.

Two authors (DB and DMS) familiarised themselves with the interview dataset, taking an inductive approach to code line-by-line and separately generate initial semantic codes, before jointly reviewing preliminary latent codes (phase 2). Both NVivo and paper post-it notes were used to collate comparable codes and construct themes to conceptualise patterns of shared meaning shown by the participants (phase 3). Once latent themes were described, further analysis of the dataset was undertaken (by DB and DMS) to ensure the themes represented and reflected the experiences of the participants (phase 4). Themes were then defined and named (phase 5) through consultation with the research team, before the written report was produced (phase 6).

2.11 Reflexivity and rigour

The first author (DB) was a Trainee Clinical Psychologist, with a history of working with children, families and working in complex, challenging environments, such as secure services. The second author (DMS) was a Health Psychologist and Senior Lecturer, with a background in exploring pregnancy and behaviour change. The third author (EO) was a Clinical Psychologist working within paediatric services and had a specialist research interest in premenstrual disorders. The fourth author (AW) was a Clinical Psychologist and Senior Lecturer, whose clinical work involved

supporting mothers with severe mental health difficulties therapeutically. The authors had varying levels of qualitative research experience and of clinical support for women with premenstrual conditions. As all authors were women and mothers, these roles could have impacted how they viewed the data, given all participants were also women and many, but not all, were mothers. To reduce bias during analysis, the first author kept a reflective journal, which she used to write down thoughts and impressions during interviews, transcription, and coding, as well as methodological decisions. These reflections were shared with all authors, when appropriate, and discussed during coding and theme generation, allowing a secondary level of reflection and consideration. The variety of experience and clinical backgrounds allowed for authors to challenge each other's assumptions and pre-conceptions.

3 Results

3.1 Survey participant characteristics

Overall, 3,906 women with a reported diagnosis of PMDD from a healthcare professional completed the survey between January and March 2020. The age of participants ranged from ten to over 60 years old and the majority were non-UK residents. Whilst most women received their diagnosis in the last nine years, some women reported receiving a diagnosis over 30 years ago (see Table 1 for further details).

3.2 Survey findings

Of 3661 women, 47% reported to have self-harmed, at least once during a PMDD crisis (see Table 2). Specifically, 9% regularly self-harmed, whilst 31% had self-harmed on occasion and 7% reported only one instance of self-harm related to their PMDD. The remaining women had self-harmed at a different time in their menstrual cycle (3%) or had never self-harmed (49%).

TABLE 1 Demographic characteristics for survey data.

		N (%)
Country	UK Resident Non-UK Resident Unknown	1,547 (40%) 1,979 (51%) 380 (9%)
Age	Under 19 20 – 29 30 – 39 40 – 49 50 – 59 Over 60 Unknown	85 (2%) 970 (25%) 1,733 (44%) 1,002 (26%) 109 (3%) 2 (<1%) 5 (<1%)
Years since diagnosis	0 – 9 years 10 – 19 years 20 – 29 years Over 30 years Unknown	1,825 (47%) 1,213 (31%) 663 (17%) 143 (4%) 62 (2%)

TABLE 2 To what extent had PMDD led to self-harm?

1. To what extent had PMDD led to self-harm?	Number (%)
I regularly self-harm during PMDD crises	322 (9%)
I have self-harmed on occasion during PMDD crises	1150 (31%)
I have self-harmed once during a PMDD crisis	274 (7%)
I have self-harmed but at a different time/s in my menstrual cycle	116 (3%)
No, I have never self-harmed basis just before my period	1799 (49%)
	3661

In total, 3768 women responded to question 2; 82% had experienced suicidal thoughts, on one or more occasion during their luteal phase (see Table 3). Of these, 6% of women reported suicidal thoughts once, and 36% had experienced suicidal thoughts on occasion. Forty percent of respondents experienced suicidal thoughts monthly.

Of 3670 women, 13% reported to have attempted suicide more than once and 13% had attempted suicide once during a PMDD crisis (see Table 4). Two percent of women responding had attempted suicide at different times in their menstrual cycle, unrelated to their PMDD and 72% had never attempted suicide.

3.3 Interview participant characteristics

Thirty-three women contacted the researcher, three women were not living in the UK and were therefore unable to participate, in line with ethical approval. Fifteen individuals did not respond to follow up emails. Thus, 14 women consented to take part and were interviewed between May and September 2022. Their ages ranged from 24 to 54 years, and they were all White British. Although the mean age of symptom onset was 22 years old, the mean age of diagnosis was not until 42 years old. All 14 women had received specialist treatment previously, eight were biological mothers of children ranging from three to 26 years old, one woman had stepchildren (see Table 5 for further demographics).

TABLE 3 To what extent had PMDD led to suicidal thoughts?

2. To what extent had PMDD led to suicidal thoughts?	Number (%)
I have suicidal thoughts on a monthly basis just before my period	1511 (40%)
I have suicidal thoughts on occasion just before my period	1364 (36%)
I have had suicidal thoughts once just before my period	244 (6%)
I have had suicidal thoughts but at a different time/s during my menstrual cycle	286 (8%)
No, I have never had suicidal thoughts	363 (10%)
	3768

TABLE 4 To what extent had PMDD led to attempted suicide?

3. To what extent had PMDD led to attempted suicide?	Number (%)
I have attempted suicide more than once during PMDD crisis	479 (13%)
I have attempted suicide once during a PMDD crisis	477 (13%)
I have attempted suicide but at a different time/s in my menstrual cycle	69 (2%)
No, I have not attempted suicide	2645 (72%)
	3670

3.4 Thematic analysis themes

Three themes were developed from women's narratives that reflected the psychological impact PMDD had on them, including their experiences of suicidal ideation and attempt (see Figure 1 for a conceptual diagram). The experiences captured within themes one and two had a direct impact on women's self-worth, as described in theme three. The three themes will be presented below with related subthemes (n=7) and pseudonymised quotes from the transcripts.

3.4.1 Theme 1: Personal relationships and social connections affected by PMDD

Women's narratives revealed numerous attempts of engaging in personal relationships and social connections whilst living with PMDD and associated suicidal thoughts each month or during a crisis. These experiences were described as complex and at times chaotic. Women recognised their relationships being negatively impacted or damaged, contributing to emotional isolation, and this in turn contributed to their experiences of suicidal thoughts or attempts. Women spoke about their romantic relationships, family members and friendships; however, they particularly highlighted the greater impact PMDD had on their role as a mother, or their ability to become a mother. This main theme consisted of three subthemes.

3.4.1.1 Subtheme 1.1: PMDD damaged relationships

In all cases, woman described a perceived link between their experiences of suicidal thoughts and the key relationships with other adults in their lives. A common view amongst the women was a recognition that these relationships were reciprocal for approximately three weeks each month. But when in a PMDD crisis and experiencing associated suicidal thoughts, this dynamic changed. One woman described the difference in her interacting with her loved ones during each luteal phase as "*unreasonable*" (Sally). Women spoke of ending their romantic relationships monthly, long-term friendships being broken and struggles to maintain connections with colleagues, all of which left them hopeless.

> *"Demons just came out and suddenly that friendship was never the same" (Catherine).*

TABLE 5 Demographic characteristics of interviewed participants.

		N (%)
Age	Under 19 20 – 29 30 – 39 40 – 49 50 – 59 Over 60	0 (0%) 3 (21%) 2 (14%) 7 (50%) 2 (14%) 0 (0%)
Ethnicity	White	14 (100%)
Highest level of education	No school attended Primary school Secondary school Collage University Other…	0 (0%) 0 (0%) 2 (14%) 3 (22%) 9 (64%) 0 (0%)
Marital Status	Single In a relationship Co-habiting Married Divorced Other…	3 (21%) 0 (0%) 5 (36%) 5 (36%) 1 (7%) 0 (0%)
Estimated age of symptom onset	Under 19 20 – 29 30 – 39 Over 40	11 (79%) 2 (14%) 1 (7%) 0 (0%)
Age when diagnosed	Under 19 20 – 29 30 – 39 40 – 49 Over 50	0 (0%) 5 (36%) 3 (21%) 7 (50%) 0 (0%)
Currently receiving treatment	Yes No	12 (86%) 2 (14%)
Previously received treatment	Yes No	14 (100%) 0 (0%)
Have children	Yes No	9 (64%) 5 (36%)

Relationships and friendships were categorised by push-pull patterns, with women trying desperately to repair the damage caused by their suicidal thoughts linked to their PMDD crisis, whilst knowing they did not have long until the same pattern repeated itself. Upon recognition of this pattern, women reported increased feelings of hopelessness and subsequent suicidal thoughts or attempts. Women described that living with them was like living with a "*roller coaster*" (Katie), and that they noticed psychological distress being experienced by their partners. According to women, partners often particularly struggled to understand the unpredictable changes and suicidal experiences expressed by them.

> *"He used to say I just didn't know what I was going to come home to. Said you'd be fine, I'd walk out the room, and I'd come back in and your face would have changed and you'd be raging about nothing and everything. Erm and at my worse he didn't know if he was going to come home and find me having killed myself"* (Katie).

3.4.1.2 Subtheme 1.2: Motherhood and loss

A women's role as a mother was described with more importance, different dynamics, and expectations to their other relationships, as detailed in the previous subtheme. Motherhood was an emotive topic discussed by all the women and was often underpinned with feelings of loss. Whilst some women described their monthly suicidal experiences as robbing them of the opportunity to be a mother, those who had children recognised the loss of the mother they had wished to be.

Furthermore, worrying about the impact PMDD would have on their children was a common experience, and some women made the difficult decision not to have children, instead choosing to have a hysterectomy and, hopefully, live a functional life. There was recognition that not being able to have children impacted on their current or future partners.

> *"I chose not to have kids because it was so bad and I thought I really don't want to, you know, I really don't want to hurt, and it's awful because I love kids"* (Hannah).

