Title: Premenstrual Disorders: A Primer and Research Agenda for Psychologists

Author: Tory Eisenlohr-Moul, PhD[1,2,3]

Affiliations: [1]Department of Psychiatry, University of Illinois at Chicago; [2]Department of Psychology, University of Illinois at Chicago. [3]International Association for Premenstrual Disorders Clinical Advisory Board.

Corresponding author contact information: Department of Psychiatry, University of Illinois at Chicago, Women's Mental Health Research Program, 912 S Wood St., South Tower, Room 335, Chicago, IL, 60612, United States. Tel.: +1 859 317 0503; Email: temo@uic.edu

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Premenstrual Disorders: A Primer and Research Agenda for Psychologists

One of the most consistent findings in psychiatric epidemiology is that of greater female risk for affective disorders; females are twice as likely to be diagnosed with depression (Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993), and three times more likely to make a suicide attempt (Canetto & Sakinofsky, 1998). Female-biased risk for depression and suicidal behaviors emerges around the typical age of **menarche**, when females begin to experience hormone cycling and menstrual bleeding; female-biased risk fades in the mid-50's, around the typical age of **menopause,** when hormone cycling stops (Kessler et al., 1993; Nock et al., 2008). Therefore, although the etiology of sex differences in affective risk is extremely complex (Hodes, Walker, Labonté, Nestler, & Russo, 2017; Rubinow & Schmidt, 2019), females' greater lifetime exposure to reproductive hormone fluctuations likely plays a role. Premenstrual disorders (PMDs) such as **premenstrual dysphoric disorder (PMDD)** and **premenstrual exacerbation (PME)** of behavioral disorders are characterized by significant fluctuations in mood and behavior across the menstrual cycle, and may help to explain why sex differences in affective risk are detectable primarily during females' reproductive years.

For too long, discussions about the role of the menstrual cycle in mood and behavior has waffled between two unhelpful extremes: (1) the argument that all females are predictably impaired each month by premenstrual changes, which is unsupported by empirical evidence (Gehlert, Song, Chang, & Hartlage, 2009), and (2) the argument that cycle effects on mood and behavior are completely culturally constructed, which is equally incorrect (Schmidt, Nieman, Danaceau, Adams, & Rubinow, 1998). Both of these positions should be replaced with a more nuanced, accurate one: most females do not experience important cyclical changes in their emotions, cognition, or behavior, and yet a minority of females (i.e., those with PMDs) do experience impairing, hormone-related changes in mood and behavior and deserve recognition, diagnosis, and treatment (Hartlage, Breaux, & Yonkers, 2014).

With the goal of catalyzing research and clinical efforts in this area, the present paper provides an introduction to PMDs as both a critical area of clinical competence and an exciting area for further clinical research. This article begins with a primer on the menstrual cycle and what is known about PMDs, followed by an overview of research methods for studying the menstrual cycle and PMDs, followed by a research agenda highlighting critical research areas for clinical psychologists interested in engaging the field of PMDs. The article closes with recommendations for working with PMDs in clinical practice. The scope of this article is limited to the basics needed to initiate clinical practice and research work in this area. Especially interested readers can complement this primer with other in-depth epidemiological and methodological reviews (Eisenlohr-Moul et al., 2017; Hantsoo & Epperson, 2015; Owens & Eisenlohr-Moul, 2018; Schiller, Johnson, Abate, Schmidt, & Rubinow, 2016; Wei, Schiller, Schmidt, & Rubinow, 2018).

A Primer on the Menstrual Cycle and Premenstrual Disorders

The Menstrual Cycle (Figure 1). The monthly female reproductive cycle, which lasts an average of 28 days, is structured around two events: *ovulation*, when an egg is released from the ovary for the purposes of possible fertilization an implantation in the uterus (i.e., pregnancy), and *menstrual bleeding*, which is the shedding of the uterine lining and the beginning of a new cycle. These events are coordinated via hormonal feedback loops between the brain and ovaries. The prototypical human menstrual cycle can be divided roughly into two halves, bisected by ovulation. The first part of the cycle – the days from onset of menstrual bleeding to ovulation - is the **follicular phase**, characterized by low progesterone and increasing estradiol that peaks just prior to ovulation. The second part of the cycle – the days between ovulation and the next onset of menstrual bleeding - is the **luteal phase,** characterized by high levels of progesterone and a secondary peak in estradiol; because it is dictated by the lifespan of the corpus luteum (the hormone-generating shell that remains after the egg is released), the luteal phase has a standard length of 12-14 days. Estradiol and progesterone fall precipitously just

prior to and during the first few days of menses (the ***perimenstrual*** days), and the cycle begins again.

