



Menstrual Cycle in Trauma-Related Disorders: A Mini-Review

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Fluctuations of sex hormones across the menstrual cycle have been linked to exacerbation of symptoms of psychiatric disorders. Women diagnosed with trauma-related disorders such as post-traumatic stress disorder (PTSD) and borderline personality disorder (BPD) have reported worsening of mood symptoms at various phases of their menstrual cycle. There is also considerable overlap between PTSD, BPD, and complex-PTSD (cPTSD) symptoms, suggesting similar biological underpinnings. This mini-review examines the influence of sex hormones and the menstrual cycle on PTSD, BPD, and cPTSD symptoms, and discusses the involvement of the hypothalamic-pituitary-adrenal (HPA) axis. We review literature showing that PTSD and BPD symptoms fluctuate with the menstrual cycle, though the effect of the menstrual cycle phase appears to be inconsistent, warranting future research. Based on the reported phasic vulnerability in individuals with PTSD and BPD, it is plausible to assume that women diagnosed with the newly introduced cPTSD may experience similar difficulties. However, no study to date has addressed this. This review highlights the importance of considering an individual's trauma history as it may influence symptom severity and diagnosis, and the phase of the menstrual cycle at the time of diagnosis. This review also highlights that additional work is needed to clarify the influence of estradiol and progesterone fluctuations on trauma-related symptoms, especially in cPTSD. Continued research on menstrual cycle vulnerability and trauma will lead to better informed management and treatment of PTSD, BPD, and cPTSD.

Keywords: PTSD, BPD, CPTSD, trauma, estradiol, progesterone

It is well-documented that the cyclical rise and fall of sex hormones across the menstrual cycle impacts symptoms of psychiatric disorders. The menstrual cycle typically lasts 23–35 days with four stages (1); menstruation, the follicular phase, ovulation, and the luteal phase. The menstrual cycle is characterized by fluctuations in gonadal hormones estrogen (in the form of estradiol) and progesterone in the central nervous system (CNS) that are driven by changes in the brain gonadotropin levels. Menstruation signifies the start of the menstrual cycle, and is when estradiol and progesterone are at their lowest. Menstruation lasts ~5 days, and is followed by the follicular phase. During this phase, estradiol increases to trigger the release of follicle stimulating hormone (FSH), which stimulates follicle (egg) development. The increase in estradiol also stimulates growth of the endometrium (uterus lining). Estradiol continues to rise to a peak, triggering increased production of luteinizing hormone (LH). The rapid surge in LH causes the release of the egg, known as ovulation. At this point, there is a rapid drop in estradiol. Finally, there is the luteal phase, where there is an increase in progesterone and estradiol to support early pregnancy. If there is no egg

fertilization, progesterone and estradiol decrease; this decline causes premenstrual symptoms and triggers the onset of menses.

Healthy women have reported increased mental health symptoms related to depression and anxiety during the late luteal and early follicular phases (2). Menstrual cycle-related mood fluctuations have also been observed across a number of mental health disorders (3). Emerging studies suggest that menstrual cycle effects are evident in individuals with trauma-related disorders such as post-traumatic stress disorder (PTSD) (4, 5) and borderline personality disorder (BPD) (6, 7). In particular, childhood traumas including physical, sexual, and emotional abuse/and or neglect are very common in PTSD and BPD (8–10). It is estimated that 15 to 82.5% of individuals with PTSD have experienced childhood trauma (11–13), and 58 to 91% for individuals with BPD (14–16).

Both PTSD and BPD are more common in women (17–19), suggesting that ovarian steroid hormones estradiol and progesterone influence the expression of PTSD/BPD symptoms (20). In fact, the hormonal changes that occur across the menstrual cycle could biologically explain the fluctuation of symptoms observed in women with PTSD and BPD (5, 6, 21). This idea is strengthened with the known overlap in symptomatology (particularly anger and irritability) between PTSD (22, 23) and BPD (24, 25), and premenstrual dysphoric disorder (PMDD). PMDD is a diagnostic classification for women who have significant functional impairment caused by moderate to severe premenstrual symptoms (17). The overlap is said to be greater between the trauma-related disorders and PMDD than PMDD and major depressive disorder (24, 26). PMDD has also been shown to overlap in symptomatology with complex PTSD (cPTSD), another mental health disorder strongly associated with trauma exposure (27, 28). Furthermore, research indicates an overlap between PTSD, BPD and cPTSD (29).