Another concern women spoke of was how they would be able to prioritise taking care of a child, when they did not feel able to care for themselves for a period of time each month. Many women also expressed worries about the psychological impact PMDD would have on their future children.

> *"I was really worried about like emotional blueprint and transference, and what happens and how traumatic potentially the child's first twelve, twenty-four months could be, 'cos even if I had the child, then what happened about the attachment and things like that, and I was like, it's one thing having, needing like psychiatric care and ending up in a mother and baby unit potentially, when you don't know, but if you anticipate that is what's going to happen, and you think that's likely, I was like I don't, I don't think I can do that to a child"* (Natalie).

Experiencing suicidal thoughts whilst parenting left women with indescribable guilt, and worry for the impact this could, or did have, on their children. Some women described what their children witnessed as trauma and worried about the possibility of their daughters also being diagnosed with PMDD.

> *"Erm, it's then it's the guilt, pressure of you know you feel low and you're shutting down on people, but you can't help it and being a mum, you've got the mum pressure of, you know, needing to be there for your children and not wanting them to see you in that kind of frame of mind, but you can't do anything about it, it just completely takes over"* (Elisa).

3.4.1.3 Subtheme 1.3: Importance of connecting with others to reduce suicide risk

Women's narratives offered ideas on what might help them cope during a mental health crisis related to their PMDD. They emphasised the importance and value of being able to connect with at least one person. Women valued this connection and viewed it to reduce the risk of acting on their impulses to self-harm or attempt to end their lives.

> *"I'm feeling really low, like I just feel like I could just literally just end it, erm, and she just stayed with me and just talked to me and just listened and that kind of got me through the crisis point"* (Ellie).

Unfortunately, women's suicidal thoughts were described as creating an emotional barrier, preventing women from connecting with other people the way they wished to.

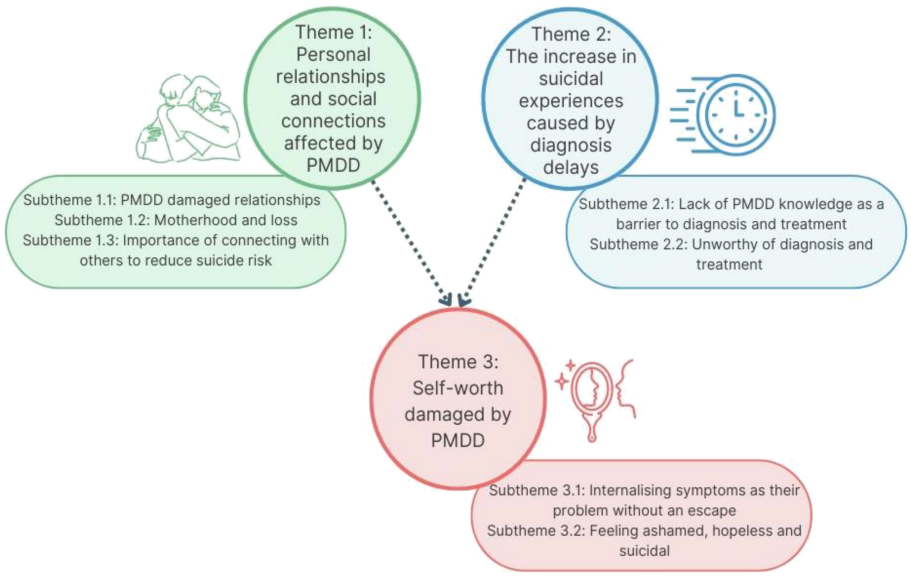

FIGURE 1
Diagram of themes from interviews.

> *"Because of how you are and what you're struggling with, so that, I think makes you feel even more lower, and more likely to feel suicidal because you just think, everyone'd be so much better off without me, because nobody understands what you're going through"* (Ellie)

Women described feeling emotionally isolated in their experiences: their friends and family rarely understood their diagnosis of PMDD, their suicidal thoughts or why their behaviour would change so drastically each month. Feeling isolated meant that women did not disclose their suicidal thoughts, perpetuating the experience of isolation. Some women described comparing their premenstrual symptoms to those of their friends, the recognition of differences left women feeling "*alone*" (Catherine).

> *"Nobody feels like this, nobody feels the way I do, nobody knows how I feel"* (Antonia).

3.4.2 Theme 2: The increase in suicidal experiences caused by diagnosis delays

The process of seeking a diagnosis and treatment for their PMDD symptoms was prolonged due to repeated visits to different medical professionals, who were often unaware of PMDD. Such difficult medical appointments left women feeling both dismissed and unworthy of help because they left no closer to a diagnosis or treatment plan than before they sought help. The length of delay also drastically increased perceptions of risk for women; the longer women waited, the more menstrual cycles and suicidal thoughts they had and the number of healthcare appointments increased. Two subthemes supported this main theme.

3.4.2.1 Subtheme 2.1: Lack of PMDD knowledge as a barrier to diagnosis and treatment

Delays in receiving a diagnosis and suitable treatment plan prolonged the hopelessness women reported feeling, which women linked this to an increased risk of suicidal thoughts. They described their journey to diagnosis and treatment as characterised by repeated visits and referrals to a wide variety of services, most of which had minimal knowledge or awareness of PMDD.

> *"Sort of reflecting on it all, I think, with that lack of support, without that understanding, etc, it put me so, so much lower, and more at risk of self-harm and suicide"* (Ellie).

Women described having had appointments with multiple different services regarding their undiagnosed PMDD, including, general practice doctors, community mental health teams, outpatient crisis teams, personality disorder services and some were inpatients on acute mental health wards. Each referral returned the women back to an indefinite wait for support they perceived a diagnosis or treatment would bring, whilst living with significant risk of self-harm or suicidal behaviours each menstrual cycle. *"PMDD just, kind of as a tsunami just washing over me, just month after month"* (Stephanie). These referrals also required women to voice their thoughts and plans to harm themselves, which was reported as incredibly traumatic, and was only made worse by the lack of appropriate support which often followed.

> *"Everything takes such a long time, doesn't it, so you're waiting, waiting, waiting, which makes everything worse, and it makes, probably makes you more angry and more tense and more anxious and depressed, because you're currently waiting and waiting"* (Scarlett).

3.4.2.2 Subtheme 2.2: Unworthy of diagnosis and treatment

When seeking support for their PMDD symptoms, including thoughts to harm themselves, from healthcare professionals, women described feeling dismissed. They recounted stories of being called a "*hypochondriac*" (Lauren), "*told to go away*" (Sally) and left appointments feeling "*pathetic*" (Catherine) that they were not able to manage their symptoms. Interactions with healthcare professionals left women feeling their experiences did not deserve a diagnosis and they were not worthy of the clarity women hoped a diagnosis could provide.

> *"She didn't know what to do, she found my suicide letter phoned the ambulance, and when I was down there a nurse said what is she doing here, she was safe in her house, she's wasting our time, so they then left me for 12 hours of my own, whilst waiting for the community mental health to come out and assess me"* (Katie).

Many spoke about being misdiagnosed: "*bipolar*" (Hannah), "*chronic fatigue*" (Sally), "*borderline personality disorder*" (Mandy) or "*eating disorder*" (Natalie). A misdiagnosis was also given despite women bringing symptom trackers, which evidenced the cyclical nature of their symptoms, to appointments. Receiving a misdiagnosis left women feeling invalidated and frustrated. Women expressed how their thoughts to harm themselves or end their lives would increase following those appointments. Women reported perceiving that they knew more about PMDD than their doctor did.

> *"I would go into the doctor surgeries and be like look I've done some research now I've been coming to you on and off every month for the last few years, with the same symptoms, I think I have PMDD and they would just be like oh what's that, I'd be like what you're not, you don't know what PMDD is, it would just be so debilitating because then I would have to explain my own possible condition to people that know a great deal more than me"* (Catherine).

During conversations about the treatment options for PMDD, women also reported medical doctors included the cost as one of the most important factors to consider. Often the cost was prioritised above the clinical indication, the women's own wishes or their desire to have children. Other women reported their only option to access treatment was to seek private medical treatment.

> *"I'd sell anything it's not about money. What price are you going to pay for your life"* (Hannah).

3.4.3 Theme 3: Self-worth damaged by PMDD

The risk of harm to themselves was ever present in women's accounts of their personal relationships and interactions with healthcare professionals, as evidenced by the previous two themes. The culmination of these experiences, for most women over many years, was described as damaging to their self-worth. Women framed their symptoms as their problem and that they were flawed due to the emergence of suicidal thoughts on a monthly basis, subsequently women reported to experience extreme guilt and shame. Being overwhelmed by these emotions increased the sense of hopelessness, risk of self-harm, suicidal thoughts, and attempts. The suicidal experiences of women varied, with some reporting one past experience of suicidal ideation, and others describing monthly attempts to end their life. This final theme was supported by two subthemes.

3.4.3.1 Subtheme 3.1: Internalising symptoms as their problem without an escape

Women stated that after years of damaged relationships and difficult interactions with healthcare professionals, they had internalised their experiences as their "*problem*" (Molly) or their "*fault*" (Stephanie). Others questioned the sudden desire to harm themselves each month: "*I was like, why am I like this, I don't understand*" (Sally). Some women described that they were failing at simply being a woman, and they were worthless.

> *"It was like, great, another thing that I'm shit at, basically"* (Laurie).

The perceived association between internalising symptoms and increase in risk of self-harm was expressed by women. The risk was framed as something they had to manage themselves at home, with minimal professional help. Internalising their PMDD experiences was described by women to lower their self-worth and damage how they perceived themselves.

> *"I wasn't good enough, and, you know, my inner voice was just so negative"* (Mandy).

For a smaller proportion of women, this internalising was somewhat alleviated after receiving a diagnosis, and helped women to recognise they were not to blame.

> *"PMDD has made me feel like I'm such an awful person, erm along with getting used to masking putting faces on so people didn't really know the pain and it was kind of a relief erm to actually find out that I wasn't just vile and there was something out my control erm a reason for it"* (Katie).

