THE CYCLIC BRAIN: A SYSTEMIC REVIEW OF PREMENSTRUAL DYSPHORIC DISORDER

EL CEREBRO CÍCLICO: UNA REVISIÓN SISTÉMICA DEL TRASTORNO DISFÓRICO PREMENSTRUAL

Lizzete Jazmín Lovera Mendoza. lizzete1@live.com. National Autonomous University of Mexico. ORCID: https://orcid.org/0009-0009-8406-5541
Gabriela Orozco Calderón. gabrielaorocal@gmail.com. National Autonomous University of Mexico. ORCID: https://orcid.org/0000-0002-4978-1667

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ABSTRACT

About 3-8% of all women of reproductive age suffer from premenstrual dysphoric disorder (PMDD), which prevents them from living a normal life during the luteal phase (premenstrual phase) of the menstrual cycle. Throughout the premenstrual phase, women may experience emotional, cognitive and physiological changes. However, premenstrual dysphoric disorder represents one of the most severe versions of premenstrual syndrome (PMS), referring to the intensity of emotional and physical symptoms that occur during the luteal phase. More research and understanding is necessary in order to find the right treatment. This work is aimed to provide a review of the most significant research around this topic, highlighting the brain and cognitive implications that many women report during the last phase of the menstrual cycle, specifically in processes such as working memory, anticipation, decision making and inhibitory control that so far are the most reported in literature.

KEYWORDS: premenstrual syndrome; menstrual cycle; cognition; neuroendocrine; hormonal fluctuations

RESUMEN

Alrededor del 3-8 % de todas las mujeres en edad reproductiva sufren de trastorno disfórico premenstrual (TDPM), que les impide vivir una vida normal durante la fase lútea (fase premenstrual) del ciclo menstrual. A lo largo de la fase premenstrual las mujeres pueden experimentar cambios emocionales, cognitivos y fisiológicos. Sin embargo, el trastorno disfórico premenstrual representa una de las versiones más graves del síndrome premenstrual (SPM), haciendo referencia a la intensidad de síntomas emocionales y físicos que se presentan durante la fase lútea. Para poder encontrar el tratamiento correcto, es necesario más investigación y comprensión de su causa; por lo que, en el presente trabajo se realizó una revisión de la investigación más significativa alrededor del tema, destacando las implicaciones cerebrales y cognitivas que muchas de las mujeres reportan durante la última fase del ciclo menstrual, específicamente en procesos como memoria de trabajo, anticipación, toma de decisiones y control inhibitorio que hasta ahora son los más reportados por la literatura.

PALABRAS CLAVE: síndrome premenstrual; ciclo menstrual; cognición; neuroendocrino; fluctuaciones hormonales

INTRODUCTION

In the current highly competitive postmodern context, the diverse symptoms associated with the menstrual cycle can interfere with various aspects of life, diminishing the physical, cognitive, and emotional well-being of women and leading to reduced performance in multiple areas. Throughout the menstrual cycle, a significant number of women experience changes in their daily lifestyle (food consumption, sleep-wake cycle, sexual desire).

Researching the relationships between cognitive, emotional, and behavioral changes during the menstrual cycle allows for the connection of two phenomena: hormonal changes and the emotional and behavioral modifications that occur

during this period. In some women, premenstrual syndrome intensifies and focuses more on affective changes, being identified as premenstrual dysphoric disorder (PMDD). However, it was not until 2017 that the World Health Organization included PMDD in its list of disorders (International Classification of Diseases, 2017). Although clinical research has been conducted since the 1990s, it was only in that year that it was characterized as a biological entity.

Nearly 25% of all women of reproductive age are affected by premenstrual syndrome (PMS) (Bäckström *et al*., 2014), and approximately 3-8% by premenstrual dysphoric disorder. It is currently estimated that affected women live 3000 days of their lives with symptoms that impact their daily lives (Lin *et al*., 2022), equating to about 8.21 years experiencing mood swings, anxiety, depression, and/or cognitive dysfunction that could be alleviated with the correct treatment.

In Mexico, the exact prevalence remains unknown, but some authors and Latin American studies suggest that the proportion of women suffering from PMDD in Latin America may exceed 12% (Ceballos, 2019).