This mini-review will now explore the influence of sex hormones and the menstrual cycle on PTSD, BPD, and cPTSD symptoms, and discuss potential underlying mechanisms.

POST-TRAUMATIC STRESS DISORDER (PTSD)

PTSD, recently re-classified as a trauma- and stressor-related disorder, is a psychiatric disorder that develops after exposure to a traumatic event. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria list four PTSD symptom sub-categories: intrusion, avoidance, negative alterations in cognitions and mood, and marked alterations in arousal and reactivity. Similarly, the International Classification of Diseases (ICD-11) lists three PTSD symptom clusters: re-experiencing of the trauma, avoidance of trauma reminders, and heightened sense of threat.

In the general population, there are higher rates of PTSD in women (10–12%) than in men (5–6%), with women being two to three times more likely to develop PTSD (30). In addition, women have also reported greater PTSD symptom severity (31) than men. The gender differences in both prevalence and

symptom severity suggest underlying sex-specific mechanisms influencing both the etiology and perpetuation of PTSD.

PTSD SYMPTOMS ACROSS THE MENSTRUAL CYCLE

Estradiol and progesterone levels at the time of trauma exposure have been suggested to contribute to the development of PTSD symptoms. For example, women with PTSD who experience trauma during the mid-luteal phase of their cycle have a greater number of flashbacks (32). Another study observed that women who refused emergency contraception following sexual assault had increased post-traumatic stress symptoms compared to those that took emergency contraception, or were already using hormonal contraceptives (33). While there are many severe psychological reactions following sexual assault, it is important to note that both emergency and standard contraception suppress progesterone and estradiol synthesis, and together with the findings of Bryant et al. (32), these suggest that low endogenous progesterone and/or estradiol has a protective effect in the etiology of PTSD, particularly in terms of preventing memory over-consolidation.

Not only do sex hormones during time of trauma exposure play a role in symptom presentation, but a recent review by Nillni et al. (5) observed that PTSD symptoms fluctuate alongside the menstrual cycle. For example, exacerbation of intrusive flashbacks appear to occur during the mid-luteal phase (when estradiol and progesterone are high), with women 4.89 times more likely to have flashbacks during this phase compared to other menstrual cycle phases (32).

Conversely, trauma-exposed women have higher PTSD symptoms during low-estradiol phases of their cycle (34). In a sample of trauma-exposed women with and without PTSD, an increase in overall psychological symptoms, as well as depression and phobic anxiety specifically, was observed in the early follicular menstrual cycle phase compared to mid-luteal phase (35). When the groups were explored separately, phobic anxiety again increased in the early follicular phase in women with PTSD, but not in women without PTSD.

An effective behavioral treatment for PTSD is exposure therapy, which involves controlled exposure to a situation or stimulus with the purpose of reducing anxiety and distress over time. Fear extinction (i.e., the decrease and cessation of a fear response through exposure therapy) appears to be influenced by estradiol levels, though findings in women with PTSD are inconsistent when exploring this by menstrual cycle phase. Greater extinction retention in females in high compared to low estradiol groups have been observed in animal studies (36) and in healthy women (37). Research suggests that estradiol levels modulate extinction memory in women with PTSD (38), though there have been inconsistencies when exploring the nature of this relationship. While Pineles et al. (39) observed poorer extinction retention during the mid-luteal phase (when there would be an increased in estradiol), other studies have reported heightened startle responses during fear conditioning in PTSD-diagnosed women with low estradiol (40). However, Glover et al. (40) did

not account for menstrual cycle phase at the time of blood sampling, which may explain the difference in findings.

Current literature indicates a phasic vulnerability in women with PTSD, with different symptoms exacerbated at different points of the menstrual cycle. It remains unclear as to whether high levels of estradiol and progesterone are protective or increase vulnerability in the maintenance of PTSD symptoms in women. It should be noted that some studies have observed stability in symptoms across the menstrual cycle, and no associations between estradiol and progesterone levels and anxiety sensitivity (41). Again, this highlights that estradiol and progesterone affects distinct trauma-related symptoms differently, warranting further research.

BORDERLINE PERSONALITY DISORDER (BPD)

Borderline personality disorder (BPD) is a chronic mental condition characterized by rapidly shifting emotional and behavioral symptoms, and difficulties maintaining stable interpersonal relationships. Common BPD features include low self-esteem, fear of abandonment, identity disturbances, impulsive behaviors, and maladaptive coping strategies (17). While BPD is not currently considered an exclusively post-traumatic phenomenon in the DSM-5, majority of individuals with BPD have experienced childhood physical (42, 43), sexual (42–44) or emotional (16, 45) abuse. The prevalence rates of early life trauma in BPD range from 58 to 91% (14, 16, 46), and 75% of people diagnosed with BPD are women (17).

