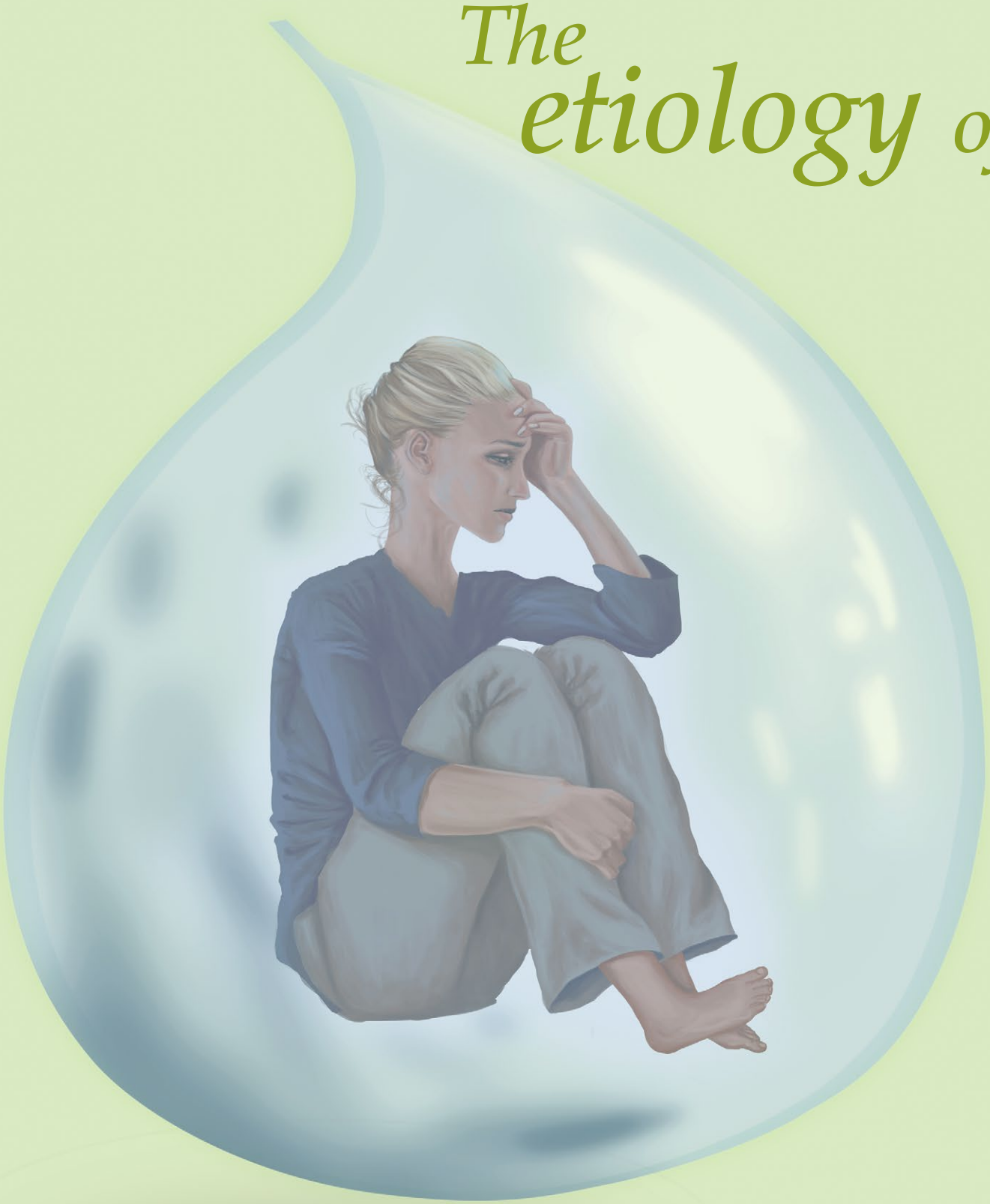
The etiology of



Web audio at **CurrentPsychiatry.com**

Dr. Raffi discusses treatment of menstrual cycle–related mood and anxiety disorders

premenstrual dysphoric disorder: 5 interwoven pieces

A better understanding of the causes of PMDD can lead to improved diagnosis and treatment

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In an age when psychiatry strives to identify the biologic causes of disease, studying endocrine-related mood disorders is particularly intriguing. DSM-5 defines premenstrual dysphoric disorder (PMDD) as a depressive disorder, with a 12-month prevalence ranging from 1.8% to 5.8% among women who menstruate.[1-3] Factors that differentiate PMDD from other affective disorders include etiology, duration, and temporal relationship with the menstrual cycle.