To find the correct treatment, more research and understanding of its cause is necessary. Therefore, the objective of this work is to provide a review of the most significant research on the topic, highlighting the cerebral and cognitive implications.

DEVELOPMENT

The menstrual cycle is a fundamental part of the female reproductive system, with an approximate duration of 28 days. It is characterized by a recurrent pattern of varying hormone levels; ovarian hormone production is regulated by the hypothalamus and pituitary gland, which are also influenced by the cerebral cortex and the limbic system.

Hormones involved in the feedback system regulating the menstrual cycle include: sex steroids (estrogens and progesterone), pituitary gonadotropins (follicle-stimulating hormone - FSH - and luteinizing hormone - LH), and the hypothalamic gonadotropin-releasing hormone (GnRH) (Zanin *et al*., 2011; Wiklund, 2017). The biological objective of the menstrual cycle is cyclical changes in the ovary and uterus, thereby establishing two parallel cycles: the ovarian cycle and the uterine cycle.

Ovarian cycle

This is primarily related to the maturation and release of the mature oocyte from the ovaries. The ovaries play a primordial role in the production and secretion of steroid hormones such as estrogen and progesterone, which are involved in the regulation of follicle-stimulating hormone (FSH), whose function is to stimulate the growth of oocytes (Martini *et al*., 2012).

During childhood, immature oocytes exist; when puberty begins, FSH promotes the growth of 6 to 12 follicles during the first days after the onset of menstruation. From this stage until menopause, maturation will be regulated by the menstrual cycle (de Pediatría & Subcomisiones, 2010; Zanin *et al*., 2011; Dorador-González & Orozco-Calderón, 2021).

The ovarian cycle can be divided into two phases: the follicular phase (pre-ovulatory), which spans from the first day of the cycle with the onset of bleeding until ovulation; and the luteal phase (post-ovulatory), from ovulation until the first day of the following bleeding (Zanin *et al*., 2011).

Uterine cycle

Parallel to the ovarian cycle, it is also termed the menstrual cycle due to the changes in the uterine lining during the cycle that concludes with menstrual flow. The uterus is a small organ within the female reproductive system. The uterine wall consists of three layers: the outermost layer, the perimetrium; the middle

layer, the myometrium; and the inner layer, the endometrium. The uterine cycle can be divided into three phases; it begins with menstruation, continues with the proliferative phase, and ends with the secretory phase (Martini *et al*., 2012).

Disorders associated with the menstrual cycle

Generally, the physical and mental symptoms presented in most women during their reproductive age are associated with the premenstrual period. However, if these symptoms do not significantly affect daily life, they are not considered a pathological entity (Farage *et al*., 2008).

Symptoms include affective changes, such as depression, irritability, mood swings, anxiety, hopelessness, tension, or restlessness; other notable symptoms include behavioral changes and pain, social isolation, sleep problems, breast tenderness, headaches, skin problems like acne, abdominal pain, constipation, or diarrhea (Zanin *et al*., 2010).

This condition related to the menstrual cycle has been termed PMS; approximately 50% of women experience it at least once in their lifetime, with the highest incidence between 24 and 40 years old (Dubol *et al*., 2020).

According to the American Congress of Obstetricians and Gynecologists (ACOG, 2001), PMS is defined as the cyclical appearance of symptoms that are severe enough to interfere with some aspects of life and that appear with a constant and predictable relationship to menstruation.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5, 2013) specifies that PMS necessarily includes affective symptoms, but behavioral and physical symptoms may also be present, unlike the diagnosis included in PMDD, which will be discussed later.

Premenstrual symptoms generally present during the late follicular phase at the highest level of LH with high serum estrogen levels (one day before ovulation)

and then continue throughout the luteal phase. These symptoms particularly present during the last part of the phase where estrogen and progesterone levels are high (Farage *et al*., 2008; Wiklund, 2017).

Premenstrual dysphoric disorder (PMDD)

PMDD is considered by some authors to be an exacerbation of PMS, with the main difference between the two being the severity of the symptoms experienced, and PMDD includes more affective symptomatology.

