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Psychiatric Symptoms Across the Menstrual Cycle in Adult Women: A Comprehensive Review

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Learning objective: After participating in this activity, learners should be better able to:
- Discuss and outline the general and overlapping effects of the menstrual cycle on women's mental health

Abstract: A growing body of research demonstrates menstrual cycle–dependent fluctuations in psychiatric symptoms; these fluctuations can therefore be considered as prevalent phenomena. Possible mechanisms underlying these fluctuations posit behavioral, psychological, and neuroendocrine influences. Recent reviews document cyclic exacerbation of symptoms and explore these mechanisms in the context of specific and often single disorders. The question remains, however, as to whether there are general and overlapping effects of the menstrual cycle on women's mental health. To address this gap, we synthesized the literature examining the exacerbation of a variety of psychiatric symptoms across the menstrual cycle in adult women. Results show that the premenstrual and menstrual phases are most consistently implicated in transdiagnostic symptom exacerbation. Specifically, strong evidence indicates increases in psychosis, mania, depression, suicide/suicide attempts, and alcohol use during these phases. Anxiety, stress, and binge eating appear to be elevated more generally throughout the luteal phase. The subjective effects of smoking and cocaine use are reduced during the luteal phase, but fewer data are available for other substances. Less consistent patterns are demonstrated for panic disorder, symptoms of posttraumatic stress disorder, and borderline personality disorder, and it is difficult to draw conclusions for symptoms of generalized anxiety disorder, social anxiety disorder, obsessive-compulsive disorder, and trichotillomania because of the limited data. Future research should focus on developing standardized approaches to identifying menstrual cycle phases and adapting pharmacological and behavioral interventions for managing fluctuations in psychiatric symptoms across the menstrual cycle.

Keywords: estrogen, progesterone, menstrual cycle, mental health, women's health

The menstrual cycle is characterized by predictable and recurrent fluctuations in hormones—namely, the ovarian hormones estrogen and progesterone. The cycle is separated into two distinct phases: the follicular phase, which consists of the first part of the cycle lasting from menstruation to ovulation and which varies in length but typically lasts 14 days; and the luteal phase, which is the second half of the cycle following ovulation and leading up to menstruation, and consistently lasts 14 days (see Mihm et al.[1] for an overview). The days immediately prior to menstruation are often termed the premenstrual phase.

During menstruation, estrogen and progesterone levels are relatively low (see Figure 1).[2] As the cycle advances through the follicular phase, estrogen levels spike, causing the pituitary gland to release a surge of follicle-stimulating hormone and luteinizing hormone—which facilitates the maturing of eggs within the ovaries.[3] When the most mature egg is released, the follicle transforms into a corpus luteum, which produces gradually increasing amounts of progesterone; a moderate amount of estrogen is also produced.[3] If the egg is not fertilized, progesterone and estrogen levels fall, the uterine lining breaks down, and the menstrual cycle resumes with menstruation, which typically lasts between 1 and 7 days.[4]

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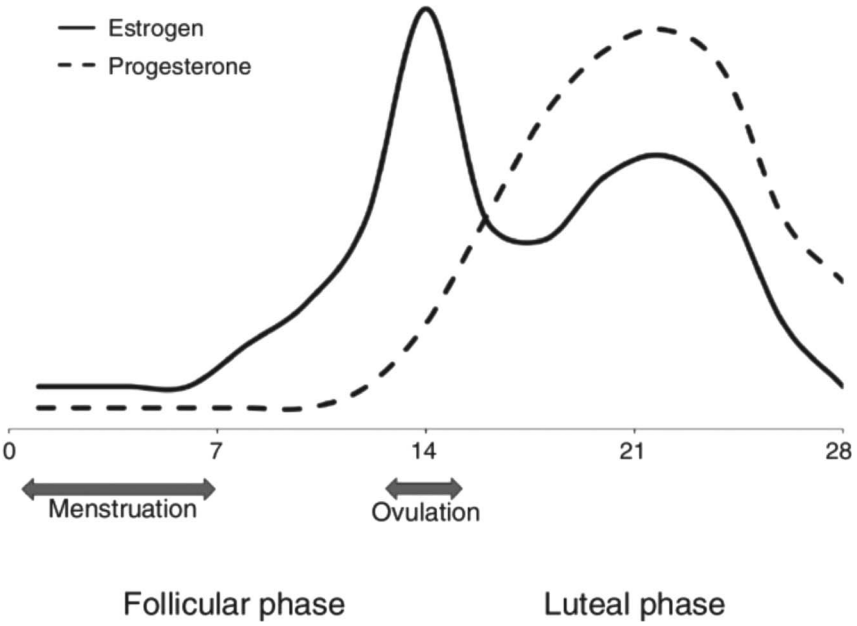

Figure 1. Estrogen and progesterone levels across a typical 28-day menstrual cycle (adapted from Glover et al. (2013).[2]

This cyclic experience may influence women's mental health through a variety of mechanisms. For example, many women experience physical discomfort (e.g., dysmenorrhea, breast tenderness, joint pain[5]) around menstruation. This physical discomfort can be associated with increases in psychological distress and irritability, and decreased self-esteem.[6] Many women additionally report increased interpersonal conflicts and reduced social engagement premenstrually and during menstruation[7,8]—which may contribute to depression and isolation.[8] Negative affect is linked with increased impulsivity,[9] substance use,[10] and nonsuicidal self-injury.[11] As such, it is unsurprising that systematic and meta-analytic reviews find exacerbations of psychiatric symptoms across the menstrual cycle (e.g., Carroll et al.[12]).

In addition to affective and behavioral impacts of the menstrual cycle, there are also several direct biological effects on mental health. For example, estrogen downregulates dopamine transmission, which mimics the antidopaminergic action of many antipsychotic medications.[13] Higher estrogen levels are hypothesized to protect against psychiatric symptoms, such as psychosis, thereby increasing vulnerability to psychosis when estrogen is low (e.g., menstruation, postpartum[14,15]). Estrogen also assists in memory consolidation through increased hippocampal activation,[16,17] which, in the context of treatment for posttraumatic stress disorder (PTSD), has been shown to facilitate fear extinction recall.[18] Progesterone can have anxiolytic effects[19] through increases in allopregnanolone and, subsequently, increased GABA potentiation.[20–22] Other progesterone metabolites, however, are not anxiolytic. In the presence of stress, progesterone is converted into cortisol, increasing stress responses and impairing emotional processing.[23] To this end, it has been suggested that progesterone may underlie menstrual-related mood symptoms.[23]

Recently, several elegant reviews documented menstrual exacerbations of numerous psychiatric symptoms,[24] including addictive behaviors,[25] psychosis,[15] suicidality,[26] anxiety, and posttraumatic stress disorder.[27] These reviews increased the scientific understanding of the effects of the menstrual cycle on women's mental health, including the more pointed effects of estrogen and progesterone. Yet, no review to date comprehensively evaluated the impact of the menstrual cycle on psychiatric symptoms. To further this growing body of research, we conducted a comprehensive review synthesizing the literature on fluctuations in a broad spectrum of psychiatric disorders and symptoms across the menstrual cycle. Summarizing these data in such a way will allow us to potentially identify patterns and draw conclusions beyond what previous reviews examined.