PMDD is a disorder of consistent yet intermittent change in mental health and functionality. Therefore, it may be underdiagnosed and consequently undertreated if a psychiatric evaluation does not coincide with symptom occurrence or if patients do not understand that intermittent symptoms are treatable.

This article summarizes what is known about the etiology of PMDD. Although there are several treatments for PMDD, many women experience adverse effects or incomplete effectiveness. Further understanding of this disorder may lead to more efficacious treatments. Additionally, understanding the pathophysiology of PMDD might shed a light on the etiology of other disorders that are temporally related to reproductive life changes, such as pregnancy-, postpartum-, or menopause-related affective dysregulation.

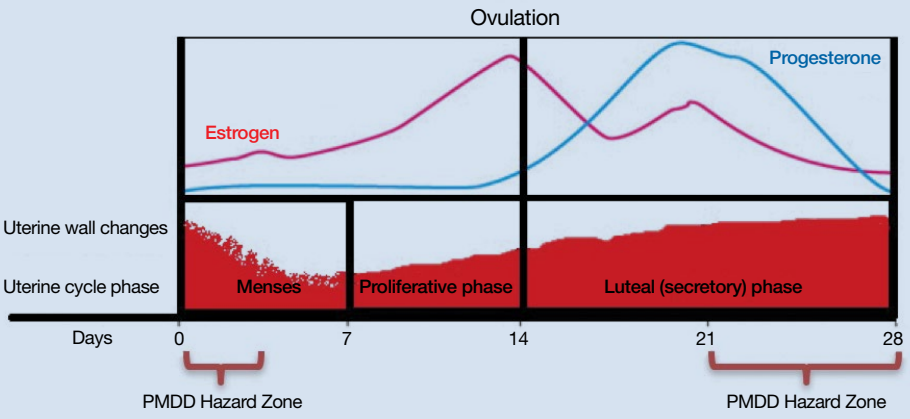
Making the diagnosis

The diagnosis of PMDD is made when a patient has at least 5 of 11 specific symptoms (***page 22***) that occur during the week before onset of menses, improve within a few days after the onset of menses (shown as the "PMDD Hazard Zone" in ***Figure 1, page 22***), and are minimal or absent

FANATIC STUDIO

Figure 1

The menstrual cycle and the 'PMDD Hazard Zone'



The diagnosis of PMDD is made when a patient has at least 5 of 11 specific symptoms that occur during the week before onset of menses, improve within a few days after the onset of menses (indicated here as the "PMDD Hazard Zone"), and are minimal or absent post-menses.

PMDD: premenstrual dysphoric disorder

Clinical Point

Perhaps the most common cause for misdiagnosis of PMDD is failing to rule out PME of another underlying or comorbid condition

post-menses.[3] Symptoms should be tracked prospectively for at least 2 menstrual cycles in order to confirm the diagnosis (one must be an *affective symptom* and another must be a *behavioral/cognitive symptom*).[3]

The affective symptoms are:

- lability of affect (eg, sudden sadness, tearfulness, or sensitivity to rejection)
- irritability, anger, or increased interpersonal conflicts
- depressed mood, hopelessness, or self-deprecating thoughts
- anxiety or tension, feeling "keyed up" or "on edge."

The behavioral/cognitive symptoms are:

- decreased interest in usual activities (eg, work, hobbies, friends, school)
- difficulty concentrating
- lethargy, low energy, easy fatigability
- change in appetite, overeating, food cravings
- hypersomnia or insomnia
- feeling overwhelmed or out of control
- physical symptoms (breast tenderness or swelling, headache, joint or muscle pain, bloating, weight gain).