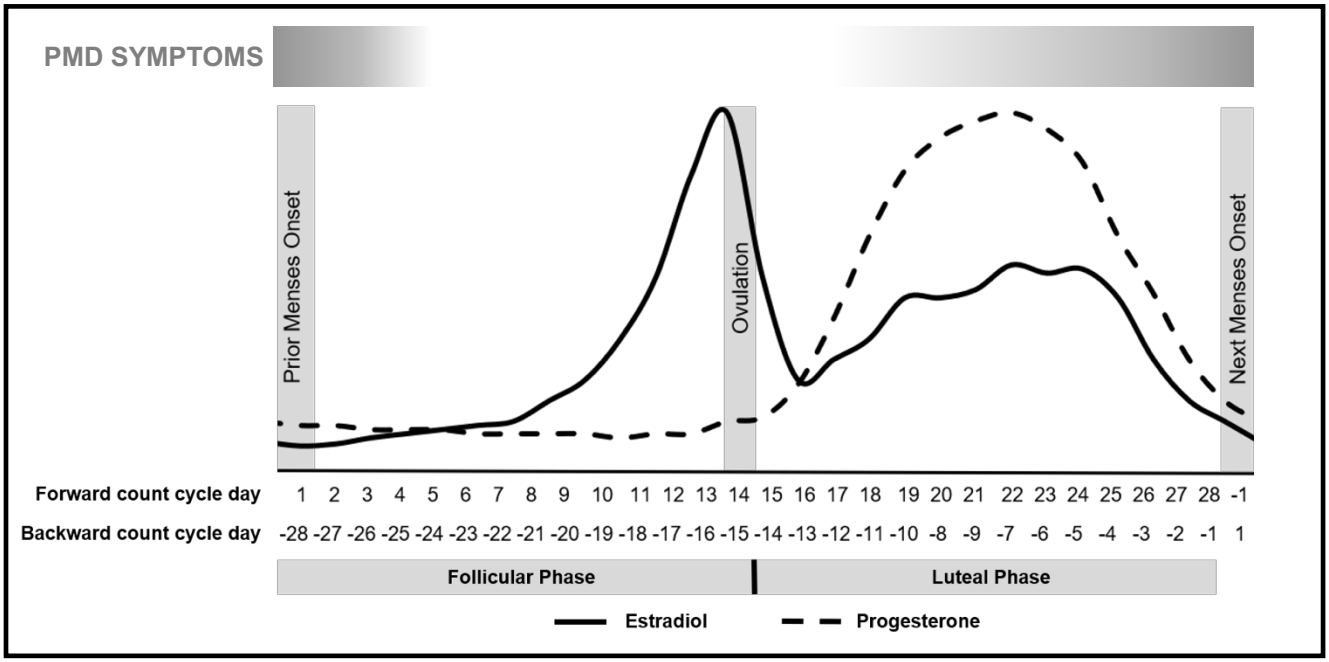

Figure 1. Structure of the menstrual cycle and typical timing of premenstrual disorder (PMD) symptoms.

Individual Differences in Menstrual Cycle Effects on Symptoms

Despite the fact that nearly all reproductive-age females experience the menstrual cycle, only a small percentage suffer from PMDs. Experimental work demonstrates prominent individual differences in neurobiological sensitivity to normal hormone changes, with normal monthly flux causing adverse mood and behavior changes only in some “hormone sensitive” females (Schmidt et al., 1998). This sensitivity likely exists on a continuum, whereby the severity of cyclical symptom change can be absent, mild, moderate, or severe (Eisenlohr-Moul et al., 2017). This work is reviewed in more detail in sections below; however, the notion of individual differences is central to the concept of PMDs and is a critical fact for undercutting the myth that all females suffer deterioration in function across the menstrual cycle. In sum, although most

females do not suffer from clinically significant cyclical changes in emotional (Schwartz et al. 2012; Hengartner et al. 2017; Ben Dor et al. 2013) or cognitive (Leeners et al. 2017; Schmidt et al. 2013) symptoms across the menstrual cycle, experimental work clearly demonstrates that the subset of females with PMDs do suffer from an *abnormal sensitivity to normal ovarian steroid changes* (i.e., ***hormone sensitivity***). Two commonly-recognized types of PMDs are described below.

Premenstrual Dysphoric Disorder (PMDD)

Symptoms, Prevalence, and History of PMDD. PMDD is characterized by the cyclical recurrence of distressing or impairing affective symptoms in the two weeks prior to menses onset (i.e., the luteal phase), with full remission of symptoms in the week after menstrual bleeding (see gradient representing symptom onset and offset in Figure 1). That is, in PMDD, there is a clear luteal phase confinement of symptoms. PMDD is categorized as a DSM-5 mood disorder, and although physical (e.g., cramping, swelling, bloating) and vegetative (e.g., changes in sleep or eating) symptoms can contribute to the diagnosis, at least one cyclical symptom must be emotional. The core emotional symptoms of PMDD in DSM-5 include mood swings, rejection sensitivity, anger or irritability, interpersonal conflict, depressed mood, hopelessness, feelings of worthlessness and guilt, and anxiety; at least one of these must be present for diagnosis. Additional DSM-5 symptoms include decreased interest, difficulty in concentration, lethargy or lack of energy, increased cravings or appetite, hypersomnia or insomnia, feeling overwhelmed or out of control, or physical symptoms (breast tenderness, muscle pain, bloating, weight gain). In addition to requiring at least one emotional symptom to show the cyclical pattern, the DSM-5 diagnosis requires five or more of these eleven possible symptoms to show a pattern of luteal phase confinement, a stringent cutoff intended to reduce the risk of overdiagnosis (i.e., pathologizing mild premenstrual changes). Although one can make a provisional diagnosis of PMDD based on self-report alone, a full diagnosis requires two

months of daily DSM-5 symptom ratings due to the high false positive rate (Roy-Byrne, Rubinow, Hoban, & Parry, 1986).

PMDD is unique among mental disorders in that it is primarily defined *not* by its content, but by its time course (i.e., luteal phase confinement of symptoms). However, observational studies do indicate that, emotionally, PMDD is characterized most commonly by irritability and mood swings, with symptoms of anxiety being the next most common, and symptoms of depression being the least common of the core emotional symptoms (Pearlstein, Yonkers, Fayyad, & Gillespie, 2005). Across patients with prospectively-diagnosed PMDD, the greatest severity of symptoms occurs between day 3–4 prior to onset of menses and 3 days after the onset of menses (Hartlage, Freels, Gotman, & Yonkers, 2012). For some, the symptoms begin following ovulation and persist through the two-week luteal phase, whereas others have symptoms only in the final week before menses. In large longitudinal studies, the point prevalence of DSM-5 PMDD is estimated around 5.5% (Epperson et al., 2012; Gehlert et al., 2009).