METHODS

Search Strategy

We conducted a comprehensive search using the PubMed database for articles focusing on psychiatric symptoms across the menstrual cycle. We used combinations of the following search terms to identify potentially relevant articles: menstrual cycle, psychosis, bipolar, mania, depression, suicide, anxiety, obsessive-compulsive disorder (OCD), body dysmorphic disorder, trichotillomania, excoriation, hoarding, impulse control, kleptomania, PTSD, eating disorder, anorexia, bulimia, binge eating, borderline personality disorder (BPD), intermittent explosive disorder, conduct disorder, pyromania, substance use, alcohol, and smoking. We compiled the results, removed duplicates, and reviewed the titles and abstracts of the remaining articles. We then read and assessed for eligibility the full texts of the remaining articles using the following criteria: studies (1) were published in English, (2) presented

original findings, (3) included premenopausal women at least 18 years old, and (4) assessed relevant psychiatric symptoms during at least two menstrual cycle phases. We did not include articles focusing on symptoms in women with premenstrual syndrome (PMS) or premenstrual dysphoric disorder, as those conditions inherently vary across the menstrual cycle. See inclusion diagram (Supplemental Figure 1, http://links.lww.com/HRP/A187), and Supplemental Tables 1–10, http://links.lww.com/HRP/A188, for full descriptions of the articles included.

Definition of Menstrual Cycle Phases

Most menstrual cycle research uses a "count" method to estimate cycle phases based on the first day of menstruation (Day 1). Estimates are often based on a 28-day cycle, although a substantial body of evidence suggests significant variation in cycle length in healthy women.[196] Indeed, the follicular phase has been found to vary by as much as 12 days.[197] The luteal phase, by contrast, lasts a relatively consistent amount of time—approximately 14 days. Some exceptions to this pattern include women with luteal phase disorders (e.g., short luteal phase).[198,199]

Many articles included in this review have varying terminology and definitions of menstrual cycle phases. For example, occasionally the "premenstrual" phase is referred to as the mid- or late-luteal phase. "Perimenstrual" can include both premenstrual and menstrual phases, whereas "early follicular" can include menstruation and the initial days following menstruation. We report the findings using the language described in the articles reviewed; however, our synthesis of the data focuses on overall patterns during specific phases, regardless of terminology.

Quality Rating

To strengthen our synthesis of study results, we developed a quality rating based on study design. We considered studies to be of high quality if they included at least one biological indicator of the menstrual cycle (e.g., basal body temperature, hormone levels), sample size was ≥30 women per group, and, when applicable, clinical diagnoses were made.

RESULTS

Psychosis

Most reports on the exacerbation of psychotic symptoms across the menstrual cycle are single case studies. These studies retrospectively rely on a patient's self-reported or clinician-observed experiences over several years or decades. In all but one[37] of the identified case studies, the authors reported recurrent psychosis during the premenstrual phase.[28,29,32–34,36,38] Often, symptom onset occurred at menarche.[34] Though many authors reported that psychotic or manic symptoms occurred during the week or days before menstruation, several noted that psychotic symptoms remitted upon menstruation.[28,38]

Findings become less clear when examining larger populations. Ray and colleagues[39] followed 40 women with schizophrenia in an inpatient unit in India. Clinicians rated patients' symptoms weekly for two consecutive menstrual cycles and found that positive symptoms of schizophrenia—namely, excitability and hostility—were highest during the premenstrual phase. Negative symptoms, such as withdrawal and difficulty with abstract thinking, were highest during menstruation. These findings complement earlier work by Harris,[30] who found that, in a sample of 39 inpatient women with schizophrenia, most women experienced affective changes, rather than overt psychosis, during the premenstrual phase. Conversely, in a large, community-based study of 278 healthy women from the United Kingdom, persecutorial thoughts increased during the paramenstrual phase (day 1 of menstruation ± 3 days) compared to midcycle (11–17 days prior to menstruation).[6] It is possible that certain menstrual fluctuations in paranoia exist in nonclinical samples and that affective fluctuations may be more common in clinical samples, where paranoia is more consistently pronounced. For women who also experience menstrual exacerbation of overt psychosis, the exacerbation appears to occur predominantly during the premenstrual phase.[31]

Results from high-quality studies The one high-quality study found that 32.4% of a sample of women with schizophrenia had cyclical worsening of psychotic symptoms.[35]

Bipolar Disorders

Several case studies document menstrual fluctuations in symptoms of bipolar disorder. All but one study[43] identified in the present review reported instances of hypomania,[47] mania,[41] or psychosis[50] during the premenstrual and menstrual phases. Kukopoulos and colleagues[40] reported that a 28-year-old Sardinian woman regularly experienced hypomania two weeks and depression two days prior to menstruation, with gradual improvement throughout menstruation. Subsequent reports similarly note the onset of mania and hypomania days prior to menstruation, with some symptoms ceasing upon menstruation[41] or days after menstruation began.[47] The sole case study to report incongruent findings described one woman's experience with menstrual onset of depression and luteal-phase onset of hypomania.[43]

Results from larger clinical and community samples speak to these individual differences, as many studies report no overwhelming effect of the menstrual cycle on bipolar symptoms.[42,45,46,48] Cyclic effects were found, however, in numerous subgroups of study samples. In one study of 41 women, increases in depression and mania were observed during the luteal phase for some women (n's of 8 and 5, respectively).[42,46] Similarly, Leibenluft and colleagues[42] found that, in a sample of 25 women with rapid-cycling bipolar disorder, 6 showed an increase in depression and 5 an increase in hypomania in the days following menstruation. Sit and colleagues[48] posit that the use of mood stabilizers and antipsychotics in treating bipolar disorders could mask patterns in symptom expression across the menstrual cycle. Indeed, one study examining menstrual cycle effects on mood in 34 Turkish women taking lithium or valproate for bipolar disorder and 35 healthy controls found greater mood variability across the cycle in healthy controls.[44] Properly treated bipolar disorder can stabilize naturally

occurring menstrual effects on mood,[49] which may explain why large studies often find little or no effects of the menstrual cycle on symptom expression. Alternatively, it is possible that, in the study by Leibenluft and colleagues,[42] mood changes among women with rapid-cycling bipolar disorder occurred too quickly to demonstrate any effect of the menstrual cycle.

RESULTS FROM HIGH-QUALITY STUDIES Only one study met criteria for being considered high quality. This study found greater mood variability across the menstrual cycle in healthy controls compared to those taking lithium or valproate.