BPD SYMPTOMS ACROSS THE MENSTRUAL CYCLE

BPD is characterized by impulsivity, and cyclical changes in ovarian hormones have been associated with several impulsive-related behaviors. Earlier studies have indicated a premenstrual increase in suicidal behavior (47, 48) and severity of suicide intent (49, 50), binge eating in patients with bulimia (51–53), and worsening of depressive symptoms (7, 24) in patients with BPD.

While women with BPD often report that affective and impulsive symptoms worsen premenstrually, empirical evidence has been inconsistent. An early small prospective study of women with BPD found no association between the phase of the menstrual cycle and affective and impulsivity (7). However, emerging work suggests potential menstrual cycle effects on BPD symptom exacerbation. Specifically, two studies revealed a link between cyclical menstrual changes and BPD-like features in non-clinical samples (6, 21). Two studies demonstrated menstrual cycle-related changes in BPD symptoms in unmedicated women with regular menstrual cycles in clinical samples (24, 54). Considering these four studies, it appears that individuals with BPD had a clear pattern of perimenstrual (i.e., late luteal phase to day 3 of menses) exacerbation, with symptoms of irritability and anger appearing in the luteal phase and peaking in the perimenstrual phase. Symptoms of depression and hopelessness were heightened in the perimenstrual phase and

persisted into the follicular phase. Symptoms improved and were least apparent in the ovulatory phase—where women had higher levels of systemic estradiol.

Aggression can be classified into reactive and proactive forms, with both types being exacerbated in different menstrual phases. A recent study examined the differential effects of menstrual cycle changes on reactive and proactive aggression in individuals with BPD (54). Reactive aggression was defined as an uncontrolled outburst of anger, while proactive aggression was defined as planned aggression or manipulation (55). The authors revealed that anger, anger expressions, and aggression were typically lowest in the ovulatory phase, although proactive aggression was increased during the ovulatory phase. In the mid-luteal phase (defined as 18–21 days after the start of menstruation), anger and irritability were elevated and reactive aggression peaked. In the perimenstrual phase, anger and irritability peaked, anger against self-increased, and reactive aggression began to decrease. Eventually, anger returned to a “baseline” level in the follicular phase. Findings from this study imply that it is also important to consider the type of aggression in reproductive aged women with BPD as reactive and proactive aggressions increase during the different phases of their menstrual cycles.

Altogether, the current literature suggests that sensitivity to gonadal hormone fluctuations in the CNS could influence the etiology and maintenance of BPD, and individuals with BPD may experience symptom changes in the type and severity of symptoms at different menstrual cycle phases. Generally, fewer BPD symptoms are experienced in the ovulatory period when CNS estradiol levels are high and BPD symptoms increase and peak around the mid-luteal and perimenstrual phases when CNS estradiol and progesterone levels are lower. There is a clear need for further research into understanding the relationship between ovarian hormones fluctuations across the menstrual cycle and BPD symptoms. Such research may well lead to more effective management of BPD with new gonadal hormone treatment strategies.

COMPLEX POST-TRAUMATIC DISORDER (CPTSD)

As described in the ICD-11, cPTSD consists of six symptom clusters: the three core PTSD symptoms (re-experiencing of the trauma, avoidance of trauma reminders and heightened sense of threat) and one symptom from each of three disturbances of self-organization (DSO) symptom clusters (emotional dysregulation, interpersonal difficulties, and negative self-concept).

Similar to PTSD and BPD, the prevalence of cPTSD is higher in women, with all three symptom clusters also reported significantly more often (18). Despite this gender difference, there are no studies to our knowledge that have explored the influence of sex hormones and/or the menstrual cycle on cPTSD symptoms. Considering the substantial overlap in symptoms between PTSD, BPD, and cPTSD, the relationship between symptom exacerbations and fluctuations across the menstrual cycle in PTSD and BPD may extend to cPTSD. This is a significant gap in the literature that needs to be addressed.

DISCUSSION

HPA Axis

While there are some differences between PTSD, BPD and cPTSD, the substantial symptom overlap indicates a similar underlying mechanism for these conditions (29). As trauma plays a key role in these disorders, it has been suggested that stress and subsequent alterations in the hypothalamic-pituitary-adrenal (HPA) axis may contribute to the aetiopathogenesis of these disorders (56–59).