After previous iterations of the diagnosis (e.g., late luteal phase dysphoric disorder) were relegated to the Appendices of DSM-IIIR, DSM-IV, and DSM-IV-TR, PMDD transitioned to full diagnostic status in the DSM-5 in 2013. Originally, the proposal to include PMDD in the DSM was met with skepticism and concern about potential stigmatization or harm; however, these issues have been thoroughly investigated and generally debunked, with the overwhelming weight of the evidence indicating that acknowledgement and treatment of PMDD is appropriate (see Hartlage et al., 2014, for a data-driven rebuttal of these issues).

Biological Mechanisms of PMDD. A pervasive misconception about PMDD is that is it caused by abnormal hormone levels, hormone metabolism, or hormone “imbalance.” In fact, those with PMDD cannot be differentiated from controls by their peripheral hormone levels or patterns across the menstrual cycle (Schmidt, Purdy, Moore, Paul, & Rubinow, 1994) or hormone metabolism (Nguyen et al., 2017); put simply, their reproductive hormone function

across the cycle is *normal.* However, a number of studies have demonstrated that most patients with prospectively-diagnosed PMDD show an abnormal behavioral response to normal hormone changes. In several key experiments, Schmidt et al. have demonstrated that inducing a reversible menopause (using GnRH analogue injections) eliminates symptoms of PMDD, whereas addback of either estradiol or progesterone causes a resurgence of symptoms (Schmidt, Nieman, Danaceau, Adams, & Rubinow, 1998). Critically, these symptoms of hormone addback subside after 2-3 weeks of stable hormone addback, suggesting that PMDD is caused not by an abnormal sensitivity to elevated levels of hormones, but rather by an abnormal sensitivity to the normal cyclical *changes* in hormones that occur each month following ovulation (Schmidt et al., 2017).

The exact mechanism (or, more likely, mechanisms) of this abnormal sensitivity to post-ovulatory hormone surges in PMDD is unknown, and the search to uncover critical pathways is ongoing (reviewed in Hantsoo & Epperson, 2015). Several lines of investigation are focused on altered luteal phase serotonergic function in PMDD (Roca et al., 2002), altered function of the GABA-A receptor and its response to GABAergic progesterone metabolites (MacKenzie & Maguire, 2014; Martinez et al., 2016), and, most recently, altered cellular gene expression relevant to hormone processing (Dubey et al., 2017). Several expert, up-to-date reviews are available for those who wish to read further about the state of the knowledge in this small but growing area (Schiller et al., 2016; Wei et al., 2018). However, for the purposes of this primer, the critical point is that *PMDD is caused by an abnormal neurobiological sensitivity to normal hormone changes across the menstrual cycle, and not abnormal or disordered reproductive hormones or function*.

Evidence-Based Medical Treatment of PMDD. At present, evidence-based treatment of PMDD is primarily medical. Nevertheless, clinical psychologists should be aware of the primary empirically-supported treatments for PMDs.

Based on a number of positive randomized controlled trials, **selective serotonin reuptake inhibitors (SSRIs)** are the first line treatment for PMDD (Casper & Yonkers, 2019; Meir Steiner et al., 2006). About 60% of prospectively-diagnosed PMDD patients respond to SSRIs (Halbreich, 2008). Notably, SSRIs work rapidly in PMDD, beating placebo after just 24 hours (Steinberg, Cardoso, Martinez, Rubinow, & Schmidt, 2012); therefore, they are equally effective when used only in the luteal phase (vs. all month long) (Meir Steiner et al., 2006).

If SSRIs are not effective, treatment moves toward suppressing hormone flux by preventing ovulation. The least invasive method of ovulation suppression is **combined oral contraceptives (COCs)** taken on a 24-4 (24 active pills, 4 inactive pills) or continuous schedule (i.e., with a shortened or eliminated hormone-free interval). Two large RCTs demonstrate a benefit of a drospirenone-containing oral contraceptive when used on a 24-4 schedule (Lopez, Kaptein, & Helmerhorst, 2012). Clinical trials using continuous COCs with levonorgestrel, another progestin, demonstrate more mixed effects (Freeman et al., 2012).

Some individuals with PMDD develop chronic mood symptoms on COCs or do not experience relief (Gingnell et al., 2013); in this case, other cycle suppression treatments can be pursued. Monthly injections of **GnRH analogues** (e.g., leuprolide acetate), which are used routinely by gynecologists to treat endometriosis and other gynecological complaints, can be used to temporarily shut down hormone production by the ovaries, causing a month-long reversible menopause. A meta-analysis of RCTs reported consistent beneficial effects of GnRH analogues in PMDD (Wyatt, Dimmock, Ismail, Jones, & O'Brien, 2004). However, in order to maintain bone and heart health while also preventing endometrial cancer, **addback of both estradiol and progesterone** is necessary while taking GnRH analogues. In the first month of this hormone addback (on top of the GnRH analogue), there is a temporary resurgence of PMDD symptoms; however, this subsides after a month of stable addback (Schmidt et al., 2017).

If the GnRH analogue plus hormone addback (often called a “menopause trial”) is an effective treatment, and the patient elects for it, a **total hysterectomy with bilateral oophorectomy** (removal of the uterus and both ovaries) is indicated to remove all hormone flux and initiate surgical menopause; longitudinal studies indicate that this surgical procedure is effective for most patients with PMDD who have experienced remission on GnRH analogues (Cronje, 2004). Of note, bilateral oophorectomy is the critical element of this treatment—if either ovary remains, ovulation (and, therefore, PMDD) still occurs. Removal of the uterus is also recommended, since it eliminates the need for post-surgical progesterone treatment, and **unopposed estradiol addback** can be used to manage menopausal symptoms and maintain bone and heart health.