Depression

Depression is a profound and often debilitating disorder that disproportionately affects women.[200] Research suggests that interactions among emotional and behavioral sensitivities to fluctuations in ovarian hormones across the menstrual cycle may be, for some women (e.g., see Schmidt et al.[201]), primary factors leading to depressive symptoms. The concept of premenstrual mood worsening has been a focus of investigation for decades, with many,[52–54,57,58,68] but not all,[7,55,56,156] studies finding some evidence of symptom exacerbation (i.e., mood worsening) in this phase. Indeed, women have been treated with hormonal therapy for improving premenstrual symptoms,[51,202] with some success. Ongoing work seeks to better characterize the nature, timing, and mechanisms of changes in depression across the menstrual cycle to help develop and evaluate additional therapies.

Epidemiological and self-report studies assessing depressive symptoms in healthy women produced inconsistent findings. In a large study of 248 adult, premenopausal women (60% White), depressive symptoms and hormone levels were measured across at least two menstrual cycles.[71] The authors found no relationship between depressive symptoms and absolute levels of hormonal changes across the menstrual cycle, although women with more depressive symptoms also had worse premenstrual mood changes. Premenstrual mood worsening was also found in an earlier study,[59] and healthy women have reported higher symptoms of depression in both early and late follicular phases compared to the mid-luteal phase.[70] Another study, however, showed no relationship between menstrual cycle phase and negative affect.[74] It is possible that premenstrual mood worsening is related to decreases in reward responsivity. In general, reward responsivity (a possible biomarker for depression, with low reward sensitivity correlated with depression), appears to be highest in the follicular phase and lowest in the luteal phase.[76,77,191,192,203] Women in the late luteal phase of the menstrual cycle may also have difficulty with emotion perception as evidenced by neural differences in brain activation compared to men,[77] which could make them vulnerable to depression at this time. Another possibility is that individual women experience different patterns of mood changes throughout the cycle, with the consequence that analyzing data as a group may obfuscate individual differences.[69]

An early study found that women with a history of treated depression reported greater symptoms of depression across the menstrual cycle compared to women without a history of depression. There was no phase-specific pattern in this sample; however, these data were collected retrospectively, which may have introduced recall bias.[61] In women with major depression, one study compared menstrual cycle phases at the time of psychiatric admissions, but these data were inconsistent[54] and did not reveal a clear pattern. In a large, community-based sample of 900 girls and women ages 13–54 years (n = 111 Black; n = 121 Hispanic), participants underwent diagnostic interviews and tracked their moods for two cycles.[65] Fifty-two participants had clinical (i.e., major depressive disorder or dysthymia) or subclinical depression. Women with clinical and subclinical depression reported greater symptom exacerbation in the premenstrual phase than did nondepressed women, though premenstrual symptom exacerbation was observed in all participants. Symptom worsening during the follicular phase was highest for clinically depressed, moderate for subclinically depressed, and low for non-depressed women. These data suggest that women with depression are at increased risk of premenstrual symptom worsening,[60] possibly due to impaired estrogen-related modulation of stress reactivity;[72] however, the pattern of increased mood symptoms premenstrually is also generally true across girls and women with and without depression.[78] Similar findings were demonstrated in a sample of Chinese women with depressive disorders.[66] Luteal phase decrease in positive affect has also been shown in women with fibromyalgia and rheumatoid arthritis,[64] and women with epilepsy show lower moods and increased seizures during menstruation.[78]

The use of oral contraceptives further complicates the identification of clear patterns of how the menstrual cycle affects mood. In Sweden, a randomized, controlled trial of combined oral contraception (n = 84) compared to placebo (n = 94) examined the effect on mood during three consecutive menstrual cycles.[75] Cycle phases were menstrual (days 1 to 4), premenstrual (days –7 to –1), and intermenstrual (all remaining days). The study found that oral contraceptive users reported a small, significant worsening of mood symptoms during the intermenstrual phase; however, additional analyses revealed that this effect was primarily driven by a subgroup of women with previous significant mood symptoms associated with oral contraceptive use. Other studies reported similar findings,[62] regardless of the type of oral contraceptive used.[63] Interestingly, another randomized, controlled trial in Germany found the opposite pattern: healthy, PMS-free women taking oral contraceptives reported slightly better mood across the cycle compared to naturally cycling women.[73]

RESULTS FROM HIGH-QUALITY STUDIES Data from the high-quality studies do not offer much clarity. Several found that symptoms of depression were not related to absolute hormone levels, although one study focusing on women with clinical symptoms of depression and one study in healthy women

both noted a premenstrual worsening of symptoms. Others found no relationship of depression to the menstrual cycle.

Suicide

Most research in this domain employs psychiatric hospitalization admission data or interviews immediately following hospitalization for suicide attempts. Research consistently demonstrates that rates of self-harm, suicide, and suicide attempts are significantly elevated during the premenstrual and menstrual phases.[81–87,92,93] Histopathological reports suggest rates of completed suicides during the menstrual phase to range from 25%[89] to 54%.[88] Via autopsy, Leenaars and colleagues[89] and Dogra and colleagues[88] compared menstrual cycle phase at time of death in women who died by suicide versus other causes (e.g., motor vehicle accident). Despite the large difference in rates of suicides occurring during menstruation noted above, both studies reported similar rates of death by other causes during menstruation: 4.5% and 6.75%, respectively. Nonetheless, a disproportionate number of suicides occur during the menstrual phase compared to other phases of the menstrual cycle and other causes of death.

These rates are largely consistent with those seen in suicide attempts, with reported rates of attempts occurring during the menstrual phase ranging between 26%[84] and 42%.[79,84] Research grouping the premenstrual and menstrual phases reported rates of 47%,[80] and one study reported luteal-phase attempt rates as high as 67%.[91] Baca-García and colleagues[83] posit that women with histories of diagnosed psychiatric disorders are five times more likely to attempt suicide during the menstrual phase than those with no such history. Variations in rates of suicide attempts across the menstrual cycle appear to be unique to naturally cycling women. Fourestié and colleagues[79] found that, in a sample of 108 French women (35 naturally cycling) who attempted suicide, 42% of naturally cycling women attempted suicide while menstruating and 12% attempted during the premenstrual phase. They did not find associations with cycle phase and suicide among women using hormonal contraceptives.

Suicide is highly heritable, with rates ranging from 17%–55%.[204–208] Furthermore, serotonergic function and the serotonin transport gene 5-HTT are highly related to suicidal behavior (as reviewed in Kenna et al.[209]). Researchers examined the possibility of gene × hormone interactions in rates of suicide and suicide attempts across the menstrual cycle. Baca-García and colleagues[84] assessed the role of allele variants in rates of suicide attempts among 104 naturally cycling, White women. Serum assays indicated that, of these women, 17 had two long alleles, 38 had two short alleles, and 49 had one long and one short allele. Among women with two long alleles, a significant proportion of suicide attempts occurred during the menstrual phase (41%). Furthermore, estradiol levels were significantly lower in women with long rather than short alleles. No significant phasic differences emerged for women with two short alleles. As such, it is possible that genetic vulnerabilities may underlie menstrual cycle exacerbations of suicidal behavior.