The HPA axis links the CNS with peripheral tissues through the involvement of the hypothalamus, the pituitary, and the adrenals. This system of neuroendocrine pathways and feedback loops regulate a broad range of physiological processes, in particular mediating the stress response, and hence is consistently implicated in trauma-related conditions.

There is overlap in the neurochemistry and neurostructural changes observed in PTSD, BPD and cPTSD, with no clear differentiation between the three conditions in regards to HPA axis function or subsequent alterations (29). For instance, HPA axis overactivity has been implicated in BPD (60) and PTSD (56), and this dysfunction in both disorders is believed to closely mirror each other (58).

There is a complex bi-directional relationship between the HPA and hypothalamic-pituitary-gonadal (HPG) axes; the latter playing a key role in regulating reproduction by controlling gonadal hormones. The activation of one axis impacts the function of the other and vice versa (61). The HPA and HPG axes need to remain in equilibrium and factors that upset homeostasis, such as stress after trauma exposure, result in neuroendocrine disruption. This ultimately affects both the actions of the gonadal hormones such as estradiol and progesterone, as well as the endocrine hormones such as cortisol. This then contributes to menstrual cycle disruptions (62), which increases the risk of PTSD, BPD, and cPTSD.

Limitations and Future Directions

Many studies, such as those dealing with BPD, lacked a control group comparison, making it difficult to determine whether the patterns observed were specific to BPD or if they were attributed simply to fluctuations in the menstrual cycle, regardless of psychological functioning (21, 24, 54). PTSD studies focused on broad classification of trauma-exposed women with and without PTSD, while most BPD studies did not consider trauma and those that did grouped women by trauma-exposed and not exposed. While group comparisons are important, studies should explore within-person symptom change, especially considering that menstrual cycles differ vastly in populations of women.

Future studies could explore the relationship between the type, severity and frequency of trauma and the exacerbation of trauma-related symptoms across the menstrual cycle. The timing of trauma is also an important factor that should be explored, since childhood trauma experienced as a toddler or pre-schooler, may have quite different impacts compared to trauma occurring at

school-age or in adolescence. In addition, as there are no studies exploring cPTSD and the menstrual cycle, future studies in this area can model existing study designs in PTSD and BPD given the overlap in biological underpinnings and symptomatology.

IMPLICATIONS AND CONCLUSION

This review provides a few practical and theoretical implications about the possible relationship between gonadal hormone fluctuations of the menstrual cycle and behavioral, emotional, and cognitive symptoms that are seen in conditions such as PTSD, BPD and cPTSD. These three psychiatric conditions are all caused, at least in part, by trauma. Hence, it is important to consider each individual's trauma history in general. We need to consider a broader definition of trauma that considers the stressful impact of poor bonding with a primary carer, emotional neglect, or invalidation, as well as actual instances of physical abuse and sexual trauma. It appears that an experience of trauma can significantly influence an individual's neurobiology. In reproductive aged women, studying the impact of both gonadal hormone fluctuations and trauma experiences on resultant psychiatric symptoms may provide new neurobiological insights. We highlight that menstrual cycle phases could influence an individuals' diagnosis, so clinicians' need to be mindful of the phase of menstrual cycle at the time of diagnosis or perform assessments at different time points to gain a better understanding of the psychiatric symptoms' presence and severity. Similarly, clinicians should consider the phase of the menstrual cycle at the time of trauma exposure as this can contribute to symptom severity.

In conclusion, the present review provides evidence that in women with trauma-based disorders, the fluctuations of gonadal hormones across the menstrual cycle appear to cause changes in psychiatric symptoms at different monthly time-points. Psychiatric symptoms of PTSD and BPD appear to vary markedly across the menstrual cycle in women who have experienced early life trauma. This suggests that trauma alters the brain's sensitivity to gonadal hormone fluctuations, resulting in marked worsening of psychiatric symptoms in the low estradiol menstrual cycle phases, and some improvement in higher estradiol phases. While the literature is lacking in cPTSD, one may assume that the alteration in brain sensitivity may extend to the cPTSD population. This review also highlights that additional work is needed to clarify the influence of estradiol and progesterone fluctuations on trauma-related symptoms. Continued research on menstrual cycle vulnerability and trauma will lead to better informed management and treatment of PTSD, BPD, and cPTSD.

AUTHOR CONTRIBUTIONS

EM and ET were equally involved in the conceptualization of the mini-review and draft of manuscript. All authors contributed to manuscript editing.

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