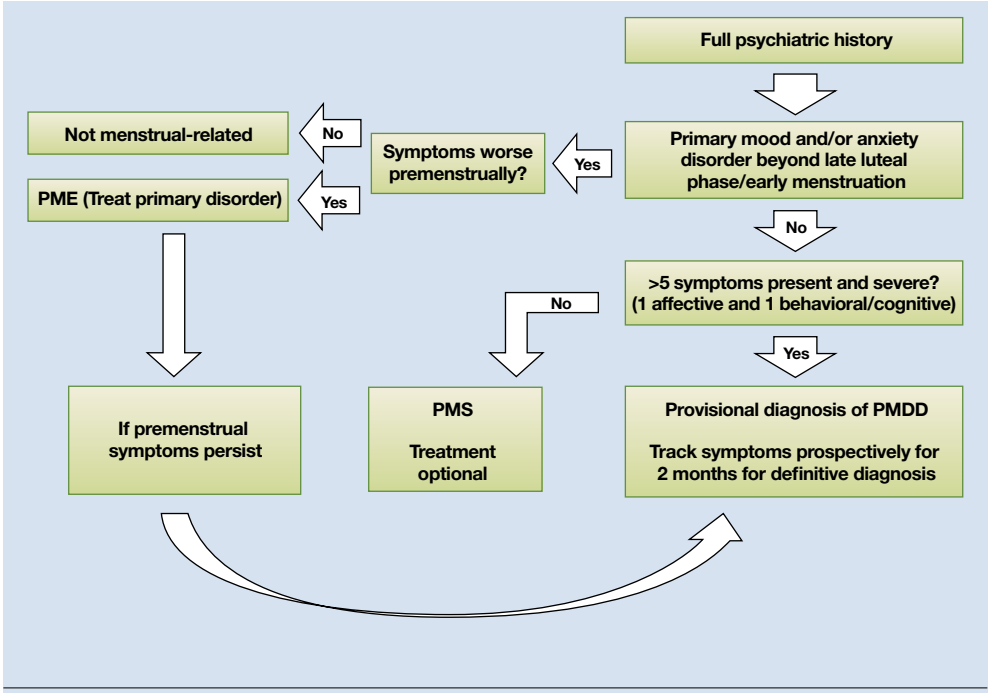
Ruling out premenstrual exacerbation (PME). Perhaps the most common cause for misdiagnosis of PMDD is failing to rule out PME of another underlying or comorbid condition (***Figure 2, page 23***). In many women who have a primary mood or anxiety disorder, the late luteal phase is a vulnerable time. A patient might be coping with untreated anxiety, for example, but the symptoms become unbearable the week before menstruation begins, which is likely when she seeks help. At this stage, a diagnosis of PMDD should be provisional at best. Often, PME is treated by treating the underlying condition. Therefore, a full diagnostic psychiatric interview is important to first rule out other underlying psychiatric disorders. PMDD is diagnosed if the premenstrual symptoms persist for 2 consecutive months after treating the suspected mood or anxiety disorder. Patients can use one of many PMDD daily symptom charts available online. Alternatively, they can use a cycle-tracking mobile phone application to correlate their symptoms with their cycle and share this information with their providers.

Consider these 5 interwoven pieces

The many variables that contribute to the pathophysiology of PMDD overlap and

Figure 2

Flow chart for the diagnosis of PMDD vs PMS or PME



PMDD: premenstrual dysphoric disorder; PME: premenstrual exacerbation of an underlying condition; PMS: premenstrual syndrome

should be considered connecting pieces in the puzzle that is the etiology of this disorder (***Figure 3, page 24***). In reviewing the literature, we have identified 5 topics likely to be major contributors to this disorder:

1. genetic susceptibility
2. progesterone and allopregnanolone (ALLO)
3. estrogen, serotonin, and brain-derived neurotrophic factor (BDNF)
4. putative brain structural and functional differences
5. further involvement of the hypothalamic–pituitary–adrenal (HPA) axis and hypothalamic–pituitary–gonadal (HPG) axis: trauma, resiliency, and inflammation.

Genetic susceptibility. PMDD is thought to have a heritability range between 30% to 80%.[3] This is demonstrated by family and twin studies[4-7] and specific genetic studies.[8] The involvement of genetics means an underlying neurobiologic pathophysiology is in place.