Results from high-quality studies

Eleven studies met criteria for being considered high quality, with nine studies indicating that rates of completed or attempted suicide were highest during menstruation and two studies indicating these rates were highest premenstrually.

Anxiety and Anxiety Disorders I: Anxiety and Stress

Symptoms of anxiety and stress have been examined in healthy women's menstrual cycles across a variety of laboratory protocols. Research focusing on daily symptoms of anxiety, as well as anxiety in response to stressors, has found clear premenstrual exacerbations of anxiety,[60,67,94–96,103,115] although six studies (three of which had very small sample sizes) found no significant changes in anxiety related to the menstrual cycle.[55,56,98,99,102,113] Some research found a divergence between self-reported stress and cortisol responses to stress in healthy women,[98,107] while high levels of trait anxiety in women are associated with cortisol only in the follicular phase.[105] State and trait anxiety were related to daily reports of anxiety during the luteal phase compared to the follicular phase in a healthy sample of 203 women,[104] although another study showed that women high in state and trait anxiety do not show changes in symptoms across their menstrual cycles.[100] In the one study that examined the role of ovulation during the menstrual cycle, there were no differences in symptoms, regardless of whether the cycle was ovulatory or anovulatory.[68] A separate study assessing acoustic startle responses in women (as a proxy for anxiety) found larger startle magnitudes during ovulation and the late luteal phase, suggesting a potential vulnerability to anxiety during these phases.[109] Other research has also shown higher levels of anxiety in response to stressors, including exercise,[119] during the luteal phase.[108]

Other psychological characteristics representative of anxiety have been explored as factors contributing to menstrual cycle symptom severity. Lower perceived levels of control over anxiety have been correlated with higher levels of menstrual severity,[111] which may be related to overall difficulty regulating emotions.[112] Similarly, higher levels of health anxiety are associated with increased perceived stress, but only during the late luteal phase of the menstrual cycle.[118] One recent study found that calmness was highest during the late luteal and menstrual phases; however, anxiety moderated the relationship between irritability and cycle phase, such that highly anxious women were more irritable during the late luteal and menstrual phases, when estrogen and progesterone levels are low.[114] Chronic anxiety may therefore be a risk factor for more severe premenstrual and menstrual symptoms.[210] In fact, high levels of estrogen may serve as a protective factor against psychosocial stress, as evidenced by changes in brain activation[110] and cardiovascular responses to stress.[106] Evidence also suggests that anxiety may be directly related to progesterone levels across the menstrual cycle,[116] although one recent study found no relationship of anxious jealousy to progesterone levels across the menstrual cycle.[117]

Despite relatively consistent evidence of premenstrual anxiety exacerbation across the menstrual cycle, data also suggest that some women experience symptom exacerbation at *mid-cycle* and decreased symptoms premenstrually.[52,69] In a sample of 213 young women attending college in Italy, participant responses were separated into four groups using cluster analysis, with two of the groups suggesting a "classic" PMS pattern, one group revealing a non-cyclic pattern, and the last group suggesting the mid-cycle pattern described earlier.[69] This study represents an important step to examining individual differences across the menstrual cycle, rather than just assuming women experience similar changes across cycle phases—an approach demonstrated by earlier research comparing community volunteers with women who reported high levels of premenstrual symptoms.[101]

Although most studies have excluded women using oral contraceptives, several studies have compared anxiety in women who were and were not using exogenous hormones. Generally, naturally cycling women demonstrate the expected pattern of anxiety (higher during menstrual and premenstrual phases), whereas women using oral contraceptives showed no change in anxiety.[97,98] One small study showed no cycle-phase or group differences in anxiety in women who were and were not taking oral contraceptives.[56]

RESULTS FROM HIGH-QUALITY STUDIES When examining high-quality studies only, the majority found no effect of menstrual cycle phase on anxiety, although women with high baseline anxiety seemed to experience more symptoms in the luteal phase.

Anxiety and Anxiety Disorders II: Generalized Anxiety Disorder

A recent study compared women with and without generalized anxiety disorder (GAD) on measures of mental and physical fatigue during the early follicular and mid-luteal phases.[121] The only difference to emerge was that women with GAD had higher mental fatigue in the early follicular phase. Furthermore, salivary estradiol and progesterone were not associated with measures of fatigue during any cycle phase. This is consistent with earlier research demonstrating increased symptoms of depression, anxiety, and hostility in women with GAD; however, symptom exacerbation was even greater for women with GAD and PMS, particularly in the premenstrual phase.[120]

RESULTS FROM HIGH-QUALITY STUDIES Neither study met our criteria for being considered high quality.

Anxiety and Anxiety Disorders III: Social Anxiety Disorder

In women with social anxiety disorder, higher social anxiety and avoidance were reported in the premenstrual phase of the menstrual cycle (week 4) compared to the three previous weeks.[122] In a separate study of Chinese women, salivary progesterone was positively correlated with self-reported social feedback sensitivity, regardless of menstrual cycle phase (late follicular or mid-luteal).[124] This finding is supported by a previous study in which progesterone levels were associated with increased attention to social stimuli.[123]

RESULTS FROM HIGH-QUALITY STUDIES Analysis of high-quality studies revealed no cycle effect of interpersonal sensitivity in healthy women, although the luteal phase was associated with greater attention to social stimuli and higher interpersonal anxiety.

Anxiety and Anxiety Disorders IV: Panic Disorder

One of the earliest studies compared retrospective versus prospective reports of anxiety and panic in a small sample of adult women with panic disorder.[127] Interestingly, most women (79%; n = 15) retrospectively reported worsening anxiety symptoms premenstrually, but prospective self-reported anxiety and daily frequency of panic attacks were similar pre- to postmenstrually. These data mirror two earlier published reports,[125,126] although another study found that prospective report of panic and anxiety clearly demonstrated premenstrual exacerbation of symptoms.[128]

Research on mechanisms of panic disorder, such as anxiety sensitivity, has produced some important findings.[211] In a 1996 study, 337 college women were screened for anxiety sensitivity, and the lower and upper quartiles of respondents participated during either the intermenstrual (days 8 to 22) or premenstrual (days 24 to 28) phase of their cycles.[130] Women in the high anxiety-sensitivity group demonstrated elevated skin conductance reactivity to anxiety-provoking scenes in the premenstrual phase compared to those with low anxiety sensitivity or those in other phases of the menstrual cycle. The authors propose that these data were the first to link both state (menstrual cycle phase) and trait (high anxiety sensitivity) factors that may contribute to vulnerability to panic in women. Similar patterns were found in more recent studies in healthy women with high/low anxiety sensitivity.[134] Additionally, women with high anxiety sensitivity report more menstrual-related symptoms,[131] and women with asthma with or without panic disorder report more state anxiety,[133] regardless of cycle phase.[135]

Laboratory-based studies often use what is known as a "CO2 challenge" to evaluate reactivity to the sensation of difficulty breathing.[212,213] In this approach, participants inhale a full lung capacity of a gas mixture (typically 35% CO_2/ 65% O_2) and rate their levels of anxiety. One of the first studies to explore menstrual cycle effects in this paradigm found that women with panic disorder experience significantly more reactivity during the early follicular phase (day 4 of the menstrual cycle) than during the mid-luteal phase (8 days prior to menstruation), whereas healthy women show no differences across the menstrual cycle.[129] A separate laboratory study demonstrated elevated skin conductance responses to anxiety-provoking stimuli during the premenstrual phase in women with panic disorder compared to women without.[132]

RESULTS FROM HIGH-QUALITY STUDIES Two studies of healthy women were considered to be of high quality. They both found no menstrual cycle effects for anxiety generally, although high anxiety sensitivity was associated with higher cognitive panic symptoms in the premenstrual phase.