Psychosocial Mechanisms in PMDD. A small number of studies have examined psychological factors associated with prospectively-diagnosed PMDD and severity of symptom expression. Compared with controls, patients with PMDD show higher trait levels of brooding rumination (Craner, Sigmon, Martinson, & McGillicuddy, 2014), and higher brooding rumination among patients with PMDD prolonged residual symptoms in the early follicular phase (Dawson et al., 2018). Patients with PMDD also report higher trait levels of avoidant or impulsive behaviors than controls (Craner et al., 2014; Petersen et al., 2016). In response to a negative affect induction, patients with PMDD report more self-focused attention, a trait associated with rumination and poor emotion regulation, than controls (Craner, Sigmon, & Martinson, 2015). Another study found that patients with PMDD showed within-person increases in self-focused attention during the premenstrual week that partially mediated degree of premenstrual mood changes (Craner, Sigmon, & Young, 2016). Finally, another found that cyclical changes in anhedonia and difficulty concentrating were the DSM-5 PMDD symptoms most strongly associated with cyclical impairment (Schmalenberger, Eisenlohr-Moul, Surana, Rubinow, & Girdler, 2017).

A larger number of studies have also examined the role of psychosocial stress in premenstrual symptoms. Although some studies using cross-sectional methods to diagnose PMDD (a method known to produce an unacceptable percentage of false positives) have observed greater prevalence of trauma exposure in PMDD vs. controls (Pilver, Levy, Libby, & Desai, 2011), more rigorous studies in which PMDD was prospectively-diagnosed did not find an increased exposure to trauma in individuals with this condition (Segebladh et al., 2011). However, another study in a sample of patients with prospectively-diagnosed PMDD found that the strength of the daily link between progesterone levels and symptoms was stronger in patients with histories of trauma exposure, suggesting a possible influence of trauma on the *severity* (rather than the occurrence) of luteal phase symptoms in PMDD (Eisenlohr-Moul et al., 2016). In addition to historical trauma exposure, current stress may increase risk for PMDD symptoms. A prospective study following medical students who were or were not beginning a stressful shift-based clinical assignment found greater increases in premenstrual mood deterioration among patients in the high stress condition (Namavar Jahromi, Pakmehr, & Hagh-Shenas, 2011). In another study, cycles preceded by higher-than-usual perceived stress showed greater premenstrual mood deterioration (Gollenberg et al., 2010). More work is needed to explore the biological and psychological mechanisms by which stress may cause increases in PMDD symptoms.

Psychotherapy for PMDD. Several RCTs have examined the impact of time-limited **cognitive behavioral therapy** (mean of 6 sessions) on symptoms of PMDD, and generally find a small-to-medium effect sizes for benefit relative to waitlist control (reviewed in Kleinstäuber, Witthöft, & Hiller, 2012)). However, a recent meta-analysis demonstrated no effect of CBT (vs. control) on PMDD symptom severity, instead finding only a significant reduction in impairment (Kleinstäuber et al., 2012). Unfortunately, several of the studies did not conduct prospective diagnosis of PMDD and did not rule out comorbid conditions, calling into question the nature of their samples; further, the total number of patients studied in these trials was only N=173.

Therefore, larger trials with more rigorous inclusion criteria are needed before a firm conclusion about the efficacy of CBT in PMDD can be made.

On the other hand, very little evidence is available regarding the emotional, cognitive, and behavioral mechanisms of PMDD, and therefore CBT protocols targeting any unique mechanisms that may exist in PMDD have yet to be developed or tested. The limited existing evidence regarding the psychopathology of PMDD indicates roles for rumination, avoidant or impulsive emotion-driven behaviors, and anger or interpersonal conflict as drivers of PMDD symptom severity (Pearlstein et al., 2005). Therefore, treatments that focus on development of concrete behavioral skills for use in responding to an array of negative emotions such as dialectical behavior therapy (DBT; Linehan, 2014) or the unified protocol (UP; Barlow et al., 2011) could, in theory, be more effective than generic CBT for reducing symptoms and impairment in PMDD. Finally, it should be noted that PMDD can be accompanied by cyclical suicidality; in such cases, DBT would seem to be a rational treatment approach for reducing suicide risk (Linehan et al., 2006).

Perimenstrual Exacerbation (PME) of Underlying Disorders

Symptoms, Prevalence, and History of PME. Premenstrual exacerbation (PME) of an underlying disorder occurs when chronic symptoms of an existing psychiatric disorder are significantly worsened before or during menses. As noted above, PMDD is characterized by a *luteal phase confinement* of symptoms, whereas in PME symptoms are chronic but worsen around the onset of menses. PME has been documented to occur in a wide variety of medical diagnoses (Pinkerton, Guico-Pabia, & Taylor, 2010). The course of PME is less well-defined than PMDD, but generally follows similar pattern in which symptoms peak in the late luteal phase and show improvement in the mid-to-late follicular phase (see gradient in Figure 1). Of note, in addition to worsened symptoms prior to menses, addictive disorders may show a primary or secondary worsening around ovulation, when surging estradiol increases reward sensitivity (e.g., Martel, Eisenlohr-Moul, & Roberts, 2017).

So far, prevalence estimates are only possible for PME of depressive disorders, highlighting the critical need for additional work in this area. In a large prospective study of females with depressive disorders in the community, around 60% of the sample demonstrated significant (>= 1 person-standard-deviation of that symptom) PME of at least one symptom across two menstrual cycles (Hartlage, Brandenburg, & Kravitz, 2004), indicating that PME is a common phenomenon in depressive disorders that may complicate the course of treatment in females. The fact that PME of depression is common may suggest that it plays a role in female-biased depression risk, since PME may serve to initiate or maintain depressive episodes (Kiesner, 2017).