3.4.3.2 Subtheme 3.2: Feeling ashamed, hopeless and suicidal

As a result of internalising their experiences, women spoke of an intense "guilt" (Elisa) and shame, specifically for thoughts of self-harm or suicide during their luteal phase and for acting on these impulses. At times this shame was so intense it would stop them seeking support.

> *"I have quite big scars on my arms, from where I hadn't gone to hospital, I hadn't had stitches 'cos I feel so ashamed of what I've done"* (Stephanie).

Women described the distress and upset their self-harm caused their family and friends, and subsequently feeling "ashamed" (Mandy). Additionally, once their menstrual cycle started and their symptoms reduced, women described almost immediately feeling ashamed about their behaviours, which, unfortunately, often led to a perceived increased risk of self-harm, suicidal thoughts and attempts to end their lives.

> *"You also feel like a burden as well, to everybody, because of how you are and what you're struggling with, so that, I think makes you feel even more lower, and more likely to feel suicidal because you just think, everyone'd be so much better off without me, because nobody understands what you're going through"* (Ellie).

4 Discussion

This study was the first to examine how many women with PMDD reported experiences of self-harm, suicidal thoughts and attempts, whilst also capturing women's lived experiences, associated with their PMDD. Over 3,600 women with PMDD responded to the online survey; just under half of the women had deliberately harmed themselves during a PMDD crisis, 82% had suicidal thoughts on one or more occasion during their luteal phase, and 26% of women had attempted to end their own life. These results support previously reported rates in the literature for self-harm (51%) (22), suicidal thoughts (72%) (22) and suicide attempts

(14%) (18) (30%) (22). Differences in rates reported may be linked to notably differing sample sizes (59 in (18); 599 in (22)) or variations in terminology used (e.g., suicidal thoughts versus active suicidal ideation). Therefore, authors should be clear and specific with their choice of terminology. Additionally, cultural differences may be affecting the rates reported, because our survey was open to women worldwide; however, Hong et al. (18) included women living in Korea only.

The potential link between the experiences of PMDD and self-harm, suicidal thoughts and attempts was examined in more detail through interviews. Women outlined that relationships were disrupted on a regular basis because of their PMDD, its associated symptoms and deterioration in their mental health. Our finding that medical delays and lack of PMDD knowledge within the medical profession, was described as having significant negative impacts on their self-worth and thoughts of ending their lives. These findings complement those by Osborn et al. (23) and Chan et al. (31), who explored the journey to diagnosis within the UK and US healthcare systems, respectively. Both sets of authors highlight the detrimental impact of time delays, with Osborn et al. (23) reporting an average delay of 20 years before PMDD was diagnosed. Delays in receiving diagnosis and treatment were linked to feeling unworthy and hopeless within these findings, the internalising of PMDD symptoms was perceived as fundamental to women's risk of self-harm, suicidal thoughts and attempts to end their lives. Interestingly, specific focus was placed on motherhood and women reported markedly different dynamics in other relationships related to their PMDD.

The role of social isolation and loneliness in increasing the risk of suicide and in contributing to poorer health outcomes has been reported (e.g., mental health issues, heart attacks, stroke) (32). However, novel insights were presented as women struggled to connect with people who rarely understood their PMDD experiences, their perceived emotional isolation intensified, and they expressed thoughts of self-harm and suicide. NICE guidance for preventing suicide and managing self-harm, and for the diagnosis and treatment of PMS, including PMDD, are reported on separately (33–35). Recommendations include suicide prevention plans, family involvement in treatment planning, and multi-agency working. However, NICE guidance fails to account for women with PMDD, whose self-harm and suicidal thoughts are nuanced and cyclical. Additionally, the benefits of safety planning interventions for individuals presenting at emergency departments expressing "suicide-related concerns" [(36) p.895] have been documented. Future research and guidance specifically supporting the cyclical risk associated with PMDD should be explored.

4.1 Clinical implications and wider recommendations

The perceived increased risk associated with delayed access to medical support highlights the clear priority to ensure women are diagnosed in a timely fashion, and therefore receive treatment and mental health support during periods of crisis. Initiatives for all individuals presenting with risk of suicide within the Nation Health Service (NHS) have been recommended (37). However, as these do not recognise the nuances of PMDD. Routine screening for PMDD and additional training regarding PMDD awareness and signposting should be implemented within services supporting women in crisis, such as paramedics, accident and emergency, mental health services, general practice doctors.

Current findings emphasise the importance of personal relationships, both for general support and at times of crisis. Following diagnosis, healthcare services should consider ways to support women's families, for example, via information leaflets. Additionally, as social connection is a protective factor against risk to self (32), services may consider post-diagnostic support groups, creating a space for mutual understanding and sharing experiences.

The relationship between shame and increased risk of suicidal behaviours has been described within this study and wider literature; services diagnosing PMDD should consider referrals to psychological services. Cognitive Behavioural Therapy (CBT) is a recommended modality for women with PMDD (38), and in addition Acceptance and Commitment Therapy (ACT) (39) or Compassion Focused Therapy (CFT) (40) may be helpful in addressing the risk and/or the shame experienced by women.

Education regarding menstruation is included in the UK school curriculum; however, premenstrual disorders, such as PMDD, are not specified. Many women in our study (79%) estimated their symptoms started whilst they were school age; however, 71% were not diagnosed until they were over 30 years old. If girls were educated about PMDD in school, it is possible that those who develop symptoms would recognise their experiences sooner and seek medical advice. Additionally, inclusion of PMDD within the school curriculum would increase awareness and understanding within the general population.

4.2 Strengths, limitations and suggestions for future studies

A strength of this study was the mixed methods approach, in which findings from the survey data were followed up by in-depth interviews. A mixed methods design enabled the aims to be studied from different perspectives: the strengths, and weaknesses of each approach complemented the other (41).

The online survey was open to women worldwide, girls and women of different ages could take part. However, it should be acknowledged that the survey questions were most likely designed with adult women in mind only. In addition, diagnosis of PMDD could not be verified for survey participants. This limitation was minimised in the interview study in which the researcher verbally confirmed diagnosis and the use of symptom trackers with each woman as part of their diagnostic assessment. Alternatively, prior to interviews a screening tool could have been used, such as the PSST (42).

Although the samples of women for the survey and the interviews were diverse in terms of age and years since diagnosis, all the interviewed women were White British and most (86%) had accessed higher education, leading to a possible bias in that study. There is also a possibility of selection bias because both the survey and interviews required internet access to participate, thereby limiting recruitment to

those with computer literacy skills and those who had an awareness of social media as a means recruitment (43).

As described within the methodology, the research team consisted of women only who had varying degrees of professional and/or personal exposure to PMDD creating parallels with the participants. However, the authors remained outsiders, researchers who were studying a group of which they were not a member (44).

5 Conclusions

Women's experiences of self-harm, suicidal thoughts and attempts in the context of their PMDD were explored in this mixed methods study. Survey data drawn from over 3,600 responses demonstrated prevalence rates as high as 82% for suicidal thoughts, whilst women's narratives further illustrated the role of that emotional isolation, delayed diagnosis and feeling unworthy, had on women's suicidal experiences. These findings underscore the need for more timely diagnosis of PMDD, better public awareness of the condition and improved health service support for women once diagnosed.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The survey was granted ethical approval via the British Broadcasting Corporation (BBC) internal processes, including a review by the BBC data protection team who provided a privacy notice to be presented alongside the survey. A data sharing agreement was signed between the BBC and University of Manchester. Ethical approval for the interviews was granted by the University of Manchester in March 2022 (Ref: 2022-12850-22464). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

DB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing. DS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – review & editing. EO: Conceptualization, Investigation, Validation, Writing – review & editing. AW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A call to integrate menstrual cycle influences into just-in-time adaptive interventions for suicide prevention

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This paper discusses the scientific rationale and methodological considerations for incorporating the menstrual cycle as a time-varying intra-individual factor in personalized medicine models, such as Just-In-Time Adaptive Interventions (JITAIs). Among patients, accumulating evidence suggests that the normal hormone fluctuations of the menstrual cycle represent a time-varying factor that can trigger or exacerbate psychiatric symptoms, including but not limited to affective dysregulation, suicidality, and irritability. While only a minority of the general female population experiences significant cyclical changes, this hormone-sensitive response appears to be greater among patients with psychiatric disorders, with studies demonstrating that a majority of patients recruited for past-month suicidal ideation demonstrate worsening of their suicidality around menses. However, no interventions target suicidality during this monthly period of elevated risk despite evidence of a clear recurring biological trigger. This unique and recurrent "biotype" of suicidality is well-suited for JITAIs. In addition to providing a rationale for the inclusion of the cycle in JITAI, we provide illustrative options and examples regarding the measurement and implementation of cycle variables in JITAIs. We discuss how JITAIs might be leveraged to use menstrual cycle data to identify states of vulnerability within people and strategically select and deploy interventions based upon their receptivity at various phases in the cycle. Furthermore, we discuss how to integrate passive measures for tracking the menstrual cycle. Although much research is needed before implementation, we maintain that the menstrual cycle represents a critically understudied time-varying feature that may markedly improve the accuracy of JITAI models for predicting suicidality.

KEYWORDS

just-in-time adaptative intervention, menstrual cycle, suicide, idiographic modeling, mobile health, digital phenotyping, passive measures, self-injury

1 Introduction

Despite decades of research, suicide deaths in the United States have not decreased, with mortality rate increasing by 35% between 2000 and 2018 (1). Nonetheless, empirical studies have yielded a critical insight: suicidal ideation (SI) and behaviors (SB) result from highly complex processes that fluctuate over time in person-specific (i.e., idiographic) ways (2, 3). In response, scientists are developing Just-in-Time Adaptive Inventions (JITAIs) for suicide prevention, which model specific time-varying risk factors for each person and intervene in timely, tailored ways (4). In tandem, longitudinal and experimental studies have begun to establish the menstrual cycle as a critical time-varying source of imminent suicide risk, especially in those with chronic suicidality (5–8). Responding to calls from the National Institute of Health to (a) use JITAIs to optimize mental health treatments (9) and (b) focus on female-specific health conditions (10, 11), we argue for integrating the menstrual cycle into JITAI development for suicide prevention. This manuscript discusses why JITAI models may be optimal for treating menstrual cycle-related suicidality, methodological recommendations, and considerations for future research.