Obsessive-Compulsive and Related Disorders I: Obsessive-Compulsive Disorder

Early retrospective studies suggested a link between exacerbation of OCD symptoms and the premenstrual phase, specifically.[136,137] The first study to evaluate this relationship prospectively included 101 women who met diagnostic criteria for OCD.[138] Approximately half of the women reported premenstrual worsening of OCD symptoms, as demonstrated by significantly higher scores on a self-report measure of OCD symptoms. In a laboratory-based study designed to measure OCD-related checking symptoms, no menstrual cycle phase differences (comparing mid-luteal and mid-follicular) were identified.[139]

RESULTS FROM HIGH-QUALITY STUDIES Only one study meeting criteria for high quality found no differences in checking behaviors.

Obsessive-Compulsive and Related Disorders II: Trichotillomania (Hairpulling)

A single published study explored the relationships among menstrual cycle phases and trichotillomania in 59 adult women.[140] Participants were retrospectively asked whether they believed whether their menstrual cycles and hairpulling were related, and 53.3% indicated that they were. Participants also reported a clear effect of menstrual phase when asked to indicate symptoms premenstrually, during menstruation, and postmenstrually, such that greater frequency and intensity of urges, greater frequency of hairpulling, and decreased ability to control hairpulling were all significantly higher in the premenstrual phase than in the other phases.

RESULTS FROM HIGH-QUALITY STUDIES The one identified study did not meet our criteria for being considered high quality.

Posttraumatic Stress Disorder

Assessment of trauma and PTSD symptoms and their relationship to the menstrual cycle is complicated by differences in when the trauma *occurred* and when it was *assessed*. One study looked at this specific issue in a large sample of women (n = 147) with various types of trauma, including motor vehicle accidents, falls, and nonsexual assaults.[141] Based on retrospective self-reports of their last menstrual periods, women who were in the mid-luteal phase at the time of the trauma (20% of the sample) or at the time of assessment (16% of the sample) reported experiencing significantly more frequent and severe flashbacks than women who experienced trauma in other cycle phases. This finding remained even after controlling for number of days in the hospital, injury severity, age, trauma type, and mild traumatic brain injury. In healthy populations,[142] women exposed to a distressing film during the early luteal phase were more likely to experience intrusive memories of the film in the days following than women who watched the film in the mid-follicular or late luteal phases (when progesterone levels are low).[143] Furthermore, the frequency of intrusions was negatively correlated with the estrogen-to-progesterone ratio, suggesting that estrogen may have protective effects and that both hormones may be important for encoding distressing memories. Similar results have been demonstrated in other intrusive-memory paradigms.[144] In the luteal phase, when the estrogen-to-progesterone ratio is lower than in the follicular phase, women may experience more intrusive memories and impaired fear inhibition.[2]

Laboratory assessment of fear also sheds light on biomarkers of PTSD. Prepulse inhibition is a neurobiological process typically assessed through a startle-response paradigm. A weaker version of the stimulus (prepulse) is administered prior to a startle stimulus (pulse), which results in a decreased startle response compared to when no prepulse is administered. This paradigm aims to measure the brain's ability to effectively filter interruptions (i.e., the startle stimulus) from ongoing processing of the prepulse stimulus.[214] Pineles and colleagues[146] examined prepulse inhibition in women with PTSD and trauma-exposed women without PTSD in the early follicular and mid-luteal phases of the menstrual cycle. Although group differences were found, there were no main effects or interactions with menstrual cycle phase, estradiol, or progesterone levels, suggesting that menstrual cycle phase was not associated with prepulse inhibition. The authors suggest that these null results may indicate that prepulse inhibition evokes early stages of information processing that may not be influenced by the menstrual cycle. Other studies comparing women with PTSD to trauma-exposed women without PTSD found that deficits in extinction learning (i.e., learning such that a stimulus previously associated with a shock is no longer associated with the shock) were present in the mid-luteal phase but only for women with PTSD.[147,150] A possible explanation for this deficit is that estrogen, which is lower in the luteal than late follicular phase, may be important for higher-order processes such as extinction learning. Relatedly, it is possible that women with PTSD have deficits in the conversion of progesterone, which is typically higher in the luteal phase, to the GABAergic neurosteroid allopregnanolone, which affects differential fear conditioning and extinction.[148] Although GABA plasma levels appear to be positively correlated with PTSD symptoms in women with PTSD compared to trauma-exposed healthy controls, menstrual cycle phase was not related to GABA levels in either group, according to a recent study.[151]

The course of other symptoms of PTSD across the menstrual cycle is not entirely clear. Anxiety sensitivity (i.e., fear of the physical symptoms of anxiety), for example, appears to be stable across the menstrual cycle in women with and without PTSD.[149] However, interpersonal sensitivity, depression, anxiety, hostility, and phobic anxiety are significantly higher in women with PTSD than in those without.[145]

Women with PTSD report more phobic anxiety in the early follicular phase compared to the mid-luteal phase, and women without PTSD report no changes across the menstrual cycle.[145]

Results from high-quality studies Three studies met our established criteria for high-quality evidence, and all of these explored intrusive memories in healthy women. The data suggest that intrusive memories are more frequent in the luteal phase and when estradiol levels are low.

Eating Disorders

Much research examining eating disorders across the menstrual cycle focuses on binge eating rather than caloric restriction or compensatory behaviors (e.g., purging). As such, results presented in this review surround emotional and binge eating. Research examining emotional or binge eating appears to indicate consistent cyclic effects (see Fowler et al.[164] and Leon et al.[152]). In both clinical and community-based studies of women diagnosed with bulimia nervosa, significant increases in binge eating were reported during the mid-luteal and premenstrual phases.[153–155,159] Similar results were noted in community samples of women without diagnosed eating disorders.[157,158,160–162] In a convenience sample of 148 women (84% White), naturally cycling women (n = 67) reported increased hunger during the menstrual phase and increased food cravings and amount of food eaten during both the premenstrual and menstrual phases.[158] Women using hormonal contraceptives (n = 81) demonstrated the same pattern with the addition of increased hunger during the premenstrual phase.