PMDD has an estimated prevalence of 3 to 8% of all women of reproductive age (Lin *et al*., 2022) and is labeled as a psycho-neuroendocrine disorder, clinically characterized by the presence of depressed mood, irritability, affective lability, and anxiety during the last week of the luteal phase; affective symptoms increase two days before menstruation and disappear after it ends. These symptoms disrupt women's lives at the family, social, and occupational levels due to their severity (Aperribai *et al*., 2016).

The fifth edition of the DSM includes PMDD as a mental disorder, adding diagnostic criteria which include: symptoms such as mood swings, irritability or anger, increased depressed mood, increased anxiety or tension, as well as diminished interest in social activities, concentration difficulties, lack of energy, appetite changes, sleep problems, decreased sense of control, and physical symptoms (American Psychiatric Association, 2013).

The disorder is observed worldwide and therefore cannot be explained as a culture-bound disorder. However, attitudes toward the disorder are influenced by cultural factors, such as the number of affected women who actually seek help, and the frequency and intensity of symptoms can be affected by cultural and environmental factors (American Psychiatric Association, 2013).

Currently, PMDD is not fully understood and is often underdiagnosed. Over recent years, possible hypotheses for its cause have been investigated, including

dysregulation of cortisol, withdrawal of opioid endorphins, and dysregulated responses to stress (Kiesner & Granger, 2016). However, the most controversial area to date is the implication of progesterone and estrogens, because the onset of symptoms only occurs during healthy menstrual cycles that include ovulation or with exogenous administration of progesterone (Bannbers *et al*., 2011), with an absence of symptoms during anovulatory cycles (Gingnell *et al*., 2013).

One hypothesis currently under study concerns the relationship between the neurotransmitter GABA and PMDD. Interest has focused on GABA concentration targeting the prefrontal cortex, hippocampus, and thalamus, structures related to emotional and hormonal regulation, learning and memory, eating disorders, or cognitive control. Therefore, it has been considered that GABA is related to the elevated symptoms of PMDD, as progesterone has a binding site on the GABA A receptor (Bäckström *et al*., 2014).

Cerebral implications

The most robust findings relate to the functional reactivity of the brain during the processing of emotional stimuli, which increases in the amygdala and insula and is reduced in the anterior cingulate cortex (ACC) of women with PMDD during the symptomatic late luteal phase of the menstrual cycle (Comasco *et al*., 2014; Gingnell et al., 2014; Protopopescu *et al*., 2008).

These results are relevant, as the ACC shows strong anatomical and functional connectivity with the amygdala and is anatomically interconnected with a variety of brain regions including the insula, thalamus, hippocampus, ventral striatum, and prefrontal region. Furthermore, these regions constitute a specific network for mood regulation (Davey *et al*., 2015) and are integrated into a recent model of the emotional brain (Pessoa, 2017; Dubol *et al*., 2020).

Previous research implicates dysfunctional regulatory activity of the medial prefrontal cortex (mPFC) and ACC in anxiety and depression (Etkin & Schatzberg, 2011), symptoms experienced by women with PMDD.

On the other hand, differential activations in both the dorsolateral prefrontal cortex (DLPFC) and the ventromedial prefrontal cortex (VMPFC) during emotional tasks seem to characterize the brain of women with PMDD, although the direction of the effects is less consistent. Reduced DLPFC reactivity during an emotion regulation task has been found in women with PMDD compared to controls, along with a negative correlation between symptom severity and DLPFC activations during the late luteal phase (Petersen *et al*., 2018).

Likewise, another functional magnetic resonance imaging (fMRI) study found lower VMPFC reactivity during the processing of negative facial expressions in women with PMDD compared to controls, which was independent of the menstrual phase (Comasco *et al*., 2014).

Another key region of the limbic system is the accumbens nucleus. A reduced response to positive words has been observed in women with PMDD compared to controls during the late luteal phase (Protopopescu *et al*., 2008), which would contribute to diminished processing of positive emotions. The accumbens nucleus is known to be involved in the processing of rewarding stimuli and motivation.

Depressed patients have been shown to fail to activate the ventral striatum, including the nucleus accumbens, when responding to positive stimuli (Epstein *et al*., 2006; Tremblay *et al*., 2005). Therefore, it is possible that a reduced response to positive words in this region is involved in the affective symptoms of PMDD, such as depressed mood and loss of interest in usual activities.