Unfortunately, epidemiological data is lacking to estimate the prevalence of PME in any other mental disorder. Many small (N<50) longitudinal studies have observed main effects of the cycle on symptom severity in various mental disorders, suggesting the likelihood that females diagnosed with those disorders are similarly at risk for (though not necessarily suffering from) PME. These disorders include bulimia nervosa (Edler, Lipson, & Keel, 2007), borderline personality disorder (Eisenlohr-Moul, DeWall, Girdler, & Segerstrom, 2015; Eisenlohr-Moul et al., 2018)), obsessive-compulsive disorder (Vulink, Denys, Bus, & Westenberg, 2006), bipolar disorder (Dias et al., 2011; Teatero, Mazmanian, & Sharma, 2014), schizophrenia (Seeman, 2012), substance abuse (Martel et al., 2017), and post-traumatic stress disorder (Nillni et al., 2015). Of note, a longitudinal study in bipolar disorder demonstrated that patients with PME of bipolar (vs. those females with bipolar without PME) suffered a more severe and chronic course of illness (Dias et al., 2011). In addition, a large number of studies have indicated an increased risk of suicide attempt and death around the onset of menses (Saunders & Hawton, 2006). Despite these main effects, it is not likely that all patients with these disorders suffer from PME; rather, similar to what was observed in PME of depression, risk for PME probably varies on a spectrum within the larger diagnostic group and may serve to exacerbate or prolong symptoms

for some female patients. In sum, it seems likely that PME is present in many—but not all—cases of female psychopathology.

Despite years of research studies demonstrating the occurrence of PME in various disorders, PME is not yet acknowledged as an official diagnostic specifier in the DSM-5 or in any other diagnostic classification system. However, one could imagine a future iteration of the DSM in which "with perimenstrual exacerbation" can be specified in order to indicate the presence of this complicating factor that may require specific adjunctive treatment. The most relevant precedent for such a specifier would be the option to specify "with peripartum onset" in the DSM-5 diagnosis of mood disorders (APA, 2013)). However, for the moment, PME is not generally acknowledged or assessed in clinical practice, despite evidence for its existence.

Biological Mechanisms and Treatment of PME. Although one might expect that the biological causes of PME are the same as that of PMDD, several recent clinical trials have demonstrated that, at least in patients with PME of depression, many PMDD-specific treatments are not effective, calling into question the notion of a globally shared PMDD and PME pathophysiology. Drospirenone-containing COCs were recently evaluated as an adjunct to SSRI for patients with PME of depression, and failed to beat placebo (Peters, Freeman, Kim, Cohen, & Joffe, 2017). Further, randomized controlled trials have demonstrated that GnRH analogues are not more effective than placebo for patients with PME of depression (Freeman, Sondheimer, & Rickels, 1997; Freeman, Sondheimer, Rickels, & Albert, 1993). Finally, secondary analyses of a subsample of patients with PME of ongoing disorders in an evaluation of isoallopregnanolone, a GABA-A allopregnanolone antagonist currently in development, found a strong benefit relative to placebo for PMDD but no benefit for patients with PME of an ongoing disorder (Bixo et al., 2017). This could indicate that PMDD is characterized by altered GABAAR function, whereas PME of some disorders (e.g., depression) is not. No trials have examined the effect of SSRI or CBT on PME of depression or any other disorder, and these remain the first-line treatments of choice for individuals with depression with or without PME. In sum, PME, especially of

depressive symptoms, may have a different biological mechanism than PMDD and may require a different treatment approach.

Given the evidence that PME of depression fails to respond to hormonal treatments for PMDD, which focus on suppression of hormones to follicular or menopausal levels, it is possible that, unlike in PMDD, individuals with PME of depression are sensitive to hormone withdrawal or depletion. This is supported by a small crossover clinical trial demonstrating a benefit of perimenstrual ovarian hormone *supplementation* (i.e., prevention of hormone withdrawal) in patients with PME of depression with accompanying suicidality (Eisenlohr-Moul et al., 2018). More work is needed in this area to determine whether and how such treatments may be broadly effective in PME of depression.

Comorbidity and Overlap Between PMDD and PME. It is important to recognize that neither PMDD nor PME are monolithic groups, and it is likely that *some* patients with PME are suffering from similar hormone sensitivities to those with prototypical PMDD and will therefore respond to similar treatments focused on reducing the negative effects of fluctuating hormones (see PMDD section above). While it is often the case that an individual has PMDD, PME, or neither, it is also possible to have both PMDD and PME (Hartlage & Gehlert, 2001). As an example, it is possible to have PME of depression (chronic depression with worsening before and during menses) and also have a PMDD pattern (i.e., luteal phase confinement) of five other symptoms—usually physical symptoms, mood swings, anger/irritability, rejection sensitivity, and anxiety symptoms that ONLY appear between ovulation and menses. In sum, more work is needed to understand who is sensitive to what kind of hormone changes, and how this can be diagnosed and treated most efficiently.

Research Priorities for Improving Understanding and Treatment of PMDs

Clinical psychologists have unique areas of methodological competencies, especially differential diagnosis and assessment, that may make them highly suited to contributing to research on PMDs. Further, given the increasing focus on research and biology in training

programs, many clinical psychologists have additional areas of expertise, such as affective neuroscience or psychoneuroendocrinology, that can be readily used to contribute to research on PMDs. Below is a primer on measurement of the menstrual cycle and PMDs, followed by a review of several important areas for further research with particular attention to the unique ways in which clinical psychologists can contribute.