Estrogen receptor alpha (ESR1) gene. Huo et al[8] found an associated variation in ESR1 in women with PMDD compared with controls. They speculated that because ESR1 is important for arousal, if dysfunctional, this gene could be implicated in somatic as well as affective and cognitive deficits in PMDD patients. In another study, investigators reported a relationship between PMDD and heritable personality traits, as well as a link between these traits and ESR1 polymorphic variants.[1] They suggested that personality traits (independent of affective state) might be used to distinguish patients with PMDD from controls.[1]

Studies on serotonin gene polymorphism and serotonin transporter genotype. Although a study of serotonin gene polymorphism did not find an association between serotonin1A gene polymorphism and PMDD, it did show that the presence of at least 1 C allele was associated with a 2.5-fold increased risk of PMDD.[9] Another study did not find an association between the serotonin transporter genotype 5-HTTLPR and PMDD.[10] However, it showed lower frontocingulate cortex activation during the luteal phase of PMDD patients compared with controls,

Clinical Point

The involvement of genetics means an underlying neurobiologic pathophysiology is in place

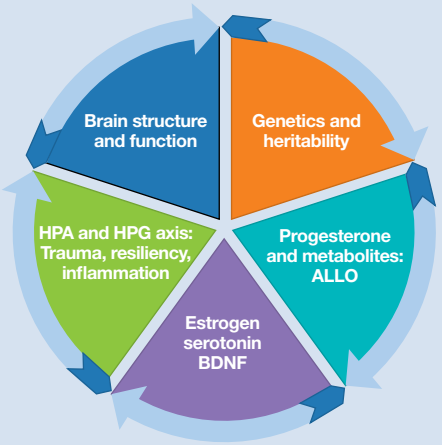
Etiology of PMDD

Clinical Point

Patients with PMDD have been reported to have decreased levels of ALLO in the luteal phase

Figure 3

The 5 interwoven pieces of the PMDD puzzle



The 5 topics likely to be major contributors to the etiology of PMDD disorder are: (1) genetic susceptibility; (2) progesterone and ALLO; (3) estrogen, serotonin, and BDNF; (4) putative brain structural and functional differences; and (5) involvement of the HPA and HPG axis. Each of the 5 factors is influenced by the other 4, either directly or indirectly, as it contributes to the pathophysiology of PMDD.

ALLO: allopregnanolone; BDNF: brain-derived neurotrophic factor; HPA: hypothalamic–pituitary–adrenal; HPG: hypothalamic–pituitary–gonadal; PMDD: premenstrual dysphoric disorder

suggesting that PMDD is linked to impaired frontocingulate cortex activation induced by emotions during the luteal phase.[10]

Seasonal affective disorder (SAD) and PMDD have shared clinical features. A polymorphism in the serotonin transporter promoter gene 5-HTTLPR has been associated with SAD. One study found that patients with comorbid SAD and PMDD are genetically more vulnerable to comorbid affective disorders compared with patients who have SAD only.[11]

Progesterone and ALLO. Chronic exposure to progesterone and ALLO (a main progesterone metabolite) and rapid withdrawal from ovarian hormones may play a role in the etiology of PMDD. Much like alcohol or benzodiazepines, ALLO is a potent positive allosteric modulator of $GABA_A$ receptors and has sedative, anesthetic, and anxiolytic properties. In times of acute stress, increased ALLO is known to provide relief.[12,13] However, in women with PMDD, this typical ALLO increase might not occur.[14]

Patients with PMDD have been reported to have decreased levels of ALLO in the luteal phase.[15-17] In one study, women with highly symptomatic PMDD had lower levels of ALLO compared with women with less symptomatic PMDD.[14] A gonadotropin-releasing hormone challenge study showed the increase in ALLO response was less in PMDD patients compared with controls.[17] Luteal-phase ALLO concentrations are reported to be lower in women with premenstrual syndrome (PMS), a milder form of PMDD.[14,17]

The efficacy of selective serotonin reuptake inhibitors (SSRIs) for treating PMDD could be the result of the interaction of these medications with neuroactive steroids,[18] possibly because SSRIs enhance the sensitivity of $GABA_A$ receptors or promote the formation of more ALLO (***Figure 4, page 25***).[19-21]

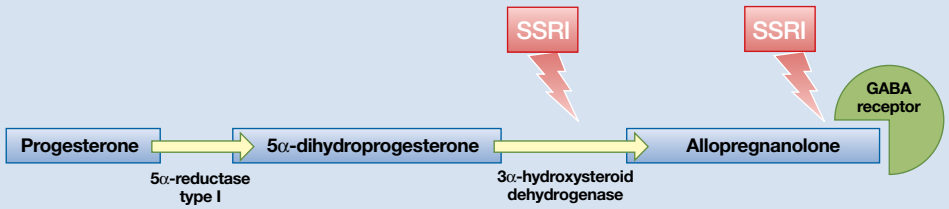
Estrogen, serotonin, and BDNF. Estrogen affects multiple neurotransmitter systems that regulate mood, cognition, sleep, and eating.[22] Studying estrogen in context of PMDD is important because women with PMDD can have low mood, specific food cravings, and impaired cognitive function.