1.1 Brief introduction to digital interventions and JITAI

Digital interventions broadly involve identifying vulnerability (e.g., adverse health symptoms) and receptivity [e.g., readiness to use supports (12)] states to deploy personalized interventions aimed at reducing both proximal (i.e., mediator pathways) and distal (i.e., ultimate clinical goals) outcomes. JITAIs tailor treatment type, timing, and intensity based on a patient's evolving needs, delivering support when it is most effective, and patients are most receptive (13). Typically delivered via smartphone, JITAIs have been studied across various health conditions (14–16). They involve decision points (when interventions can be delivered), intervention options (treatments available at decision points), tailoring variables (when and how to intervene), and decision rules (guidelines for choosing and timing interventions).

1.2 JITAI is a promising method for personalized suicide prevention

There is growing interest in applying JITAI to psychopathology research and practice, including suicidality (4, 17, 18), given the dynamic nature of mental health symptoms (19, 20). JITAIs may enhance evidence-based treatments for mental health conditions (4), for example, by promoting coping skill use during critical moments in between psychotherapy sessions. Specifically, JITAI aims to deliver the best-suited evidence-based intervention for an individual at any given moment based upon the individual's previous data. While there are no published studies on JITAIs for suicidality, researchers are currently theorizing the best methodology (regarding feasibility, statistics, and ethics) for building these models (2, 4). This work builds on previous suicide research, indicating that suicidality is (a) heterogeneous, with no singular antecedent, content, or function (2, 21), and (b) time-varying (3), and that (c) mobile and internet interventions for suicide prevention show positive treatment effects (22). Thus, JITAI is a promising method in development for suicide prevention.

1.3 The menstrual cycle as a powerful idiographic predictor of suicide risk and associated symptoms for JITAI models

While suicide death is more common among males, females exhibit a greater risk of depression, SI, and suicide attempts—particularly during reproductive years, when ovarian hormones are elevated and fluctuating (23, 24). The menstrual cycle is the primary source of these fluctuations, responsible for a predictable monthly pattern of ovarian hormone change. While most females do not experience significant affective changes in response to the cycle, a substantial minority experience distressing symptoms requiring diagnosis and treatment (25, 26). The menstrual cycle represents a recurring time-varying risk factor for imminent suicide risk in some—but not all—females. Cross-sectional studies demonstrate that patients are more likely to make a suicide attempt just prior to and during menses (27, 28). Among females recruited for past-month SI, most patients demonstrate peak affective symptoms and SI around menses onset, with the cycle accounting for approximately 25% of the within-person variance in daily SI (7, 8). Similarly, suicide risk is elevated among patients with prospectively-confirmed premenstrual dysphoric disorder (PMDD)—a severe form of emotional premenstrual symptoms (29). In a global study of PMDD patients, 71.6% indicated lifetime active SI, 48.58% planning, and 34.72% reported lifetime attempt. A smaller, more tightly controlled study observed high rates (~40%) of current SI in the luteal phase of patients with prospectively-confirmed PMDD (29).

The menstrual cycle is not only a crucial biological predictor of suicide risk but also of suicide-related symptom networks that can guide targeted interventions. Recent work has identified several affective symptoms (e.g., depression, perceived burdensomeness) as mediators of the relationship between the menstrual cycle and suicidality (8). Additionally, distinct hormonal events within the menstrual cycle trigger different symptom clusters associated with suicidality. For instance, progesterone surges in the luteal phase are linked to irritability, interpersonal conflict, and hyperarousal, while estrogen withdrawal before and during menses is associated with depression, anhedonia, and impaired cognitive function (6, 28). These symptom profiles—one driven by progesterone and the other by estrogen—provide a framework for understanding how menstrual cycle phases can correlate with specific patterns of suicidality and pave the way for JITAI models to match hormone-driven suicide-symptom clusters to specific interventions that deploy at the appropriate time in the cycle.

In summary, the luteal/perimenstrual phase of the menstrual cycle may represent the only recurrent, biological, predictable, idiographic variable capable of predicting phases of increased

suicide risk and associated symptom clusters. Incorporating the menstrual cycle into JITAI models offers the opportunity to better predict when an individual is most likely to experience suicidality and which hormone-driven affective symptom cluster is most linked to suicidality for the individual, all in service of delivering timely and effective evidence-based treatments (6, 29, 30). In Figure 1 we review a schematic model of how the menstrual cycle may be leverged for JITAI models.

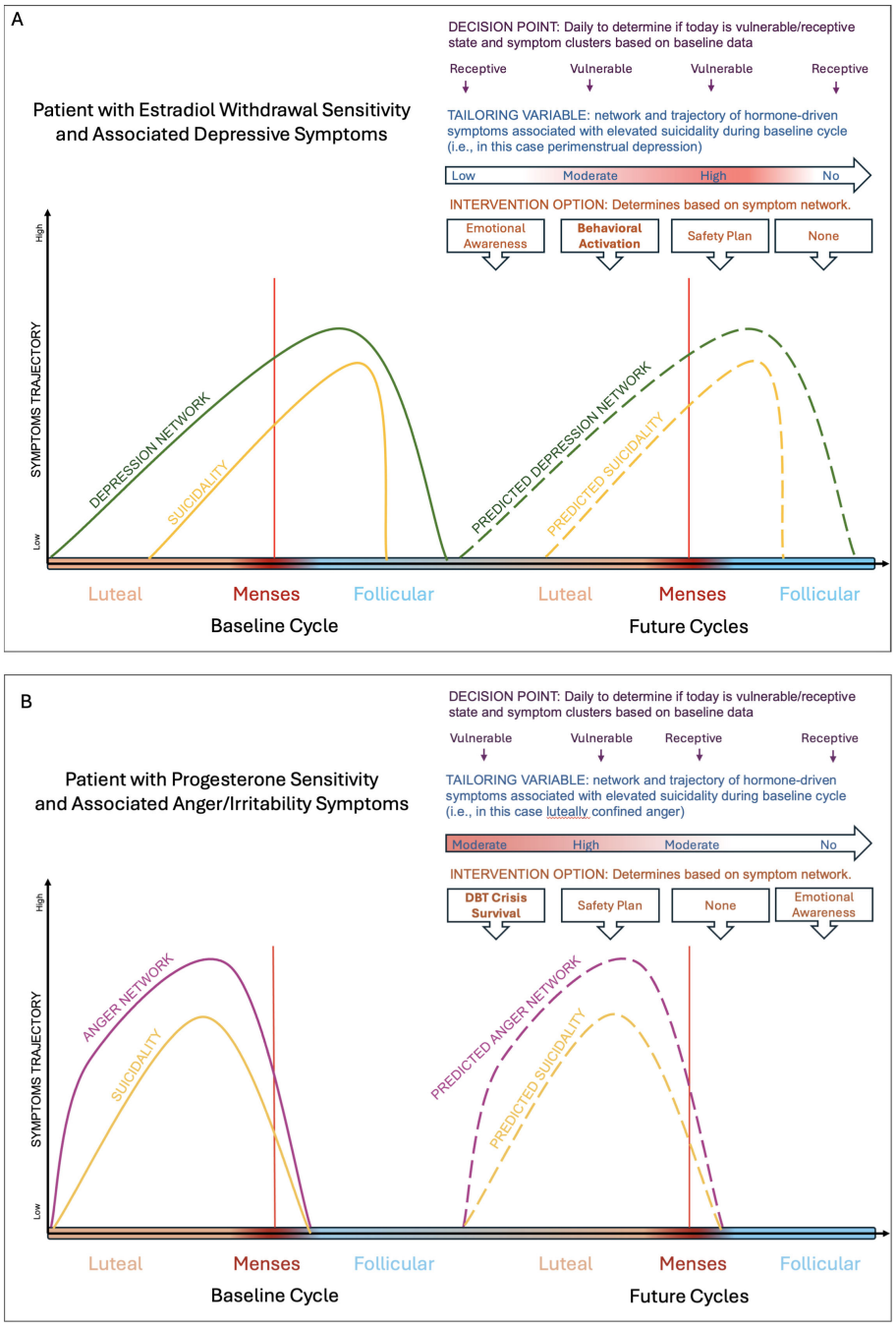

FIGURE 1
Schematic figure depicting how JITAIs can be used to identify risk states and interventions for patients who experience changes in their suicidal thoughts and behaviors across the cycle from their baseline ratings. Panel **(A)** is a schematic of a patient experiencing premenstrual exacerbation (i.e., worsening of their symptoms around menses onset) of their psychiatric symptom, with the peak worsening a few days after menses onset. The idiographic driver of their suicidal thoughts and behaviors worsening is depression and hopelessness. In this case, behavioral activation could be deployed to mitigate depression and hopelessness. Panel **(B)** is a schematic of a patient experiencing luteal confined symptoms, with the symptoms worsening a few days prior to menses onset and completely clearing out a few days post menses. The idiographic driver of their suicidal thoughts and behaviors is anger and interpersonal conflict. In this case, skills from Dialectical Behavioral Therapy may be deployed such as crisis survival skills may be deployed.