To better understand the biological underpinnings of these fluctuations, researchers investigated associations among progesterone, estradiol, and eating behaviors. In a sample of nine women with bulimia nervosa and eight healthy controls (82.4% White), Edler and colleagues[155] found significant negative associations between binge eating and estradiol, and significant positive associations between binge eating and progesterone. Similarly, Baker and colleagues[163] reported that, when women had low progesterone levels, an inverse relationship between estradiol and body dissatisfaction emerged. When progesterone levels were high, however, positive relationships among estradiol, body dissatisfaction, and binge eating emerged.

Results from high-quality studies Data from the three high-quality studies do not reflect a consistent pattern, with two studies reporting no direct hormonal associations, and one study reporting positive associations, among emotional eating, progesterone, and estradiol.

Borderline Personality Disorder

BPD is characterized by intense and frequent emotional dysregulation, often resulting in anger and aggressive behavior toward others. Individuals with BPD are highly sensitive to criticism and may experience intense mood fluctuations throughout a day. However, few studies examined the role of the menstrual cycle or ovarian hormones in BPD symptoms. In a convenience sample of 226 undergraduate women, researchers found that women using oral contraceptives endorsed significantly more BPD symptoms on a self-report questionnaire.[165] Moreover, the phase of the menstrual cycle when estrogen was rising (days 5 to 10; mid- to late-follicular phase) was associated with more symptoms than those in a low-estrogen phase (days 0 to 3 and 26 to 29). This association was confirmed in a second study reported in the same article that measured salivary estradiol and found a significant positive relationship between rising, but not absolute, estrogen levels and BPD symptoms.

Subsequent studies sought to better understand the relationship between estrogen-to-progesterone ratios and key symptoms. One study found that within-person higher-than-average progesterone levels and lower-than-average estrogen levels predicted increased symptoms for women with high baseline BPD symptoms.[166] In another study of women with BPD, symptoms were generally worse in the perimenstrual phase than mid-luteal, ovulatory, and follicular phases. High-arousal symptoms (e.g., anger) returned to baseline, however, in the early follicular phase (i.e., when estrogen levels are low), whereas low-arousal symptoms (e.g., depression) persisted until ovulation (i.e., when estrogen levels are high).[167] In this same sample, anger/irritability was highest in the perimenstrual phase, with reactive aggression highest in the mid-luteal phase and proactive aggression highest during ovulation and lowest perimenstrually.[168]

Results from high-quality studies Two high-quality studies of BPD symptoms in healthy women suggest that BPD symptoms may change as a function of variability in estradiol and progesterone, as opposed to being associated with absolute ovarian hormone levels.

Substance Use Disorders I: Alcohol Use

The literature assessing the relationship between alcohol use and the menstrual cycle is mixed.[169–171] In a 2015 meta-analysis, Carroll and colleagues[12] found that 7 of the 13 identified articles reported increased drinking during the premenstrual phase, one reported decreased drinking during the premenstrual phase, and five reported no significant menstrual cycle effects. More recent research suggests that drinking may indeed fluctuate across the menstrual cycle, and this may be linked with progesterone-to-estradiol ratios. In a study by Joyce and colleagues,[173] 94 naturally cycling women (76.6% White) documented the quantity of alcohol consumed and reasons for drinking across a full menstrual cycle. Women reported slight increases in drinking during the premenstrual and menstrual phases, and motivations related to coping were significantly associated with these increases (see also Hayaki et al.[174]). Similarly, social motivations (e.g., "because [drinking] makes social gatherings more fun") were associated with alcohol consumption around ovulation.[173] These findings align with Martel and colleagues' work[172]

demonstrating increases in drinking and binge drinking during the premenstrual phase and ovulation. High levels of estradiol predicted alcohol consumption, and these effects increased when progesterone was low and decreased when progesterone was high. Mood may also moderate these effects. Research shows that, when progesterone is low, women are more likely to drink when their mood is negative and that, when progesterone is high, women are more likely to drink when their mood is positive.[175] Taken together, recent research has elucidated that menstrual cycle effects may be moderated by positive or negative affect.

RESULTS FROM HIGH-QUALITY STUDIES The two high-quality studies reported relatively consistent findings. When progesterone is low in the premenstrual and menstrual phases, alcohol consumption appears to be associated with negative mood. Around ovulation and when progesterone rises, alcohol consumption appears to be associated with positive mood.

Substance Use Disorders II: Smoking

Studies have examined menstrual cycle effects on ad lib smoking (i.e., smoking at will), subjective effects of nicotine, cravings, withdrawal symptoms, and smoking cessation. We found no consistent pattern for ad lib smoking, with studies documenting no cyclic effect,[187] increased smoking during the luteal phase,[179,184] or increased smoking during menstruation.[176] In a study by Schiller and colleagues,[183] 98 female smokers (79% White) attended two laboratory sessions spaced two weeks apart, during which they smoked ad lib for one hour. Researchers found that women's progesterone-to-estradiol ratios were negatively associated with smoking behavior; women with lower levels of progesterone compared to estradiol smoked more. The authors proposed that these relative levels may partly explain inconsistencies in the extant literature, as relative amounts of these hormones may be an important factor in menstrual cycle–related smoking behavior.

Progesterone may also diminish subjective effects of nicotine.[185] In a study by Goletiani and colleagues,[186] 23 naturally cycling female smokers rated the subjective effects of cigarettes throughout two-hour ad lib smoking sessions twice during their menstrual cycles. No phasic effects were found on subjective effects of cigarettes. However, when data collected during the luteal phase were grouped based on progesterone levels, researchers found that women with high levels of progesterone reported significantly lower subjective effects. Similar findings show the effects of progesterone on reducing cravings.[181,188,189,215]

Conversely, symptoms of nicotine withdrawal appear to be highest during the luteal phase.[177,178] This increase may be related to premenstrual symptoms, which are greater during the luteal phase and include symptoms like those of nicotine withdrawal (e.g., fatigue, headache, anxiety; see Weinberger et al.[216]). It is unclear whether this is related to the effectiveness of smoking cessation (e.g., quit attempts); however, while the research is limited, there are studies that indicate superior outcomes for smoking cessation initiated during both the luteal[182] and follicular[180] phases. These studies are also limited as they vary regarding whether cessation is assisted by pharmacotherapies such as nicotine replacement, bupropion, or varenicline. Given the negative correlation between progesterone-to-estradiol ratios and smoking behavior,[183] quit attempts made during the follicular phase may be more successful.

RESULTS FROM HIGH-QUALITY STUDIES Seven studies assessing smoking behavior across the menstrual cycle were considered high quality. Overall, these studies suggest that cravings and affective responses to nicotine are lower in the luteal phase, when progesterone levels are relatively high, compared to the follicular phase, when progesterone levels are relatively low.