Estrogen–serotonin interactions are thought to be involved in hormone-related mood disorders such as perimenopausal depression and PMDD.[23,24] However, the nature of their relationship is not yet fully understood. Ovariectomized animals have shown estrogen-induced changes related to serotonin metabolism, binding, and transmission in the regions of the brain involved in regulation of affect and cognition. Research in menopausal women also has provided some support for this interaction.[24]

Positron emission tomography studies in humans have found increased cortical serotonin binding modulated by levels of estrogen, similar to those previously seen in rat studies.[24-27] One study showed an increased binding potential of serotonin in the cerebral cortex with estrogen treatment. This study further showed an even greater binding potential with estrogen plus progesterone, signaling a synergistic effect of the 2 hormones.[28]

Figure 4

Conversion of progesterone to ALLO and the SSRI influence



SSRIs enhance the sensitivity of $GABA_A$ receptors or promote the formation of more ALLO as shown here. This is one possible mechanism by which they could be helping to alleviate PMDD symptoms.

ALLO: allopregnanolone; GABA: γ-aminobutyric acid; PMDD: premenstrual dysphoric disorder; SSRI: selective serotonin reuptake inhibitor

SSRIs are an effective treatment for the irritability, anxiety, and mood swings of PMDD.[29-30] Although the exact mechanism of action is unknown, the serotonergic properties are certainly of primary attention. For some PMDD patients, SSRIs work within hours to days, as opposed to days or weeks for patients with depression or anxiety, which suggests a separate or co-occurring mechanism of action is in place. In a double-blind, placebo-controlled crossover study, researchers administered the serotonin receptor antagonist metergoline to women with PMDD whose symptoms had remitted during treatment with fluoxetine and a group of healthy controls who were not receiving any medication.[31] The women with PMDD experienced a return of symptoms 24 hours after treatment with metergoline but not with placebo; the controls experienced no mood changes.[31]

BDNF is a neurotransmitter linked to estrogen and likely related to PMDD. BDNF is critical for neurogenesis and is expressed in brain regions involved in learning and memory and also affects regulation.[32] BDNF levels are increased by serotonergic antidepressants, affected by estradiol, and have cyclicity throughout the menstrual cycle.[33-35]

Putative brain structural and functional differences. Imaging studies have suggested differences in brain structure in women with PMDD, with a focus on the amygdala and the prefrontal cortex. Women with PMDD have greater gray matter volume in the posterior cerebellum,[36] greater gray matter density of hippocampal cortex, and lower gray matter density in the parahippocampal cortex.[37]

Some studies have shown a functional variability of the amygdala's response to stress in women with PMDD vs healthy controls.[38,39] A proton magnetic resonance spectroscopy (1H-MRS) study of the displays the possibility of an altered GABAergic function in patients with PMDD.[40]

Patients will PMDD have enhanced dorsolateral prefrontal cortex reactivity when anticipating negative stimuli (but not to the actual exposure) during the luteal phase. A positive correlation between this reactivity and progesterone levels also was observed.[41] Some researchers have suggested that prefrontal cortex dysfunction may be a risk factor for PMDD.[42]

HPA axis and HPG axis: Trauma, resiliency, inflammation. Altered cortisol levels (higher during the luteal phase[43] and lower during times of stress[14,44]) suggest a possibly altered HPA axis in some women with PMDD. However, studies on this topic have been few and inconsistent.

Dysregulation of the HPG axis could cause vasomotor symptoms, sleep dysregulation, and mood symptoms during menopause; women with PMDD can also experience these symptoms. The influence

Clinical Point

Prefrontal cortex dysfunction may be a risk factor for PMDD

Etiology of PMDD

Clinical Point

One study found increased levels of proinflammatory markers in women with PMDD compared with controls

of estrogen and progesterone on mood is also highly dependent on this axis.