How to measure the menstrual cycle in longitudinal studies

Using cycle counting methods to establish menstrual cycle day (and categorical menstrual phase) is an inexpensive and powerful way to understand or covary the effects of the cycle on a repeated outcome of interest in a longitudinal study. In order to generate both cycle day and cycle phase variables for use in models, three dates are needed: the date of the observation, the date of the prior menses onset, and the date of the subsequent menses onset (see Figure 1 for counting visuals). Backward-counting from the day before menses onset (day -1) to day -15 is recommended for delineating the luteal phase and its sub-phases; forward-counting from the day of menses onset (day 1) to day 10 is recommended for delineating the follicular phase. (Of note, without backward count, cycle day and phasing is highly inaccurate and untrustworthy, since the length of the follicular phase is variable both between and within people). This results in a “cycle day” variable (of note, without a day 0) that can be used to graph the impact of the entire cycle from ovulation to the next mid-follicular phase; it can also be further categorically coded into a within-person cycle phase variable (e.g., Edler et al., 2007). For more information about the many options for coding menstrual cycle phases from this cycle day variable in order to test hypotheses about the impact of cycle phases on an outcome of interest, see our recent methodological paper on this topic (Schmalenberger & Eisenlohr-Moul, 2019). Additional biological measures, such as urine luteinizing hormone testing, basal body temperature, or hormone measures can be used to validate and correct cycle phasing decisions (Schmalenberger & Eisenlohr-Moul, 2019); however, when both backward and forward counting

are possible for a given observation (see Figure 1), this is a reliable and valid method of measuring the impact of the menstrual cycle in research studies.

How to study PMDs

Simply put, studying PMDs requires repeated measures in order to carry out meaningful hypothesis tests about cyclical symptom changes. Given that retrospective measures of PMDD (and PME) lack specificity, single-time-point self-report measures of PMD symptoms are not acceptable for publication or citation as evidence of such symptoms. In order to conclude that a female has cyclical mood change or a PMD, symptoms must at least be measured at weekly (and preferably daily) intervals.

Our laboratory has developed a standardized scoring system for making the diagnosis of PMDs called the Carolina Premenstrual Assessment Scoring System based on daily ratings (C-PASS; Eisenlohr-Moul et al., 2017). A worksheet with detailed instructions, an excel macro, and a SAS macro are available in the resources section for facilitating use of the C-PASS system (see Resources section below). The details of this scoring system can be found in the validation paper (Eisenlohr-Moul et al., 2017); in brief, for symptom to meet C-PASS criteria for the PMDD pattern in a given cycle, it must meet four different requirements: *relative symptom elevation:* percent symptom elevation during premenstrual phase relative to postmenstrual phase >=30% (percent change calculations are explained in the linked worksheet above); *absolute clearance*: postmenstrual week maximum <=3; *absolute severity*: premenstrual week maximum >=4; and *duration:* at least two premenstrual week days >=4). The cycle-level diagnoses of PMDD are made by counting the number of DSM-5 symptoms meeting criteria on all four dimensions in a given cycle (must be >=5) and noting if a core emotional symptom meets criteria (number of core symptoms >=1). Next, the C-PASS makes the diagnosis of PMDD at the person level by counting the number of cycles meeting diagnostic criteria for PMDD (cycles meeting criteria >=2). The diagnostic procedure for PME is exactly the same, with one exception: the requirement for *absolute clearance* is omitted from the process. The C-PASS scoring system

(Eisenlohr-Moul et al., 2017), including the excel and SAS macro, can be used in research either to **diagnose individuals categorically** (e.g., individual A meets criteria for PMDD across two cycles of daily ratings, whereas individual B does not) and **measure symptom cyclicity dimensionally** (e.g., individual A showed an average of 45% premenstrual elevation of depression across two cycles; individual B showed an average of 28% premenstrual elevation of depression across two cycles). In addition to these methods, which use daily ratings to create between-person variables, daily symptoms can also be modeled directly as repeated outcomes in multilevel models, using coded menstrual cycle variables (Schmalenberger & Eisenlohr-Moul, 2019) as categorical or continuous predictors (e.g., as in (Dawson et al., 2018; Eisenlohr-Moul et al., 2018).

If one simply wishes to exclude potential participants who might have a PMD, retrospective questionnaires such as the Premenstrual Symptoms Screening Tool (PSST) can be used (Steiner et al., 2003), since it has good sensitivity (but inadequate specificity for clinical diagnosis). Although use of this type of retrospective questionnaire will also exclude many individuals who do not actually have PMDs (e.g., false positives), it will also likely eliminate nearly all individuals with PMDs (Eisenlohr-Moul et al., 2017).

Critical Research Areas in PMDs

Improving Assessment of PMDs. There are many unanswered research questions in the field of PMDs related to assessment, an area in which clinical psychologists are well-trained. As noted above, problems of poor specificity in retrospective PMD assessments have led to the DSM-5 requirement that PMDD can only be officially diagnosed after observing the relevant pattern in two months of daily symptom ratings. This is extremely burdensome, and it is possible that new measurement developments could reduce this burden for patients and providers and improve detection of PMDs. Improvement of this process could take many forms, including identification of other retrospective self-report questions about PMD symptoms that provide greater specificity in predicting a positive diagnosis based on daily ratings, use of passive

tracking of behavior or physiology, or integration of informant retrospective report of PMD symptoms as more specific diagnostic indicators.