Ko *et al*. (2014) reported that women with PMDD show higher reward sensitivity compared to healthy women, and that reward sensitivity scores correlated with the severity of PMDD symptoms during the late luteal phase.

Women with PMDD present greater sensitivity to food reward and are more likely to have positive emotional and craving responses to sweet, high-fat foods compared to controls (Yen *et al*., 2010; Yen *et al*., 2018). Furthermore, irritability and impulsivity have been associated with the desire for a very sweet diet in women with PMDD, further suggesting an association between the reward system and the psychopathology of PMDD.

Other structures that have been studied include the cerebellum. Reduced cerebellar reactivity to negative emotional stimuli has been demonstrated in women with PMDD compared to healthy controls using fMRI with a facial expression matching task (Comasco *et al*., 2014).

In women with PMDD, the increase in cerebellar metabolism from the mid-follicular phase to the late luteal phase has been positively correlated with the change in scores on the «Daily Record of Severity of Problems» scale between these phases (Rapkin *et al*., 2011). Therefore, patterns of cerebellar dysfunction appear to be associated with emotion and cognition related processes in PMDD.

Although the cerebellum has long been thought to participate exclusively in motor functions, deep brain stimulation experiments and lesion studies have demonstrated its influence on emotional and cognitive regulation, suggesting an important role for this region in psychiatric disorders.

Specifically, the posterior midline vermis and the fastigial nucleus have been conceptualized as the «limbic cerebellum», as vermis abnormalities have been associated with emotional disturbances and inappropriate behaviors (Schmahmann, Oblak & Blatt, 2021), because the cerebellum is closely interconnected with limbic and paralimbic structures, including the midbrain,

amygdala, hippocampus, hypothalamus, ACC, prefrontal cortex, and parahippocampus (Shakiba, 2014). In addition to what has been reported, increased grey matter volume in the emotional cerebellum has been observed compared to controls, further supporting the involvement of the cerebellum in the pathophysiology of PMDD.

It has been hypothesized that increased cerebellar functioning in PMDD would reflect an altered prefrontal-cerebellar feedback circuit regulating emotional and cognitive processing (Rapkin *et al*., 2011).

Therefore, while the findings included in this review point to functional and structural alterations of the cerebellum associated with PMDD, differences in the functional paradigms and imaging techniques applied prevent conclusions about the direction and specificity of the effects of these cerebellar networks and their involvement in PMDD symptomatology.

Cognition in premenstrual dysphoric disorder

Steroid hormones such as estrogen and progesterone deal a very important role in memory and learning. In parallel, the limbic system has a great influence on reproductive functioning and neuroendocrine homeostasis, as well as memory storage and retrieval, emotional processing, and decision-making (Wiklund, 2017). In this sense, research indicates that these structures are involved in the cyclical fluctuating behaviors of menstruation, thus causing changes in its different phases (Catenaccio *et al*., 2016).

As it is said, women during the premenstrual phase experience emotional and physical symptoms. However, cognitive symptoms are also very common, such as difficulties in the sensation and perception of some senses, like hypersensitivity to smell, sound, and light. Additionally, difficulties in memory, concentration, and disorganized thinking that project into language difficulties (Wiklund, 2017; Yen *et al*., 2023), with the luteal phase being the most evident.

Research in this area has found changes across the menstrual cycle in different processes, for instance: smell, vision, perception, memory, executive functions, or visual-spatial skills, to name a few.

Regarding PMDD, significant changes have been found mainly in processes such as anticipation, working memory, cognitive control, and inhibitory control. In anticipation, it has been observed that during the luteal phase in women with PMDD, there is a drastic change. Dreher *et al*. (2007) were interested in studying the relationship with changes in cognitive functioning during the menstrual cycle, especially in a random reward anticipation; it was studied in women during both phases of the menstrual cycle using fMRI and a task involving monetary reward.

The results indicated greater activation during reward anticipation in the follicular phase, with increased activation observed in the orbitofrontal cortex, amygdala, middle frontal convolution, medial orbital sulcus, and the previous prefrontal cortex. It was concluded that the reward system is more activated during both the anticipation and receipt of reward in the follicular phase compared to the luteal phase. Thus, in healthy women, greater activation for reward anticipation would be expected during the follicular phase. However, a deterioration has been found in in women with PMDD for anticipating emotions.