Substance Use Disorders III: Cocaine Use

Like menstrual effects on nicotine use, research indicates an attenuation of subjective effects of smoked cocaine when progesterone levels are high (see Collins et al.[193] and Reed et al.[194]). Sofuoglu and colleagues[190] reported that women (n = 21) had lower ratings of feeling "high" and "stimulated" during the luteal phase than the follicular phase. Evans and colleagues[191] similarly reported that, although women (n = 11; 91% African American) reported greater desire for cocaine during the luteal phase, their ratings of drug effects such as feeling "high," "stimulated," "alert," and "self-confident" were significantly reduced compared to ratings in the follicular phase. Evans and colleagues[192] later examined subjective responses to smoked cocaine in 11 naturally cycling women (91% African American) during the follicular phase, luteal phase, and follicular phase with exogenous progesterone administration. Ten men served as a control group. Subjective effects of cocaine were significantly lower during the luteal phase and when the follicular phase was supplemented with exogenous progesterone compared to the follicular phase and men's responses. No differences were found between follicular phase responses and men's responses, which continues to suggest that progesterone modulates subjective responses to smoked cocaine.

To assess the potential role of allopregnanolone, a progesterone metabolite, on cocaine cravings, Milivojevic and associates[195] randomized 46 cocaine-dependent men and women (n's of 29 and 17, respectively; 73.9% African American) to receive either a progesterone supplement or placebo, and measured blood concentrations of allopregnanolone and self-reported cravings. They found that, through increases in allopregnanolone, those who received progesterone supplementation reported significantly lower cravings than those who received placebo.

RESULTS FROM HIGH-QUALITY STUDIES No study in this section met our criteria for being of high quality.

Miscellaneous Disorders

We found only one study relating to symptom fluctuation in a woman with kleptomania.[217] The authors did not formally

test her symptoms during different cycle phases, but the patient reported experiencing intensified urges to steal during the luteal phase. We felt that the data from this single case study were not sufficient to justify inclusion in the review. There were no studies available for body dysmorphic disorder, excoriation, hoarding, intermittent explosive disorder, conduct disorder, or pyromania.

DISCUSSION

The aim of this comprehensive review is to describe the findings of previous research examining psychiatric symptom variability across the menstrual cycle. Each study included (1) a comparison of at least two menstrual cycle phases, (2) data not derived from evaluation of an intervention, and (3) premenopausal women, age 18 years or older. Across psychiatric diagnoses, we saw evidence of symptom exacerbation primarily in the luteal, premenstrual, and menstrual phases.

Evidence of Potential Mechanisms Involved in Symptom Fluctuation

Several studies included in this review examined possible mechanisms that may underlie menstrual-related changes in symptoms. Regarding depression, for example, the literature indicates that both healthy women and women with a depressive disorder experience perimenstrual increase of depressive symptoms. However, data exploring potential mechanisms are not as clear. fMRI studies examining functional brain changes show inconsistent results.[218,219] Similarly, estradiol may help regulate stress for healthy women but not for women who have experienced clinical depression,[72] suggesting that even a history of depression could make women vulnerable to increased perimenstrual mood changes.[61] These data highlight the complexities of determining how depression changes over the course of the menstrual cycle and whether these processes may be different between healthy and clinical populations, perhaps suggesting the need for different treatment approaches.[220,221]

Ovarian Hormone Mechanisms

Several studies hypothesized a specific link between ovarian hormones and symptom fluctuation. Regarding substance use, the decrease in cravings in the luteal phase may be due, in part, to increases in allopregnanolone, a progesterone-derived neuroactive steroid. Allopregnanolone produces anxiolytic and hypnotic effects via increased GABA potentiation (see Lambert et al.[21] for a review), which could lessen the subjective effects (e.g., reportedly feeling "high," "stimulated") of substances such as cocaine. High levels of progesterone in the mid-luteal phase are also associated with release of glucocorticoids, which help consolidate memories, potentially increasing susceptibility to developing PTSD.[18,141] Once symptoms of PTSD have developed, reductions in the conversion of progesterone to allopregnanolone and pregnanolone can further impair learning of new, non-fearful associations.[150] These and other studies have led to the hypothesis that allopregnanolone-to-progesterone ratios may be better biomarkers for psychiatric symptoms, as decreases in this ratio from the follicular to luteal phases are evident despite increases in absolute levels across the menstrual cycle.[222] Impairments in allopregnanolone synthesis may further impair GABAergic function and leave some women at risk for psychiatric disorders,[20,22] although this causal link has not yet been clearly demonstrated.

Additionally, according to the estrogen hypothesis, estrogen is protective against psychosis (see Reilly et al.[15] for a review). Reductions in estrogen can facilitate or exacerbate psychosis—which is exemplified by the increased risk of psychosis in postmenopausal and postpartum periods. It is therefore consistent with these data that increases in psychotic experiences tend to occur as estrogen levels decline throughout the premenstrual phase.

Regarding cyclic effects on emotional and binge eating, there are likely both hormonal and genetic underpinnings of these behaviors. The pattern of decreased food intake during the first half of the menstrual cycle and increased food intake during the second half of the menstrual cycle is observed in many mammalian species (see Schneider et al.[223] for a review). From an evolutionary standpoint, it is theorized that this pattern allows for a shift in motivational priorities from reproduction to eating. During the first half of the menstrual cycle, motivational priorities surround increasing sexual desire as ovulation approaches. As the likelihood of conception decreases the further from ovulation a woman is in her cycle, motivational priorities shift toward eating.[223] One hypothesis is that a gene × hormone effect could exaggerate this process in women who have binge-eating behavior.[161] For example, an individual who is genetically vulnerable to binge eating may experience increased activation by certain concentrations of estradiol and progesterone during the luteal phase of the menstrual cycle compared to someone without this genetic predisposition.

Finally, the ratio between progesterone and estradiol appears to play an important role in symptom expression, though not in a consistent direction. Lower levels of progesterone coupled with higher levels of estradiol, for example, have been associated with increased smoking,[183] alcohol consumption,[172] and body dissatisfaction.[163] Conversely, higher levels of progesterone compared to estradiol has been associated with increases in intrusive memories in the context of PTSD.[143]

Although we did not examine reproductive mood disorders (e.g., premenstrual dysphoric disorder, postpartum depression, perimenopausal depression) specifically, the literature in these areas suggests that there is a large amount of individual variability in mood sensitivity to ovarian hormones.[201,224–226] Indeed, it is likely that a minority of women exhibit psychological sensitivity to ovarian hormones across the menstrual cycle and that collapsing participant data into groups may mask this variability. As such, researchers are encouraged to assess for subgroups when analyzing menstrual cycle data.

It is also possible that psychiatric symptoms may be a delayed response to hormonal changes and may therefore not reflect the hormonal phase when the symptoms arise. For example, symptoms that have onset in the luteal phase may be

in response to increases in estradiol or progesterone, and symptoms in the early follicular phase may be a response to hormone withdrawal. Indeed, research suggests that some symptoms may peak several weeks following exogenous hormonal manipulation.[201] Schmidt and colleagues[226] argue that menstrual cycle studies may not be able to accurately tease apart the effect of hormonal changes versus absolute hormone levels on psychiatric symptoms, and they encourages the use of hormonal manipulation to address this possible limitation.