An additional area in desperate need of effort is the estimation of prevalence of PME in DSM-5 disorders other than depression; given the requirement of prospective daily confirmation, this will necessitate the use of large representative samples followed across several cycles (e.g., Hartlage et al., 2004). A better understanding of the scope of PME across each DSM-5 disorder is necessary to underscore the public health relevance of PME in different disorders. Given the heterogeneity of PMDs, more work is needed to identify whether there are subtypes of PMDs with respect to time course across the cycle or symptom type. This work may be useful for predicting differential responses to treatments. For example, it could be the case that PME of certain anxiety disorders show more in common with PMDD (in terms of cyclical course or content) than does PME of depression, which could have important implications for treatment of PMEs. We also need information about the impact of PME on resistance to standard treatments in various disorders, as it may be the case that PME of some disorders is more detrimental to female outcomes than PME of others (e.g., Dias et al., 2011).

Identifying Key Psychological Mechanisms of PMDs. As noted above, only a handful of studies have examined the psychological mechanisms (e.g., rumination, self-focused attention, emotion-related impulsivity) of cyclical symptom expression in PMDD; and virtually no attention has been paid to psychological mechanisms of cyclical symptom exacerbation in PME of other disorders. Many potential avenues in this area remain untapped. For example, in order to intervene early in the luteal process of PMDD symptom expression, it will be critical to understand which symptoms appear first, and which symptoms may be central to driving expression of the rest. Network analysis studies of premenstrual symptoms, as well as longitudinal changes in network structure across the cycle, could help to clarify the core processes that might be targeted by psychotherapies. Additionally, nearly all studies of PMDs have used self-reported symptoms, whereas directly observed *behavior* in PMDs remains

unstudied. This is a critical area for laboratory studies in experimental psychopathology research. Finally, given the evidence that interpersonal symptoms such as anger/irritability, rejection sensitivity, and interpersonal conflict are among the most common and impairing symptoms in PMDD (Pearlstein et al., 2005), laboratory studies focused on behavioral analysis of dyadic interactions are also warranted to clarify how PMD symptoms may change interpersonal interactions, and whether interpersonal skills training or partner-supported therapies may be rational treatment avenues.

CBT interventions for PMDD have failed to show significant effects of symptom severity in a recent meta-analysis (Kleinstäuber et al., 2012). Perhaps this is unsurprising, given that so little is understood about the cognitive and behavioral mechanisms of PMDs. Before developing and testing further psychotherapeutic interventions for PMDs, more information may be needed about the time course of various symptoms in the luteal phase, and therefore how specific cognitive and behavioral processes might be modified to reduce symptom escalation. Existing studies in PMDD have implicated emotion dysregulation, impulsivity, rejection sensitivity, interpersonal conflict, and cognitive problems in the expression of PMDD; it seems warranted to examine these processes further in laboratory settings, and to evaluate which skills might mitigate luteal (vs. follicular) emotional and physiological reactivity in the moment for those with prospectively-diagnosed PMDD. Once key mediators and promising skills have been identified, rational treatments can be constructed and evaluated in clinical trials.

Clarifying Biological Underpinnings of PMDs. The pathophysiology of PMDs (mostly PMDD) is a small but rigorous area of neurobiological research, historically carried out primarily by a few psychiatrists and behavioral scientists without clinical training (Wei et al., 2018). Increasingly, clinical psychologists receive basic training in the neurobiological bases of mood, cognition, and behavior, and often receive advanced training in affective neuroscience, psychoneuroendocrinology, and other areas relevant to the study of PMDs. Accordingly, many clinical psychologists have specific skills (e.g., in randomized controlled trials, peripheral

endocrine and immune measures, and imaging methods such as fMRI, EEG, or PET) that can be readily applied to generating knowledge about the biological underpinnings of PMDs. Of particular note, researchers have yet to uncover the fundamental causes of abnormal hormone sensitivity in PMDs. Studies using mechanistic trials to uncover the brain mechanisms of evidence-based (or novel) treatments represent one key area that could lead to a clearer understanding of the pathophysiology of PMDs. Thoughtfully-designed observational studies are also needed to uncover possible neurobiological PMD subtypes of change across the cycle, which may help to identify more granular, useful treatment targets in PMDs, or help to predict responses to existing treatments.

The biological underpinnings of PME in females with depression is a critically understudied area. Around 60% of females with a depressive disorder experience clinically significant worsening of at least one symptom (Hartlage et al., 2004), and it has recently become clear that the pathophysiology of PME in females with depressive disorders is unique from that of PMDD (reviewed above). Therefore, a fresh set of clinical trials, experimental laboratory studies, and longitudinal analyses are needed to understand the pathophysiology of this condition. Studies are also needed to understand whether PME of other disorders, such as borderline personality disorder, are also underpinned by a unique pathophysiology, or whether they share important biological underpinnings with PMDD. Suppressed metabolism of hormones to GABAergic metabolites in females with depression (Agis-Balboa, Guidotti, & Pinna, 2014) and PSTD (Pineles et al., 2018) may lead to a greater sensitivity to perimenstrual hormone withdrawal in some individuals, and a preliminary trial in our laboratory provides initial support for this hypothesis (Eisenlohr-Moul et al., 2018). It will be critical to replicate and probe the mechanisms of such effects using diverse methodologies.

Finally, there is currently no longitudinal evidence about how PMDs develop and interact with psychopathology during critical developmental periods, although a theory has recently been proposed (Kiesner, 2017). Longitudinal work is sorely needed in this area and could

uncover interactive roles of genetics and particular environmental stressors in the onset of PMDs. Further, this work may help us to understand whether and how cyclical mood changes and chronic psychopathology mutually reinforce and perpetuate one another over time. This work may ultimately lead to detection and treatment of PMDs at critical time points that could prevent a long-term impact of PMDs on female-biased risk.