1.4 The implementation of JITAI is useful for scientific and treatment research on menstrual cycle-related psychiatric changes

Currently, the only cycle-related psychiatric diagnosis is PMDD, which affects 5.5% of females (31) and is characterized by significant affective, cognitive, and physical symptoms during the week prior to menses that become minimal or absent by the time menses ends. However, similar cyclical changes appear to be more prevalent among psychiatric patient populations, termed *premenstrual exacerbation (PME);* in which psychiatric symptoms persist throughout the cycle but worsen premenstrually (32). PME has been observed frequently among those with depression (31), suicidality (8), and other psychiatric disorders, including borderline personality disorder, eating disorders, and bipolar disorder (33, 34). However, there is currently no DSM-V diagnosis or specifier for PME. Although these clinical categories (i.e., PMDD/PME) are helpful in specific clinical contexts, there is more variability and dimensionality in symptoms across the cycle than can be captured by these trait-like diagnoses.

Integrating JITAI with the menstrual cycle addresses methodological challenges of high false positive rates in cross-sectional assessments of premenstrual symptom change (34, 35)]. Moreover, JITAI's reliance on ecological momentary assessment (EMA) allows for a baseline assessment in which symptoms are rated daily across two menstrual cycles to inform the timing of future assessment and intervention. JITAI also allows for a dimensional/continuous approach to modeling affective and suicidal symptoms across the cycle—without being hindered by the need for discrete diagnostic categorization (i.e., PMDD/PME).

Most importantly, JITAI approaches align with the unmet treatment needs of patients with cyclical affective symptoms (i.e., PMDD/PME) and suicidality. JITAI's person-specific data collection and modeling are well-suited to support understanding the role of the menstrual cycle in patients' unique symptom trajectories, which is critical given the significant heterogeneity in the timing and content of premenstrual symptoms (30, 36). Therefore, JITAIs seem well-suited to enhance treatment for this population, given the limited number of effective treatment options, limited expert providers, and the strong patient desire for psychosocial interventions (37).

2 Preliminary methodological recommendations for integrating menstrual cycle-related suicidality in JITAI development

Idiographic suicide research has been primarily qualitative (i.e., suicide notes, case studies, and chart reviews) rather than quantitative due to statistical constraints. However, computational advancements (e.g., machine learning) enable more complex modeling that accommodates the heterogeneity of suicide processes across time and unique to each patient (21, 38, 39). We argue that JITAIs can predict how cycle phase drives certain symptoms that exacerbate suicidality and then select the appropriate intervention based on those hormone-driven symptoms. Below we describe how menstrual cycle data can be used in a variety of ways as a digital biomarker (40).

2.1 Selecting patients

JITAI for menstrual cycle-related suicidality is designed for patients experiencing predictable symptom changes across their natural menstrual cycle and patients with PMDD. Thus, the first prerequisite is selecting individuals who are "naturally cycling" without additional hormone variability [e.g., not pregnant, on hormonal birth control, or perimenopausal; for further details see (41)]. Next, this naturally cycling patient must demonstrate menstrual cycle-related suicidality; thus, at least two months of baseline symptom ratings are needed. This will allow for accurate modeling of the typical timing of symptom onset relative to the percent of cycle phase elapsed and symptom clusters. Alternatively, if patients already have prospectively confirmed PMDD or PME of SI diagnoses from a provider, they may benefit from this JITAI as well.

2.2 Statistical models for identifying subgroups of individuals for whom the menstrual cycle significantly impacts suicidality

Currently, algorithms for assessing PMDD and PME are available [C-PASS (42] although they remain strict in their diagnostic categorization, similar methods could be applied flexibly to understand cyclical change. As an initial approach, one might compare the mean of the highest-risk premenstrual days (3 days prior to menses onset to the first two days of menses) to the mean of the lowest-risk postmenstrual days (days 6-12 after menses onset) and evaluate if there is >=15% change in suicidality (8, 42). However, other statistical methods could be applied, as well, see (Table 1).

2.3 Measuring the menstrual cycle, using wearable technology to detect cycle status, and identifying risk states

There are various ways to measure the menstrual cycle in service of identifying vulnerable states. Given the variability in cycle lengths between and within individuals (43, 44), baseline cycles' menses onset and ovulation dates can be used to standardize time across the menstrual cycle, providing the percentage of cycle (or cycle phase) elapsed rather than days of the cycle. This approach enhances the precision of continuous modeling strategies in identifying future risk windows, aligning more accurately with ovarian hormones and symptom changes.

When only menses onset dates are available, the duration of each cycle is calculated from one menses onset to the day before the subsequent menses. This duration can then be used to determine the percentage of the cycle elapsed. This percentage is mapped onto

TABLE 1 Identification of individuals with Menstrual Related Suicidality Changes and their discrete risk states across the menstrual cycle.

Pre-Assessment: Determining subgroups of people and finding their states of vulnerability.	
Examples of statistical models used to examine subgroups of people based on menstrual cycle-dependent symptom variability; using menstrual cycle-dependent symptom data as a diagnostic biomarker (40)	*Examples of statistical models used to determine vulnerable states across the menstrual cycle; using menstrual cycle data as a monitoring biomarker* (40) *to identify high-risk states*
Latent Class/Profile analysis (50): models for understanding if distinct subgroups of participants, based on both concurrent symptoms and menstrual cycle variables, predict engagement in suicidality.	**Multilevel Models** (41, 51): can use spline models and place knots at biologically relevant timepoints such as menses onset or ovulation to determine rate of change between knot points. Polynomials can also be used to flexibly model nonlinear change across the cycle.
Group-based trajectory modeling (36, 52, 53): non-linear applications can be used to subgroup patients based on how suicidality changes over the menstrual cycle, which may support understanding which participants experience significant variability	**Hidden Markov models** (54, 55): machine-learning approach for finding discrete states of suicidal risk within a series of menstrual-cycle and concurrent symptoms across time, as well as finding the probability at a given time-point of transitioning between high-risk and low-risk states.
Group Iterative Multiple Estimation Model (21, 39, 56): creates networks of symptoms and shared paths for each patient and then subgroups patients based on shared networks. The menstrual cycle can be added as an exogenous variable to determine if it meaningful contributes to patient's suicide network.	**Individual Regression models:** apply regression models to an individual's menstrual cycle and concurrent symptoms time series data to predict engagement in suicidality.
Carolina Premenstrual Assessment Scoring System (C-PASS) (42): algorithms developed based on DSM-5 PMDD diagnosis and PME; can compare the maximum mean of the high-risk premenstrual days (7 days to 1 day prior to menses onset) and the minimum mean of the low-risk postmenstrual days (4 days to 10 days after menses onset) and see if there is at least a 15% change in suicidality symptoms	**Vector Autoregression Models** (57, 58): models applied to an individual's data that may be used to understand how menstrual cycle variables may dynamically associate with concurrent symptoms or suicidality over time (cross-lagged effects) and how menstrual cycle, psychopathology, or suicidality variables may persist over time (autoregressive effects).

subsequent cycles to predict days of increased risk. For example, if a patient has cycles of 32 and 30 days, and symptoms worsening or onsetting at day 28 and 26, respectively, corresponding to 87.5% and 86.7% of their cycle, future cycles may have an estimated duration of 31 days, with symptom onset at approximately 87% of the way through the cycle.

When both menses onset and ovulation dates are available, the luteal phase duration can be calculated from the day after ovulation to the day before the next menses onset, and the follicular phase from menses onset to estimated ovulation (from which percentage of each phase elapsed can be determined for each day). For instance, if a patient's first cycle has a 14-day follicular phase and a 12-day luteal phase, with symptom onset 10 days into the luteal phase (83.3% elapsed), and the second cycle has a 15-day follicular phase and an 11-day luteal phase with symptoms onset 9 days into the luteal phase (81.8% elapsed), these percentages can inform future risk predictions.

Wearable and smartphone technologies can also be used to track menses dates and identify ovulation. Cycle-tracking applications, such as Apple® Health, collect daily self-reported data on menses status (bleeding vs. not bleeding) and use proprietary algorithms to forecast future menses start dates (45), with a study indicating 40% of the assessed cycles had daily recordings (46). Wearables monitor physiological functions impacted by the cycle, such as thermoregulation and heart rate variability. A high-specificity method for passively detecting ovulation is a wearable tracking basal body temperature (BBT). Progesterone's thermogenic effect causes an abrupt (surpassing 37°) and sustained temperature elevation in BBT, indicating ovulation. Another potential indicator is heart rate variability (HRV), which is downregulated in the luteal phase, correlating inversely with progesterone (47, 48). Studies are underway to validate passive HRV measurement to determine cycle events (49). Wearables (e.g., Apple Watch®, FitBit®, Oura Rings®) that can passively detect either BBT, HRV, or both would significantly reduce participant burden by passively detecting ovulation. However, for validation of these approaches, it may be prudent for cycle-focused studies to initially include urine luteinizing hormone (LH) testing to evaluate the occurrence and timing of ovulation (LH surges and peaks prior to ovulation), as described in (41).

2.4 Identifying discrete vulnerability states across the menstrual cycle for suicidality based on person-level fluctuations

Once patients are identified as having menstrual cycle-related suicidality (or PMDD/PME), we may pinpoint their vulnerability states throughout the cycle. Group studies suggest peak suicidality occurs three days before and two days after menses onset (7). For JITAI, various statistical models (see Table 1) can identify specific times of suicidality risk based on menstrual cycle time elapsed. These vulnerable states should be stratified into "no", "low", "moderate", and "high" risk days. Interventions can be tailored based on symptom networks exacerbating suicidality.

2.5 Proximal and distal outcomes

We propose person-specific, symptom clusters that mediate the cycle-suicide relationship as the proximal outcome in our example JITAI. The aim of the example JITAI is to deploy interventions that reduce these monthly states of increased hormone-driven symptoms, in order to prevent future suicidality, our distal outcome.

2.6 Decision point

The daily decision point for this JITAI will identify if today is a vulnerable day in the cycle (i.e., a day associated with elevated suicide risk based on baseline cycles). While we anticipate

predictable trajectories for SI and SB, we currently recommend daily self-report assessment of suicidal symptoms. However, future JITAI research may move beyond self-report with the development of valid, passively collected prognostic biomarkers of suicide risk, such as smartphone typing patterns (59), fewer phone calls and messages (indicating social withdrawal), and so on.

