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Guest Editorial

Premenstrual exacerbation of psychiatric symptoms: from misdiagnosis to management

Jayashri Kulkarni and Eveline Mu

Summary

Premenstrual exacerbation of existing mental illnesses (PME) is a condition where symptoms of mental disorders worsen during the luteal phase. Unlike premenstrual syndrome or premenstrual dysphoric disorder, PME is poorly recognised, with misdiagnoses and inadequate treatment. Understanding the brain impact of gonadal hormone fluctuations in PME is crucial.

Keywords

Premenstrual exacerbation; premenstrual dysmorphic disorder; premenstrual syndrome; gonadal hormone treatment; mood disorders.

Premenstrual exacerbation (PME), also referred to as premenstrual aggravation and premenstrual magnification, affects the lives of many women and is poorly understood. PME refers to the worsening of existing psychiatric disorders in the luteal phase of the menstrual cycle, which occurs after ovulation and before menstruation. Although premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) have received more attention, PME remains largely underrecognised, often resulting in misdiagnoses and poor treatment. The confusion surrounding menstrual cycle-related conditions, coupled with the lack of acknowledgement of the critical role gonadal hormones play in brain function, highlight the urgent need for better diagnostic and management strategies.

Understanding PME

PMS and PMDD have been recognised as menstrual-related mood disorders. PMS affects about 80% of women and is characterised by mainly physical symptoms and mild to moderate emotional symptoms that occur in the luteal phase, and resolve shortly after menstruation begins. PMDD affects about 3.2% of the reproductive female population[1] and is a severe form of PMS, with accompanying symptoms of sadness, 'brain fog', rage, irritability and severe anxiety. As a form of depression, PMDD can interfere with daily functioning and result in profound debilitation every cycle. The symptoms typically begin premenstrually and cease with menstruation. Importantly, the symptoms often begin and end suddenly, underlining a 'biological switch' aetiology.

PME is a recently described third menstrual cycle-related mental health condition. Women with PME have pre-existing psychiatric disorders of depression, anxiety, bipolar disorder, attention-deficit hyperactivity disorder, schizophrenia and other mental illnesses. Individuals with PME experience a marked worsening of the symptoms of their pre-existing mental disorder in the luteal phase. Women with PMS and PMDD experience symptoms during the premenstrual phase, and usually have good mental health during the rest of the monthly cycle. Women with PME experience mental illness throughout their entire menstrual cycle, but with particularly severe symptoms in the premenstrual phase, requiring a new treatment approach for PME.

The intersection of PME with psychiatric disorders

PME exacerbates symptoms of many psychiatric disorders, complicating their management. For example, women with pre-existing major depressive disorder (MDD) and PME may experience a significant worsening of depressive symptoms, leading to an increased risk of suicidal ideation and further impaired daily functioning in the luteal phase. The cyclic nature of PME can also make it difficult to understand the cause of intermittently worsening depressive episodes, with potential misdiagnoses and inappropriate treatment. Women with bipolar disorder and PME can experience increased mood instability, with more frequent and severe mood swings during the luteal phase. This exacerbation adversely affects mood stability achieved through mood stabiliser medications, necessitating potential adjustments in treatment and careful monitoring. Similar exacerbations occur in women with co-existing PME and other psychiatric disorders, requiring a new approach to diagnosis and management.

The interaction between gonadal hormonal fluctuations and neurochemistry underpins these exacerbations, leading to increased distress and functional impairment. For example, in women with schizophrenia and PME, the interaction between oestrogen levels and dopamine regulation is thought to be a key factor, since oestrogen has been shown to have antipsychotic-like effects, and its decline may lead to worse psychosis symptoms.[2]

The role of gonadal hormones in the brain

The menstrual cycle is driven by fluctuating levels of gonadal hormones, primarily oestrogen, progesterone and the pituitary hormones luteinising and follicle-stimulating hormones. These hormones regulate reproduction and also have significant effects on brain function, including emotional and cognitive regulation.

The luteal phase, characterised by high levels of progesterone and a rapid decline in oestrogen, is particularly critical in understanding PME. Oestrogen, in particular, has many neuroprotective properties and modulates neurotransmitter systems involved in mood and attention regulation, such as serotonin and

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dopamine.[3] It enhances serotonin receptor expression and serotonin availability in the brain, and boosts dopamine transmission in prefrontal brain regions,[4] which are critical for executive functioning, attention and mood stabilisation. As a result, higher oestrogen levels, such as those seen in the follicular phase, are associated with improved concentration, cognitive function and emotional well-being.

In contrast, during the luteal phase, the sharp drop in oestrogen levels can lead to reduced neurocircuitry functions, potentially triggering mood and cognitive disturbances in susceptible individuals.

Progesterone and its metabolites, particularly allopregnanolone, also play a crucial role in mood regulation. Allopregnanolone is a potent modulator of the gamma-aminobutyric acid (GABA) receptor, the primary inhibitory neurotransmitter in the brain. Although GABA typically promotes relaxation and reduces anxiety, fluctuations in allopregnanolone levels during the luteal phase can paradoxically lead to increased anxiety, irritability and mood instability in some women.