Clinical Applications

Psychotherapy Patients as a Group at Risk for PMDs

The majority of patients seeking psychotherapy are females of reproductive age (Vessey & Howard, 1993), who either have a monthly menstrual cycle or are taking hormonal medications that can cause hormone fluctuations (Willis, Kuehl, Spiekerman, & Sulak, 2006). These facts alone are sufficient to recommend that all psychotherapists receive some rudimentary training in the menstrual cycle and PMDs; however, clinical psychology and other psychotherapy training programs do not yet provide training in this area. There have been good reasons for caution around these issues in the past, such as a concern about stigmatizing or disempowering females and a lack of empirical evidence about the scope of PMDs (Hartlage et al., 2014); however, given the strong experimental evidence for individual differences in hormone sensitivity that has accumulated over the past 30 years (Wei et al., 2018), the time is right for psychotherapists and clinical scientists to receive basic training in and contribute more regularly to the field of PMDs.

Clinical psychologists (both non-prescribing and those with prescribing privileges) can and should take an active role in the assessment, treatment planning, and management of PMDs. Many psychologists may feel that biological processes such as the menstrual cycle are beyond there scope of practice or area expertise. However, a basic knowledge of the menstrual cycle and PMDs can be conceptualized as similar to knowing how sleep, diet, exercise, caffeine intake, or alcohol use affect mood in some individuals. Although clinical health psychologists and others with a biological bent may engage more intensively in the PMD treatment process,

all clinical psychologists can quickly gain a basic understanding of the menstrual cycle and PMDs.

Recommendations for Assessment, Referral, and Treatment of PMDs

The basic clinical tasks for a psychologist in this area can be summarized as (1) assessment and diagnosis of PMDs using daily ratings across two cycles, (2) referral to a prescriber with an awareness of evidence-based guidelines for PMD treatment, (3) helping the patient monitor progress using daily ratings, and (4) using psychotherapies to reduce PMD-related impairment and treat comorbidities. The first step, assessment and diagnosis, is appropriate for all females with concerns about premenstrual symptoms who are naturally-cycling (i.e., those who are not pregnant, breastfeeding, or using the contraceptive pill, patch, or ring—each of which prevent ovulation and the natural cycle). Assessment begins by having the patient track their symptoms daily across at least two menstrual cycles, preferably using the Daily Record of Severity of Problems (DRSP; Endicott, Harrison, & Nee, 2006), which measures all DSM-5 PMDD symptoms. Next, graphs are inspected to determine whether symptoms are confined to the luteal phase (PMDD), an exacerbation of a chronic disorder (PME), a mixture of both (e.g., chronic depression with PME as well as >=5 other symptoms confined to the luteal phase, i.e., PMDD), or none of the above. Tools such as Prementrics App and the C-PASS scoring system, which can streamline collection and diagnosis of daily ratings, are linked in a Resources section below. Referral to a competent prescriber comes next. Starting with a reproductive psychiatry specialist is ideal, but not always possible; in the absence of an expert, most prescribing providers with access to evidence-based treatment guidelines (linked in the resources section) can carry out first-line treatments and eventually refer to a gynecologist if a GnRH analogue trial or oophorectomy with hysterectomy is desired. Finally, as the patient engages in medical management of their symptoms, the psychologist can help the patient to continue tracking their symptoms and any side effects of treatment using the same method used for diagnosis; this allows an objective evaluation of how treatments are impacting symptoms

and empowers the patient to communicate clearly with their prescribing provider. Although CBT is not yet evidence-based for reduction of symptoms in PMDD, it is effective for reducing impairment and may be required for treatment of comorbid conditions (Kleinstäuber et al., 2012).

Summary and Conclusion

Premenstrual disorders (PMDs) such as premenstrual dysphoric disorder (PMDD) and premenstrual exacerbation (PME) of underlying conditions represent an important public health problem with bearing on the female-biased risk of affective disorders and suicidal behaviors. Furthermore, although the majority of psychotherapy patients and psychological research subjects are females of reproductive age who are at high risk of cyclical mood changes, clinical psychologists do not usually receive basic training or engage in this area of work. Very reasonable concerns about perpetuating stereotypes about female fragility or the empirical status of PMDs may have prevented psychologist training and engagement in PMDs in the past. However, the current evidence unequivocally supports the acknowledgement, clinical engagement, and research study of PMDs by clinical psychologists, and the application of psychologist expertise to these understudied and undertreated conditions will undoubtedly enrich the field.

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RESOURCES

Assessment of PMDs:

- **Paper and Pencil** version of the Daily Record of Severity of Problems (DRSP) for collecting daily symptom ratings:
  - https://www.aafp.org/afp/2011/1015/afp20111015p918-fig1.pdf
- **Prementrics App** for collecting, graphing, and sharing daily symptom ratings**:**
  - https://itunes.apple.com/us/app/prementrics/id943769267?mt=8
  - https://play.google.com/store/apps/details?id=com.sraoss.prementrics&hl=en_US
- **C-PASS Scoring System** for diagnosing and quantifying PMDs symptom-by-symptom in complex clinical cases or research studies:
  - https://www.med.unc.edu/psych/wmd/resources/clinicians-researchers/

Treatment of PMDs:

- **Evidence-Based Treatment Guidelines**
  - https://www.uptodate.com/contents/treatment-of-premenstrual-syndrome-and-premenstrual-dysphoric-disorder
  - https://www.rcog.org.uk/globalassets/documents/guidelines/gt48managementpremensturalsyndrome.pdf

International Association for Premenstrual Disorders:

- www.iapmd.org
  - Evidence-based educational content for patients, providers, and caregivers
  - Free peer-support services for patients
  - Provider directory