2.7 Tailoring variables

The tailoring variable for this JITAI is the cluster of symptoms driving perimenstrual worsening of suicidality for the individual. Individual baseline data is used to define cycle days associated with increased suicide risk as well as symptom networks that drive this increase in suicidality (e.g., anger/conflict in response to a progesterone surge, depression/anhedonia in response to estrogen withdrawal).

2.8 Intervention options and personalization

We propose using network models from baseline data to tailor interventions based on individual symptom clusters. JITAI holds the potential to match evidence-based interventions to distinct symptom clusters linked with hormone-driven suicidality within an individual. To illustrate: on risky cycle days, individuals may benefit from receiving a reminder to increase awareness of this vulnerable cycle phase (e.g., "You are at a point in your cycle when depression, hopelessness, and guilt worsen, increasing SI risk"). As risk increases, luteal-phase irritability and affective lability could be targeted with skills from Dialectical Behavior Therapy (e.g., TIP, opposite action to anger). Meanwhile, perimenstrual depression could be targeted with behavioral activation.

Micro-randomized control trials, a type of clinical trial where each relevant decision point is randomly assigned within each person (60), are needed to identify optimal treatments and receptivity states for menstrual cycle-related suicidality and co-occurring affective symptoms. Although current research does not specify receptivity states across the menstrual cycle, we hypothesize that patients may be more receptive to learning and applying skills during non-risky days (e.g., follicular phase). Adapting frameworks such as the multiphase optimization strategy (MOST), which involves a screening, refining, and confirming phase of building a digital interventions, which allows examination of individual components of intervention and delivery (61) may be helpful.

Patients may opt to take their baseline rating to their providers for psychoeducation and diagnosis of PMDD, if applicable. For patients with PMDD, selective serotonin reuptake inhibitors (SSRIs) are an effective treatment option, with some patients seeing symptom reduction within 24-48 hours of taking their medications (62). SSRIs for PMDD patients are prescribed either continuously or to be taken just in the luteal phase (62). For patients who are taking a luteal phase-only SSRI regimen, JITAI can send daily scheduled reminders for medication adherence starting the first day post-ovulation.

2.9 Decision rules

In the schematic decision rule below, we present an example of an operational system that increases participant awareness of their risky phase and deploys interventions well-matched to suicide-related symptoms during their specific vulnerable state.

If the baseline maximum risk score for this menstrual cycle day number is "no risk":

Then: "No message"

Else if baseline risk score for this menstrual cycle day number is "low risk":

Then: "Send auto-message that they are entering a vulnerable window in their cycle and recommend non-judgmental awareness of emotions"

Else if baseline risk score for this menstrual cycle day number is "moderate risk" OR "high risk:

Then: "Send patient tailored skill based on the symptom network (e.g., behavioral activation for depression related to estrogen withdrawal or DBT skills for anger/mood swings related to progesterone surge"

3 Discussion

For many patients, the menstrual cycle is a recurring biological predictor of suicide risk. However, there is currently no evidence-based treatment for menstrual cycle-related suicidality. Given the complex, idiographic, and dynamic impact of the menstrual cycle on suicidality, we propose that JITAI are a promising avenue for further exploration. Integrating menstrual cycle variables into JITAI models can leverage a biological variable to predict when and which symptoms are exacerbating suicidality, with the goal of deploying timely, effective interventions. While self-report is a key component of currently proposed models, the advancement of wearable and smartphone-based cycle tracking technologies may allow for low-burden, passive measurement in the future.

3.1 Challenges and future directions

While JITAIs offer promise in addressing menstrual cycle-related suicidality, there are distinct challenges in their development and implementation. First, atypical menstrual cycles, related to anovulation, contraceptive use, peripuberty, or perimenopause (63), pose obstacles to accurate prediction of risky timeframes. Thus, research should account for nuances in cycle variation. Ethical concerns arise regarding intervention timing and methods for high-risk patients. Clear protocols must address imminent risk, balancing intervention efficacy with confidentiality and potential need for hospitalization. Although in this hypothesized model, daily variables were used for tailoring variables, we hope that eventually, suicide and menstrual research will move past daily measurement to more within the moment (i.e, hourly to seconds) detection of states of vulnerability and receptivity, allowing for more timely responses to perimenstrual

suicide changes. Finally, before the deployment of JITAI for menstrual cycle-related suicidality, randomized controlled trials are needed to determine (a) which cycle-timed interventions are most acceptable to patients, (b) when patients are most receptive to interventions (12), and (c) whether targeting monthly risk windows with JITAI reduces future suicide attempts. Finally, while our manuscript primarily addresses menstrual cycle-related psychiatric changes, we acknowledge that the menstrual cycle has an impact on broader biological systems [i.e., migraines and epilepsy (64)] and emphasize that the broader digital therapeutic research accounts for menstrual-related changes.

4 Conclusion

We advocate for integrating the menstrual cycle into JITAI models for suicide prevention to address individual variability in suicidality and psychiatric symptoms. Despite implementation challenges, we propose including the menstrual cycle as a variable in JITAIs, particularly for suicide prevention.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

HT: Conceptualization, Methodology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. DC: Conceptualization, Writing – original draft, Writing – review & editing, Methodology. AR: Methodology, Writing – original draft, Writing – review & editing. AN: Conceptualization, Writing – review & editing. JR: Supervision, Writing – review & editing. MN: Supervision, Writing – review & editing. TE: Conceptualization, Methodology, Supervision, Writing – review & editing, Writing – original draft.

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Conflict of interest

MN receives publication royalties from Macmillan, Pearson, and UpToDate. He has been a paid consultant in the past three years for Apple, Microsoft, COMPASS Pathways, and Cambridge Health Alliance, and for legal cases regarding a death by suicide. He has stock options in Cerebral Inc. He is an unpaid scientific advisor for Empatica, Koko, and TalkLife.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Unveiling the burden of premenstrual dysphoric disorder: a narrative review to call for gender perspective and intersectional approaches

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The present narrative review discusses the burden of Premenstrual Dysphoric Disorder (PMDD) and highlights the lack of awareness by analyzing the following key points: -Prevalence and Diagnosis: PMDD affects a significant portion of women during their reproductive years, but diagnosis is often delayed due to limited understanding and awareness. -Mental Health Burden: PMDD increases the risk of suicide attempts and negatively impacts quality of life. There are also economic costs associated with absenteeism and healthcare use. -Cultural and Gender Perspectives: Societal stigma surrounding menstruation and mental health likely contributes to underdiagnosis. -Lack of Sex and Gender Perspective in the Healthcare System: Research bias towards male subjects and historical neglect of women's health issues contribute to limited knowledge about PMDD. -Non-Intersectional Approaches: Disparities in access to healthcare and the unique experiences of women further complicate PMDD diagnosis and treatment. -Vicious Cycle: The lack of research and awareness creates a vicious cycle where PMDD remains misunderstood and inaccurately treated. Finally, it emphasizes the need for increased awareness, education, and research on PMDD, particularly with a gendered and intersectional optic. The situation in Latin America is presented as a particular concern due to a lack of recent data and potentially higher prevalence due to socioeconomic factors.

KEYWORDS

premenstrual dysphoric disorder, burden of illness, gender perspectives, intersectionality, call to action

1 Introduction

During reproductive age, females are more susceptible than males to suffer mood disorders (1, 2), and there are female-specific psychiatric conditions such as Premenstrual Dysphoric disorder (PMDD), the severe form of premenstrual syndrome (PMS) (3). According to the last version of the Diagnostic and Statistical Manual (DSM-5), PMDD is characterized by depressive mood, anxiety, mood liability, and somatic symptoms that usually appear during the late luteal phase of the menstrual cycle and typically disappear during the first week after menses (3). The symptoms are presented cyclically across the menstrual cycle (4), and there are subtypes of premenstrual symptoms (5) that do not necessarily commit to the temporal course stated in the classical manual diagnosis. Additionally, the DSM-5 criteria require the presence of at least five core symptoms in two consecutive cycles; however, this criterion is not always met in clinical practice. A commonly used diagnostic tool for Premenstrual Dysphoric Disorder (PMDD) is the "Daily Record of Severity of Problems" (DRSP), which prospectively screens for PMDD symptoms (6).

The recent systematic review and meta-analysis of Reilly et al. (7) found a pooled prevalence of 3.2% (95% Confidence Intervals (CI): 1.7%–5.9%) in samples with confirmed diagnosis and 7.7% (95% CI: 5.3%–11.0%) in samples that had provisional diagnosis. Provisional diagnoses are the ones in which the studies did not use prospective symptoms according to DSM criteria (3). When restricted to studies fully adhering to DSM diagnostic criteria for a confirmed diagnosis, in community-based samples, the pooled prevalence was 1.6% (95% CI: 1.0%–2.5%).

Following Reilly et al. (7) location matters, as there was a significant effect of the continent from which the sample was taken ($p<0.001$), with the highest prevalence in African samples, 27. 8% (95% CI: 14.6%–46.3% and lowest in North American samples, 2.8 (95% CI: 1.7 -4.5). There was a significant effect of sample type ($p = 0.007$), with the highest prevalence in university samples. It should be noted that all samples from Africa used provisional diagnosis so it may be an overestimation of the true prevalence. Notably, there were not any studies in Latin America, which is *per se* informative of the situation about the omission and overlooking of PMDD in this region. There were only three in Brazil that showed a high prevalence of 13.1 (95% CI: 7.6-21.6), that it is higher than in other zones such as North America.

Interestingly, a meta-analysis (8) reported the prevalence of premenstrual syndrome (PMS) across various regions, including Europe, Asia, Africa, and Brazil. The pooled prevalence of PMS was 47.8% (95% CI: 32.2-62.9), with the lowest prevalence observed in France (12%, 95% CI: 11-13) and the highest in Iran (98%, 95% CI: 97-100). This study highlighted significant regional disparities, with high prevalence rates reported in Iran, Turkey, Pakistan, Nigeria, Brazil, and Spain (up to 50%). The contrast between the high prevalence of Spain and the lower rates in France and Switzerland suggests that cultural and social factors may influence the development of PMS and PMDD.