Ultimately, the interplay between the HPA axis and the HPG axis is important. One study found that women with PMDD who had high serum ALLO levels (HPG-related) had blunted nocturnal cortisol levels (HPA-related) compared with healthy controls who had low ALLO levels.[45]

Significant stress and trauma exposure have been associated with PMDD. A study of 3,968 women found a history of trauma and PTSD were independently associated with PMDD.[46] Another study of approximately 3,000 women found a strong correlation between abuse and PMS.[47] However, a third study found no correlations between PMDD and trauma.[48]

Patients with a predisposition to PMDD may be more vulnerable to develop a posttraumatic stress-related disorder, perhaps due to decreased biologic resiliency. For example, the startle response (hypervigilance) has been shown to be different in women with PMDD. One study suggested that suboptimal production of premenstrual ALLO may lead to increased arousal and increased stress reactivity to psychosocial or environmental triggers.[49]

The possible role of inflammation in PMDD deserves further investigation. The luteal phase entails an increase in the production of proinflammatory markers.[50,51] A 10-fold increase in progesterone is correlated with a 20% to 23% increase in C-reactive protein levels.[52,53] Women with inflammatory diseases (eg, gingivitis or irritable bowel syndrome) show worsening of symptoms prior to menstruation.[54-56] One study found increased levels of proinflammatory markers in women with PMDD compared with controls.[57]

Putting together the 5 pieces of the puzzle

Because PMDD is heritable, it must have an underlying neurobiologic pathophysiology. Brain imaging studies show differences in structure and function in women with PMDD across the menstrual cycle. Conversion of progesterone to ALLO and the GABAergic influence of this metabolite is a topic of interest in current research. Similarly, the role of estrogen and its connection to serotonin and other neurotransmitters such as BDNF have been implicated.

The link between a history of stress, trauma, and PMDD raises the question of biologic resiliency and illness in these patients, as it connects to the HPA and HPG axis and production of inflammatory stress hormones and steroid hormones and their metabolites. PMDD can be conceptualized as variable sensitivity to hormonal response to stress,[58] thus contextualizing biochemical and psychological resiliency.

Further research is needed to clarify the possibility of a shared pathophysiology between endocrine-related mood disorders such as postpartum depression (PPD) and PMDD because current research is controversial.[59,60] In PPD, women who are exposed to high levels of progesterone and estrogen during pregnancy (just like in the mid-luteal phase) have a sudden drop in these hormones postpartum.

The 'withdrawal theory.' The affective symptoms of PMDD resolve almost instantaneously after the start of menstruation. Perhaps this type of immediate relief is akin to substance use disorders and symptoms of withdrawal. It could be that reinstatement of a certain amount of gonadal steroids in the follicular phase of the cycle diminishes a withdrawal-like response to these steroids.

Currently, the main leading theory is that PMDD is a result of "an abnormal response to normal hormonal changes."[61] A new study also has shown that the change in estradiol/progesterone levels (vs the steady state) was associated with PMDD symptoms.[62] Thinking of PMDD as a disorder of withdrawal offers an alternative (yet complementary) perspective to the current theory: PMDD may be caused by the absence or diminishing of the above-named hormones and their metabolites in the late luteal phase (in the context of developed "tolerance" during the early- to mid-luteal phase).

Considering the interplay between neurotransmitters and neurosteroids, both a "serotonin withdrawal theory" (caused by a drop in steroid hormones) and a "GABAergic withdrawal theory" (due to

the decline in progesterone) could be proposed. This theory would be supported by the fact that SSRIs seem to mitigate symptoms of PMDD as well as the genetic association between PMDD and ESR1. It is more than likely that the "withdrawal" is caused by the interactions between estrogen-serotonin, progesterone-ALLO, and GABA receptors, and the complementary fashion in which progesterone and estrogen influence each other.

Related Resources

- Lanza di Scalea T, Pearlstein T. Premenstrual dysphoric disorder. Psychiatr Clin North Am. 2017;40(2):201-216.
- Massachusetts General Hospital Center for Women's Mental Health. http://www.womensmentalhealth.org.

Drug Brand Name

Fluoxetine • Prozac

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Clinical Point

The link between a history of stress, trauma, and PMDD raises the question of biologic resiliency and illness in these patients

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continued

Bottom Line

A systematic approach to the diagnosis of PMDD is essential and should include ruling out premenstrual exacerbation of another underlying or comorbid mood or anxiety disorder. The etiology of PMDD is complex. PMDD may be a disorder of withdrawal caused by a transient decline in neurosteroids.

Etiology of PMDD

Clinical Point

PMDD may be caused by the absence or diminishing of hormones and their metabolites in the late luteal phase

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