For women with pre-existing psychiatric disorders, these hormonal fluctuations can exacerbate symptoms. For instance, women with MDD may experience a deepening of depressive symptoms during the luteal phase, because of the drop in oestrogen and altered GABAergic function. Similarly, women with bipolar disorder may experience increased mood instability, with a higher risk of depressive or manic episodes during this time. Furthermore, women with attention-deficit hyperactivity disorder may experience heightened symptoms of inattention, distractibility and impulsivity during the luteal phase, because of the decline in oestrogen and altered dopamine function.

Management strategies for PME

Managing PME requires a multimodal approach that addresses both the underlying psychiatric disorder and the menstrual-related exacerbation of symptoms. Treatment should be tailored for the individual, with consideration of the severity of the psychiatric disorder, the extent of the impact of PME and the woman's treatment preferences.

Given the role of gonadal hormones in causing PME, it seems obvious that hormone treatments would be effective.[3] Hormone contraceptives, particularly those that suppress ovulation, may stabilise gonadal hormone levels and reduce the cyclical fluctuations that contribute to PME. However, the response to hormone treatments varies depending on the type and doses provided. Some women may experience worsening symptoms, particularly in response to many synthetic progestins, hence necessitating careful monitoring.[5,6] A newer generation combined oral contraceptive pill, containing 1.5 mg 17-beta oestradiol and 2.5 mg nomegestrol acetate, appears to be better tolerated and shows promise as an effective treatment for women with menstrual cycle-related mood disorders. It has shown potential in clinical practice for the treatment of PMDD,[7] and might be a useful addition to treating women with PME. Clinical trials augmenting standard antidepressant, antipsychotic or mood stabiliser medications with the combined oral contraceptive pill to achieve gonadal hormone stability across the menstrual cycle need to be performed. Based on the good response in PMDD, this type of hormone treatment might tentatively also provide relief for PME sufferers.

Selective serotonin reuptake inhibitors (SSRIs) are commonly used to treat PMS and PMDD. Women with pre-existing depression and PME may already be taking SSRIs, and the dose of the same medication may need to be increased premenstrually. Of course, careful monitoring for withdrawal symptoms when the dose is lowered needs to occur. Nonetheless, women with PME and MDD may wish to self-titrate small dose changes of their SSRI medication across the cycle, with medical supervision. This utilises clinical experience from intermittent treatment with SSRI for women with PMDD.[8] Serotonin and norepinephrine reuptake inhibitors (SNRIs) are commonly associated with significant withdrawal symptoms, and are therefore more difficult to use intermittently. If the woman is stabilised on a SNRI, then continuous use of this is better with respect to withdrawal symptoms. More recently, agomelatine appears to be a useful antidepressant for premenstrual disorders such as PMDD, with decreased side-effects on intermittent use and increased efficacy in treating sleep disturbances.[9] Women with PME that involves worsening depressive symptoms may improve with the addition of agomelatine to their existing antidepressant medication during the luteal phase.

For women with bipolar disorder or schizophrenia, optimising mood stabilisers or antipsychotic medication dose and type during the luteal phase may be necessary to manage PME. Adjustments in dosing during the luteal phase or adding a small extra dose of a different class of medication may help the PME-caused mood destabilisation or worsening psychosis.

Psychotherapy, in general, and particularly psychoeducation about PME, can be beneficial. Psychoeducation usually involves teaching women how to track their symptoms and identify patterns that indicate PME. Moreover, educating women about the nature of PME and its relationship to the menstrual cycle can empower them and their loved ones to recognise and manage their symptoms more effectively. Regular exercise, a balanced diet and stress reduction techniques can also play a role in managing PME.

The path forward

Given the significant impact of PME on women's mental health, improving diagnostic accuracy is crucial. Clinicians need to be aware of the potential for PME in women with pre-existing psychiatric disorders, and actively assess for cyclical patterns in symptom exacerbation. A detailed menstrual history should be a routine part of psychiatric assessments, particularly in women of reproductive age. Relatedly, the timing of diagnostic assessments is also critical. Significant fluctuations in symptoms across the menstrual cycle can greatly affect the risk of suicide and self-harm. Hence, the early clinical diagnosis of PME is critical to enable treatment planning that may well prevent great harm.

Tracking symptoms across the menstrual cycle by using daily mood charts or symptom diaries can help identify the pattern of PME. Tools such as the Daily Record of Severity of Problems (DRSP) can be useful in differentiating PME from PMS and PMDD. The DRSP enables careful documentation of symptoms and their severity in relation to the menstrual cycle. In this way, detailed data can be discussed in clinical consultations, and a collaborative management plan can be formulated to prevent monthly deterioration in the woman's mental state.

Although PME has been recognised in recent years, significant gaps remain in our knowledge of its pathophysiology, diagnosis and treatment. Future research should prioritise elucidating the mechanisms driving PME, particularly the influence of gonadal hormones on psychiatric symptoms. Longitudinal studies that track hormone levels, brain function and symptom fluctuations across the menstrual cycle could provide valuable insights into the biological basis of PME. Equally important is increasing awareness among healthcare professionals and the public. Greater efforts are needed to educate clinicians to recognise PME and distinguish it from other menstrual-related disorders, ensuring accurate diagnoses, appropriate treatment and validation of their female patients' observations.

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Jayashri Kulkarni, HER Centre Australia, Department of Psychiatry, School of Translational Medicine, Monash University, Melbourne, Australia; **Eveline Mu**, HER Centre Australia, Department of Psychiatry, School of Translational Medicine, Monash University, Melbourne, Australia

Correspondence: Jayashri Kulkarni. Email: jayashri.kulkarni@monash.edu

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