Supporting this idea, a recent study (9) examined the impact of PMS and PMDD on the academic performance of university students in the United Arab Emirates. A substantial proportion of participants reported experiencing PMS (78.9%) and PMDD (16.3%), indicating that these conditions can significantly affect academic activities in 90% of cases.

Worryingly, symptoms appear around age 15 on average, while the diagnosis occurs on average at age 35 according to a previous report (10). To endure twenty years of not having a diagnosis is a significant health burden to the suffering person. For years, women's mental health has been undervalued and dismissed (11), leading to delays in diagnosis.

There may be significant health benefits for women to receive timely diagnosis, as women who are diagnosed later in life are more likely to attempt suicide (12). Nevertheless, there are limited options for treatment because of the lack of understanding of the etiology of PMDD, "the lack of ability to test for biomarkers for PMDD, and the complex nature of the behavioral and affective symptoms" (12). However, following Chan et al. (12) demonstrated that healthcare providers often minimize patients' symptoms, a phenomenon known as "medical gaslighting". This practice involves a recurring dismissal of symptoms and lack of empathy by healthcare providers.

Overlooking Premenstrual mood disorders can negatively impact the quality of life, and it is imperative to discuss the burden of these disorders, which is often exacerbated by the challenges women face within a healthcare system primarily oriented and designed by men (11). Here, we aimed to review and point out key elements that need to be discussed to raise awareness about premenstrual mood disorders. We will discuss how economic, cultural and societal factors can impact the mental health experiences of women, particularly in developing regions.

2 The burden of PMDD in mental health: focus on suicidal risk

It is undoubtedly that a psychiatric condition will impact individuals in various spheres and in different ways. These conditions may lead to a wide-ranging spectrum of outcomes. In this sense, the termination of life comprehends the most fatal consequences in outcomes taxonomy in clinical studies (13). Suicide comprehends ideation, planning, non-fatal and fatal attempts (14). Overall, the literature suggests that men die by suicide in more proportion than women. However, rates of suicide attempts are higher in women than in men (15). As Vijayakumar (15) opportunely points out, there is a significant gap in the literature regarding reports that exhaustively evaluate the complex interplay between gender and suicide. Therefore, gender-perspective studies are necessary to elucidate the complex social, -environmental, and biological demands that may underlie suicide attempts in the female population.

Previous reports have found different risks of suicide attempts and ideation in females with PMDD. For instance, a meta-analysis reported that having PMDD duplicates the risk of suicidal ideation and attempts (16). Moreover, suicidal ideation was reported in 40% of women with PMDD (17). Notably, another meta-analysis that included a higher number of studies (18) found that women with

PMDD have 7 times higher risk of suicide attempt (OR= 6.97) and nearly 4 times higher risk of suicide ideation (OR= 3.95) respect to no-PMDD subjects. Eisenlohr-Moul et al. (19) observed higher rates of suicidal ideation in 72% of females with PMDD, while planning in 49%, attempt in 34%. Most participants (92.4%) were females from English-speaking countries, with less than 1% belonging to Latin America regions. While the study unequivocally establishes a connection between suicide and PMDD, the unrepresentative number of participants originating from Latin America regions, limits the ability to draw a perspective on how PMDD is affecting menstruating individuals in this region.

3 The economic burden of PMDD

The diagnosis and epidemiology of PMDD have been exhaustively reviewed acknowledging that PMDD is a legitimate disorder deserving of research and clinical attention (20). Being PMDD a health condition, it comes with the so-called burden of disease. The burden of disease refers to the financial costs, mortality, morbidity, and quality of life impact that illnesses bring along (21). For instance, PMDD increases the risk of visiting a specialist physician three times or more during 12 months (22) implying economic costs and resources to receive medical care. Women with PMDD have increased rates of absenteeism of more than 8 hrs per menstrual cycle (23), impairing productivity. Moreover, indirect costs of absenteeism and presentism were estimated over $4,000 usd annually when premenstrual symptoms are presented (24). The scenario might get worse considering that a menstruating person may experience around 480 menstrual cycles during their reproductive life, and the potential negative impact of PMDD becomes even more significant. In line with this idea, women with PMDD reported a general decline in health, poorer sleep quality, increased alcohol consumption, heightened anxiety and depression, a disrupted work-life balance, lower levels of psychological resilience, and increased perceived work demands (25). The overview of PMDD burden is given mainly by studies conducted in developed countries. While these studies have revealed significant data demonstrating the actual burden of PMDD, this disorder has been overlooked in developing countries within Latin American regions. Moreover, to this day no clinical attention or treatment is well known to be effective for this condition to dampen the negative impact of PMDD. Treatment options for PMDD may include ovarian suppression with gonadotropin-releasing hormone or oophorectomy but typically include pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) (26), dietary and nutritional interventions (27), as well as lifestyle changes and psychotherapy (28). Access to these treatments may vary depending on factors such as healthcare infrastructure and socioeconomic status within different Latin American countries.

4 The burden of cultural and gender perspectives

PMDD is a complex entity (29): from its not fully understood etiology to the influence of cultural perspectives. While menstruation is a natural biological process that indicates healthy coordination between the brain, the ovaries, and the uterus (30), the narrative of menstruation is surrounded by cultural perceptions, that may stigmatize it as taboo or shameful (31, 32). A recent review exhaustively explored societal, cultural and religious beliefs that contribute to taboos in sexual health, leading to secrecy, isolation, myths and misconceptions (33). These can result in inadequate menstrual hygiene management, missed educational opportunities, and perpetuate gender inequality. The social context can influence how individuals experience and express premenstrual symptoms. In rural areas, menstruation was often treated as a private or taboo topic when compared to urban areas, which discouraged open discussions and healthcare consultations when needed (34).

It is known that negative attitudes towards menstruation, often rooted in sexism, can lead to feelings of rejection and embarrassment (35). Following Marván et al. (35) perceptions and attitudes towards menses predict affective symptoms. Having a psychiatric diagnosis comes with a social stigma that negatively impacts self-concept and impairs recovery (36). Now, if we talk about a psychiatric disorder related to menstruation, the stigma around might be overwhelming. Due to double stigma (from mental health disorders and menstruation), the prevalence of PMDD is likely underestimated, particularly in countries with more traditional views and practices on gender, such as those in Latin American regions.

Gender perspectives influence even professional clinicians (37, 38). Regarding PMDD, a previous study found that female gynecologists are more frequently engaged in treating premenstrual mood disorders compared to male practitioners, and females tend to use prospective diagnoses in a higher proportion than men (39). Authors suggest that female gynecologists tend to stick to diagnosis guidelines for PMDD more rigorously than males, perhaps due to a more professional optic of the clinical condition. Healthcare professionals need to be aware and sensitized to detect premenstrual-related symptoms and to warrant accurate diagnosis. Otherwise, misdiagnosis or subdiagnosis could lead to invalidation of the negative experience and add more stress to a situation lacking empathy and denying access to treatments (as there would not be any condition to treat).

5 The burden of lack of sex-gender perspective in the healthcare system

Women's mental health has been marginalized and dismissed as exaggerated and/or insignificant throughout history (11). For years, preclinical and clinical health research has primarily focused on male subjects across different species (40), often excluding females from scientific findings for several reasons, including concerns about hormonal fluctuations that may *interfere* with the results. This exclusion has led to a significant gap in our understanding of sex-specific health differences. Experimental designs have also frequently omitted biological sex as a co-variating factor, failing to consider potential biological variations. For example, steroid hormonal fluctuations such as estradiol and progesterone occur each 28-32 days in human females (41) while in males, androgens

fluctuations occur in 24 hours (42), and these hormones impact on brain functions in both sexes. Then, it is crucial to understand the biological substrates underlying some pathologies due to sex differences impact on the prevalence, clinical manifestations and progression of the diseases (43). Consequently, diagnostic and treatment guidelines are mainly based on research conducted primarily in male subjects.

Female-specific conditions are beyond reproductive health. Historically, women's health has been restricted to gynecological and obstetric issues, and other than these, are either invisible or not important enough (44). In the USA, the policy of including women in clinical research trials was stated in 1993, however, it was not until 2014 that the inclusion of sex as a biological variable (SABV) was mandatory in research funded by NIH (40). Despite the advancements in policies, there is still a long way to go, particularly in mental health research. A previous report that surveyed papers on psychiatric research revealed that only 19% of studies during 2009-2019 included an adequate design to elucidate potential sex differences (45). Worryingly, reports studying only females are barely 5% (46), suggesting that female-specific pathologies are scarcely considered in health literature and are far from being fully understood. Omissions of females in health-related scientific literature have stressed the disparities and bias in the healthcare system, often experiencing misdiagnosis or underestimation of symptoms leading to undertreatment of health conditions. Further, Silverio (11) argued that treatments for women's mental health should be based on evidence derived from studies focused specifically on women, rather than relying on studies using men as a model. Also, the author proposes the concept of *Female Psychology* that frames mental health positively by considering both periods of strength and distress within women's life course (47). Although sex and gender are different constructs, sex can influence the societal conformation of gender and the characteristics typically assigned to men and women (40). Gender refers to social constructs and norms that influence roles, relationships, and power positions for all people across their lifetimes. All these variables are suitable for change, which is why it is proposed that gender should not be a binary term (43). Transgender people have been excluded and underrepresented in scientific literature and clinical research. To this date, there is no systematic data on the prevalence of transgender people and premenstrual mood disorders. The transgender community is often susceptible to attacks, discrimination, abuse, physical and psychological violence (48). Transgender people are also at economic disadvantage (49). Only 1 out of 10 transgender persons have formal employment leading to inequities and difficulties in health access (50). Therefore, we stress the need that intersectionality must be involved in mental health matters.