In a study conducted by Bannbers et al. (2011), the acoustic startle response was analyzed in patients with PMDD. The results showed an increased anticipation of both positive and negative stimuli during the luteal phase, implying that the capacity to respond to emotional stimuli was heightened and more sensitive during this phase.

Gingnell *et al*., (2013) researched the relationship between emotional anticipation, actual emotional stimulation, and PMDD using emotionally charged images. Brain scans were performed using fMRI during the mid-follicular and late luteal phases in 14 women with PMDD and 14 control women. The results indicated differences in women with PMDD compared to controls regarding the

anticipation of emotional stimuli, but not in the actual emotional response. This response was observed as activation in the previous medial prefrontal cortex, as well as in the DLPFC (dorsolateral prefrontal cortex) during the luteal phase when exposed to negative stimuli. However, this activation was only observed in relation to the anticipation of negative emotion and not to the actual negative stimuli. This suggests that women with PMDD might experience elevated activation in response to stimuli they believe are negative.

It has been postulated that the previous prefrontal cortex is involved in regulating the nervous system, particularly in fear-inducing situations. Therefore, the activation of the previous prefrontal cortex and the anticipation of negative stimuli could describe a relationship between recurrent symptoms of rumination and a greater propensity for anxiety in women with PMDD (Gingnell *et al*., 2013).

Another extensively studied process is working memory. A decrement in this process has been observed in women with PMDD during the luteal phase compared to control women (Reed *et al*., 2008; Yen *et al*., 2012). The impairment in working memory observed in women with PMDD during the luteal phase, in turn, implies difficulties in the ability to use functions, such as problem-solving or organizational capacity.

Consequently, this could be related to the difficulties in concentration experienced by women with PMDD during this phase of the menstrual cycle (Lin *et al*., 2022; Yen *et al*., 2023).

Other studies have detected that in working memory tasks, women with PMDD and women with moderate premenstrual symptomatology had difficulties in working memory tasks from the follicular phase, exacerbating in the luteal phase, as they omitted stimuli and their responses were slower to task demands (Slyepchenko *et al*., 2017).

Cognitive control and inhibition are part of the processes known as «executive functions», which allow us to make decisions to select an appropriate response and behavior for certain situations.

Women with PMDD try to experience difficulties with impulse inhibition during the late luteal phase of the menstrual cycle, thus experiencing a reduced capacity for cognitive control.

In recent studies, such as the one conducted by Lin *et al*., (2022), women with PMDD made more mistakes in Stroop tasks due to stimuli interference during the late luteal phase.

Similarly, it has been shown there are inhibition difficulties during the early luteal phase, which is attributed to increased activation of the insula, a region correlated with inhibition.

On the other hand, it has also been stated that in women with PMDD, there is a preference for deliberation and impulsivity caused by irritability, suggesting that cognitive control would depend on these processes for daily functioning, making mood a determining factor in cognitive performance.

Other processes that have been studied, but remain under debate, include attention, memory, visuospatial skills, psychomotor function, and learning. In spite of this, what is clear is that these cognitive difficulties are only reflected during the luteal phase and improve once it ends.

Furthermore, cognition is primarily permeated by the drastic emotional changes during this phase, which would affect performance, with impulsivity being the most prevalent in women with PMDD (Yen *et al*., 2023).

CONCLUSIONS

Studies indicate that ovarian hormones can affect the women´s brain structure throughout their lives. Therefore, early morphological differences that distinguish the PMDD brain and the maladaptive structural changes existing due to hormonal fluctuations during the late luteal phase could be involved in the pathophysiology of this disorder. Cortico-limbic activation in response to emotional stimuli could be a distinction of the PMDD brain, namely, amygdala hyperactivity and front cortical hypoactivity. Neuronal differences in these regions could explain the symptomatology of PMDD, as most of them play important roles in emotional and behavioral regulation, as well as in cognitive processing. However, evidence is still scarce to propose a consistent model of the processes underlying PMDD. Therefore, it is essential to continue conducting such studies in the future, from a cyclical understanding perspective in the population of interest, to provide timely healthcare.

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