Results from High-Quality Studies

Overall, a paucity of studies met our criteria to be considered of high quality. Of the 16 areas examined, three (GAD, trichotillomania, and cocaine use) had no high-quality studies, and three (psychosis, bipolar disorders, and OCD) each had one high-quality study. As such, no strong conclusions can be made for these psychiatric disorders/symptoms. It is recommended that future research continue to explore the presentation of these psychiatric disorders/symptoms across the menstrual cycle. Furthermore, researchers are encouraged to use the flexible design recommendations made by Schmalenberger and colleagues[227] (e.g., using within-subjects designs, incorporating ovulation predictor testing) to enhance study quality and validity of results.

Social anxiety disorder, PTSD, alcohol use, and smoking each had two to three high-quality studies demonstrating relatively consistent results. For social anxiety disorder and PTSD, it appears as though symptoms may worsen in the luteal phase (e.g., greater interpersonal anxiety, more frequent intrusive memories). Alcohol use across the menstrual cycle appears to be influenced by mood such that alcohol use is associated with negative mood in the premenstrual and menstrual phases and is associated with positive mood around ovulation. Regarding smoking, cravings appear to be lower in the luteal phase than in the follicular phase. This may help to explain why quit attempts appear to be more successful when made during the follicular phase: if women experience a reduction in cravings in the luteal phase following quit attempts made during the follicular phase, women may be able to sustain these attempts for a longer period.[178] Cumulatively, these results provide a preliminary understanding of the effect of the menstrual cycle on these symptoms, and more high-quality research within each area is needed.

Results from the two to three high-quality studies for each of the following diagnoses—panic disorder, eating disorders, and BPD—were unclear or inconsistent, and more research is needed to determine the effect of the menstrual cycle on these disorders. We identified 7 high-quality studies examining depression and 14 examining anxiety/stress. Similarly, results from these areas were unclear or inconsistent. Given that the studies in these two areas yielded inconsistent results, it may be that the menstrual cycle has no consistent effects on symptom expression in these areas, although a history of depression or higher levels of baseline depression or anxiety may be a risk factor for menstrual cycle–related exacerbation of symptoms. Alternatively, it may be that the ways in which any menstrual cycle effect is expressed are nuanced and possibly masked by the varying populations and study designs in these studies. Future research aimed at replicating study designs used in these high-quality studies would help elucidate any true menstrual cycle effects.

Research on suicide/suicide attempts was the only area sufficiently studied, with 11 studies meeting criteria to be considered high-quality and yielding consistent results. Overall, results from these studies indicate that rates of suicide/suicide attempts are highest during menstruation.

Limitations

Overall, the data on psychiatric symptoms across the menstrual cycle are limited because of the lack of prospective studies of women with a range of psychiatric disorders in which standardized assessment of the menstrual cycle is collected. This limits our understanding and knowledge of these phenomena, including the implications for specific disorders and the investigation of underlying mechanisms. Varied definitions and assessment of menstrual cycle phases, as well as a lack of standardized assessments of the menstrual cycle—including biological assays of estrogen, estradiol, allopregnanolone, and progesterone, along with their relative ratios, on and off oral contraceptives—all limit existing information. Inconsistencies in the literature may also result from individual variation (see Kiesner[69] for a review). In addition, studies vary in standardization of symptoms for specific psychiatric disorders, further limiting assessment of the existing data.

Varied definitions and assessment of menstrual cycle phases

Menstrual cycle phases are termed and calculated differently across research groups, which may mask or inflate true symptom variability. For example, some researchers define ovulation as a distinct phase or window of days,[174] and others include ovulation as a part of the luteal phase.[164] Assessment of cycle phase is further complicated when comparing studies using hormonal measures and those employing self-reports. Assessing menstrual phases through self-reported days since menstruation is complicated by the known variability in the length of menstrual cycle phases.[196] As such, 16 days since menstruation could, for example, fall during the luteal phase for one woman, coincide with ovulation for another, and, in the case of short luteal phase disorder, fall during the follicular phase for yet another woman.

Lack of standardized assessment of symptoms

Across multiple disorders, symptom assessment is inconsistent. In some studies, researchers employ self-reports, others use behavioral tasks, and still others use observations. These inconsistencies could complicate findings as research indicates there are discrepancies across some forms of symptom assessment.[228] Additionally, psychiatric disorders are comprised of constellations of symptoms, all of which may change independently throughout the menstrual cycle. Laboratory paradigms use

tasks as proxies for stressors or psychophysiological measures. Taken together, these factors create a highly complex and nuanced picture that can be hard to interpret. Just as one example, in BPD, high- and low-arousal symptoms are each affected separately by the menstrual cycle; teasing apart arousal symptoms may shed additional light on cycle-related and hormonal relationships.[229] Across disorders, better understanding these relationships may help inform treatment options or guidance.[230,231]

Sampling biases With few exceptions,[191,192,195] most studies reviewed either included samples of primarily White women or did not provide information on participants' racial and ethnic backgrounds. Given the failure to include this information and the general lack of representation of racial and ethnic minority groups, the generalizability of these findings is an open question. Women from underrepresented groups may experience symptom changes differently, either because of the experience of different acute or chronic stressors (e.g., racial trauma) or because of varying cultural interpretations of symptoms or menstruation.

CONCLUSIONS AND FUTURE DIRECTIONS

The existing literature demonstrates that menstrual-related exacerbation of psychiatric symptoms occurs most commonly during the premenstrual and menstrual phases, and that, for some symptoms, progesterone-to-estradiol ratios play important roles in this relationship. Effective treatment for women with psychiatric disorders will require an understanding of the role of ovarian hormones and other neuroactive steroids such as allopregnanolone but perhaps others as well.[13] To further elucidate the role of ovarian hormones in psychiatric symptom expression, researchers are encouraged to employ prospective designs and incorporate hormone assays in their relevant research, as research has found that retrospective[140] and self-reported[232] assessments of the menstrual cycle are less accurate, which may obfuscate potential findings. Given the mixed findings on the influence of oral contraceptives on mood symptoms,[73,75] as well as research indicating the likely importance of progesterone-to-estrogen ratios, researchers are also encouraged to further assess the effects of various types of oral contraceptives (e.g., androgenic vs. antiandrogenic; high vs. low doses of ethinylestradiol) on psychiatric symptoms. These findings would better highlight the roles of progesterone and estrogen in women's mental health, and also possibly identify oral contraceptives that may assist in symptom stabilization. Furthermore, given the lack of diversity in the included samples, future research should focus on women from racially and ethnically diverse backgrounds to assess the generalizability of these results. Clinicians should also be routinely assessing symptom variability across the menstrual cycle in their patients. The ability to predict worsening of symptoms allows clients to better prepare and utilize effective coping strategies to help manage emotional changes. Clinicians are further encouraged to assess other factors that influence ovarian hormone expression, such as pregnancy status and hormonal contraceptive use.

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