It is acknowledged that gender inequalities in the healthcare system come from fundamental disparities between men and women (51). Thus, for years it has been thought that particular female diseases, such as premenstrual disorders and postpartum depression are *normal and inherent* in women's lives. It is time to stop the normalization of adverse experiences by incorporating a gender perspective into the healthcare system. Health professionals could make a difference in how women transit throughout their reproductive and non-reproductive years (11).

6 The burden of non-intersectional approaches

Approaches that do not consider intersectionality significantly affect the detection, prevalence, prevention, and treatment of Premenstrual Dysphoric Disorder (PMDD) because they overlook the multifaceted and interacting social identities that shape women's experiences. Intersectionality (52) recognizes the overlapping systems of oppression, such as those based on race, gender, class, and sexuality. Based on the intersectionality concept, Purdie-Vaughns and Eibach (53) propose an "interactive model" that assumes "multiple subordinate identities". Therefore, individuals with multiple marginalized identities experience heightened prejudice and discrimination. This may predispose to health problems, as a previous report found the highest prevalences of mental disorders in black women, while the lowest prevalence was found in white men (54). This suggests that gender and race may be contributing to mental health outcomes. Moreover, Smolen et al. (54) report that women were underemployed or underpaid respect to men independently of race. Thus, Julia Monárrez (55) urged the consideration of the interaction with other factors of social exclusion, such as racial, gender, and sexual discrimination, that exacerbate the disadvantages of poor and working-class women.

Then, by not adopting an intersectional approach, research continues to perpetuate a gap in understanding how multiple subordinate identities affect women's mental health. As Pilver et al. (56) emphasized, the Office for Women's Health Research has acknowledged the need for increase research on PMDD among ethnic minority women. Policies developed without an intersectional framework might fail to address the root causes of health inequities.

Non-intersectional approaches often produce generalized data that fail to accurately represent the specific subgroups of women who are most affected by PMDD. For instance, ethnic minority women are often underrepresented in studies (56), and their unique symptoms experiences are not adequately explored when included. Also, they show that subtle forms of discrimination (e.g., rudeness, unfair treatment) are significantly associated with PMDD in ethnic minorities (56). Without an intersectional optic, these nuanced experiences of minority women and their contributions to PMDD prevalence are overlooked, resulting in an incomplete understanding of the disorder's epidemiology.

Prevention programs that do not account for the interplay of race, class, and other social determinants may fail to address the specific needs of subgroups. Several factors such as low income, malnutrition, and domestic violence are particularly relevant in developing countries (57). Intersectional approaches would tailor preventive measures to address these socioeconomic variables. Moreover, non-intersectional approaches neglect how stress and adversity are disproportionately experienced by rural or low-income populations, contributing to the dynamic nature of PMDD prevalence (58). Intersectionality would guide more targeted prevention strategies, focusing on mitigating stressors specific to these communities.

Regarding treatment, approaches neglecting intersectionality can perpetuate biases within the healthcare system. For example, low-income, underinsured, and minority women often encounter limited access to mental health resources and face higher discrimination in healthcare settings (59). This might lead to inadequate or inappropriate treatment due to a lack of understanding of their unique circumstances.

Adopting an intersectional perspective in treatment plans would consider the simultaneous impact of multiple forms of oppression and identity factors, leading to more comprehensive and personalized therapeutic approaches. Ignoring intersectionality can result in one-size-fits-all treatment paradigms that ignore the compounded adversities that disadvantaged groups face.

7 The burden of a vicious cycle

The overlook of premenstrual mood disorders contributes to the lack of data regarding the burden of illness. This may conform a vicious cycle: the absence of gender perspective leads to a lack of recognition which in turn leads to underestimation of the disorder's prevalence. Lower prevalence results in reduced awareness among public authorities and decision-makers, leading to a lack of resources allocated for research on the epidemiology, etiology and treatment of the disorder. Without research, there's no knowledge, and without knowledge, there's no awareness. Worryingly, this vicious cycle is affecting women's lives for more than 30 years, as symptoms usually begin around age 15, and misdiagnosis and mistreatment can last for 20 years before receiving the correct PMDD diagnosis. Even after diagnosis, the lack of gender perspective may lead to mistreatment, as PMDD symptoms may still be mistakenly attributed to the natural process of menstruation (10) (Figure 1).

The situation in Latin America is concerning. There have been no recent studies on the prevalence or burden of premenstrual disorders (PMDD) in the past decade. We still rely on outdated data from developed countries, which suggests that 8% of females of reproductive age suffer from PMDD (60). However, it is reported that adverse situations in the form of minimal health facilities, security not guaranteed, and high unemployment rates, are higher in developing countries with respect to developed countries (61). These adverse conditions can increase the risk of PMDD and worsen premenstrual symptoms (62). It is plausible then, that developing countries may have high rates of premenstrual mood disorders, beyond the 8% that we have historically considered.

8 Conclusion

Here, we have discussed the burden of aspects that worsen the experience of having PMDD in a non-gendered perspective health system that builds a barrier to understanding and properly addressing PMDD. It is undoubtedly the omissions and debts that people with PMDD face when they transit through this condition. From the invalidation of the symptoms to the ~20 years it takes to have a proper diagnosis. The delay in diagnosis can lead to prolonged psychological distress for those affected. The evidence (and the lack of it) highlights the crucial need to address gender perspective actions to bridge the inequalities within health systems that lead to improved mental health outcomes.

Here is a call to foster actions that overcome invalidation, minimization, underdiagnoses, misdiagnosis, and social stigma that surround premenstrual mood disorders. We can start by opening the conversation around menstruation and how unique this may be for every menstruating person.

We strongly appeal to implement actions that raise awareness and educate on PMDD, from healthcare providers, policy makers and the general population. Actions targeting public awareness through campaigns in public spaces, social media, among others, can help to destigmatize PMDD and encourage people to look for help if they are experiencing symptoms. Promote healthcare professionals to look at the unique experiences and particular

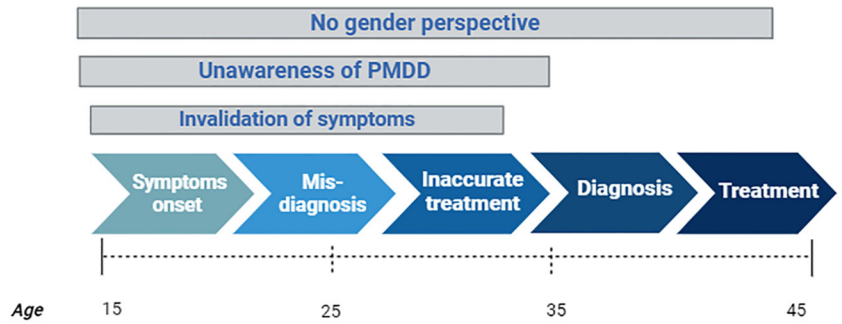

FIGURE 1
Pathway of individuals with PMDD symptoms and the impact of invalidation, unawareness and gender bias in each stage over time. Created with Biorender.com.

needs of persons experiencing premenstrual symptoms. Health providers must receive proper training in gender-based care to positively impact in women's lives. It is essential to encourage and fund further research into the neurobiological, psychological, and social factors that contribute to PMDD. We have to create useful knowledge to develop more effective diagnostic tools, preventive strategies and treatment options. The UK research agenda for PMDD (63) exemplifies a collaborative effort to identify key research priorities. Developed by a diverse group including individuals with PMDD, their families, healthcare professionals, researchers, support organizations, and emergency responders, the agenda prioritizes five key areas: diagnosis and management of PMDD, best approaches for psychological support, suicide and self-harm prevention, the impact of PMDD on life, and hormonal triggers for PMDD. Additionally, the agenda highlights several other potential research areas, such as the causes and biology of PMDD, destructive behavior, surgery and post-surgery support, barriers to support, the burden of PMDD, premenstrual exacerbation of existing disorders, neurodivergence, support from the welfare system, and PMDD education and training. This comprehensive approach underscores the multifaceted nature of PMDD and the need for multidisciplinary research to address its various aspects.

Finally, approaches that ignore gender perspective and intersectionality result in a fragmented understanding of PMDD, leading to ineffective prevention and treatment strategies that do not meet the nuanced needs of diverse groups of women. Recognizing and integrating intersectional factors are essential for creating comprehensive and equitable solutions in healthcare.

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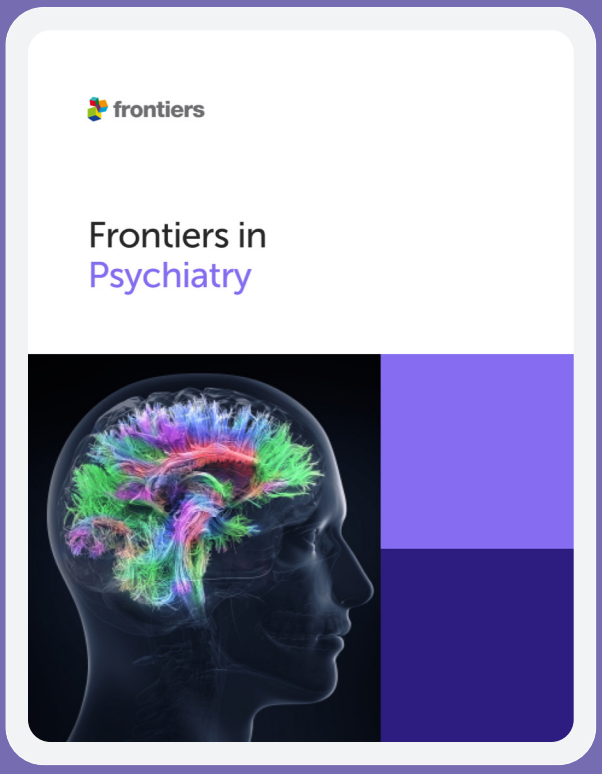

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