**Premenstrual Exacerbation of Mental Health Disorders: A Systematic Review of Prospective Studies**

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**Abstract**

Purpose: Mental health disorders can be exacerbated during periods of hormonal fluctuation (e.g., pregnancy, menopause) and the risk factors for sensitivity to these fluctuations are similar to those of mental disorders (e.g., trauma). However, the extent to which hormonal fluctuations during the menstrual cycle impact symptoms of pre-existing mental disorders remains unclear. Prospective methodology is considered the gold standard for measuring symptoms across the menstrual cycle. Thus, the aim of the review was to address this knowledge gap by summarising all available studies prospectively measuring symptoms of mental disorders across the menstrual cycle.   
Methods: A systematic review with narrative synthesis was conducted; meta-analysis was precluded due to methodological heterogeneity of included studies. Electronic databases MEDLINE, Embase, PyschINFO and CINAHL were systematically searched from inception. Risk of Bias for individual studies was assessed using a modified version of the Newcastle Ottawa Scale. Results: The search identified 629 studies from which 35 met inclusion criteria. There was clear evidence of symptom exacerbation during the perimenstrual phase for Psychotic Disorders, Panic Disorder, Eating Disorders, Depression and Borderline Personality Disorder. Less consistent evidence was found for Anxiety, and a different pattern of symptom exacerbation was observed in Bipolar Disorder. Sample size and methodology varied considerably amongst studies. Conclusion: Overall, there was mixed evidence for perimenstrual exacerbation across mental disorders, which could be partly explained by methodological limitations of the studies. However, hormonal fluctuations during the menstrual cycle may exacerbate psychiatric symptoms in a subgroup of individuals who are hormone sensitive.

**Introduction**

Sex differences have been established in the prevalence, onset, symptomology, and prognosis of various mental health disorders (Reicher-Rossler, 2017). For example, females are twice as likely to be diagnosed with depression and experience more ‘atypical’ symptoms (Angst et al., 2002; Bromer et al., 2011; Douglas & Scott, 2014). The underlying reasons are not fully understood and are likely to span biological, psychological, as well as social factors (Kuehner, 2016; Riecher-Rossler, 2017).

Epidemiological research consistently demonstrates patterns of susceptibility for mental illness corresponding with reproductive events (Soares & Zitek, 2008). For example, puberty, premenstruum, pregnancy, postpartum and menopause (O’Hara et al., 1996; Hu et al., 2016; Kessler et al., 2001). These are characterized by major hormonal change and point to the role of reproductive hormones such as oestradiol (the main derivative of oestrogen) and progesterone in exacerbating or triggering an episode of mental illness (Li & Graham, 2017; Kulkarni et al., 2008).

Various biological mechanisms underpinning the relationship between reproductive hormones and symptoms have been identified (Li & Graham, 2017). Oestradiol and progesterone have potent effects on brain regions and neurotransmitter systems involved in emotional disorders (Schiller et al., 2016; Comasco & Sundstrom-Poromaa, 2015). Further, the “oestrogen protection hypothesis” proposes that oestrogen has a protective and neuromodulatory role in psychotic disorders such as Schizophrenia (Gogos et al., 2015). Whilst hormones provide one explanation, psychosocial factors surrounding menstruation and other reproductive events are also likely to influence mental health (Luoma et al., 2018; Eisenlour-Moul et al., 2018; O’Flynn, 2006).

The impact of fluctuating hormones during the menstrual cycle (MC) has been largely overlooked in current conceptualisations of mental disorders (Li & Graham, 2017; Green & Graham, 2021). Premenstrual Disorders (PMDs) including Premenstrual Dysphoric Disorder (PMDD) and Premenstrual Exacerbation (PME) directly implicate the MC in mental disorders (IAPMD, 2020). PMDD is a psychiatric diagnosis characterised by affective symptoms (e.g., depressed mood, irritability, hopelessness) present only in the luteal or premenstrual phase, after which symptoms remit completely (APA, 2013; IAPMD, 2020). PME refers to the worsening or exacerbation of an *existing* mental disorder during the premenstrual phase (O’Brien et al., 2011). The perimenstrual phase refers to the period just before and during menses, and a recently proposed definition suggests it constitutes days -3 to +2 of the MC (Schmalenberger et al. 2021).

PMDs are considered to result from abnormal sensitivity to normal hormone fluctuations, such that only individuals with this sensitivity are affected (Schmidt et al., 2017; Wei et al., 2018). Mental illness and hormone sensitivity have several shared risk factors including history of trauma, recent stressful events, and current stress (Bertone-Johnson et al., 2014; Gordon et al., 2016; Eisenlohr-Moul et al., 2016). This would suggest some individuals with mental disorders may be vulnerable to hormonally related exacerbations in symptoms across the MC.

Several reviews have previously highlighted the evidence for exacerbation of symptoms across the MC for mental disorders including psychotic disorders, panic and anxiety disorders, mood disorders, eating disorders and substance use disorders (Nillni et al., 2015; Reilly et al, 2020; Hendrick et al., 1996). Reilly et al. (2020) conducted a meta-analysis investigating perimenstrual exacerbation of psychotic disorders and found rate of psychiatric hospital admission was 1.48 times higher during this phase. In addition, several reviews suggest an increased risk of suicides and self-harm during the perimenstrual phase (Saunders & Hawton, 2006; Jang & Elfenbein 2019).

However, there are key methodological challenges in this area of research (Schmalenberger et al., 2021). This includes the use of retrospective assessment of PME which is limited by its reliance on memory and potential for biased recollection (Hart et al., 1987; Schmalenberger et al., 2021). A more robust method is prospective assessment which collects data on symptoms in ‘real-time’ (e.g., daily, or weekly) over the course of the MC. Prospective assessment of symptoms is considered the gold standard and represents the most methodologically sound measurement of PME (Rubinow et al., 1984).

It is important to accurately establish the existence of PME, as these frequent and significant fluctuations in symptom severity could have considerable implications for risk assessment and diagnosis, and potentially yield inappropriate treatment plans depending on whether assessment is performed during a time of hormonal exacerbation (Jang & Elfenbein 2019; Yum et al., 2019).

The aim of this systematic review is to examine whether individuals with mental disorders experience systematic exacerbation of their symptoms during the perimenstrual phase of the menstrual cycle, when measured in prospective observational studies.

**Methods**

**Protocol and registration**

A systematic review with narrative synthesis was conducted in accordance with PRISMA guidelines. The protocol was published on the PROSPERO website on 26th April 2021 (PROSPERO-ID CRD42021251352).

**Eligibility criteria**

Eligibility was defined using the PICOS framework (Higgins & Green, 2011) and studies were included if they met the following criteria: (a) individuals between menarche and menopause (b) with a current diagnosis of a mental health condition based on standard diagnostic criteria (c) measured symptom/s specific to this diagnosis (d) on at least two occasions in distinct cycle phases (including the pre/perimenstrual/luteal phase) (e) for a minimum of one menstrual cycle (f) using prospective methodology (g) repeated measures design (i.e., internal comparison) (h) in English language. To maximise number of studies eligible, there are no date restrictions or exclusion criteria based on age, gender, symptom severity, other psychiatric comorbidities, or medication.

**Search strategy**

Search terms were structured around the menstrual cycle (concept 1) and mental health disorders (concept 2). A full outline of search terms can be found in Appendix A. Medline (Ovid), Embase (Ovid), PsycINFO (Ovid) and CINAHL were searched separately. The search was conducted between April 2021 and February 2022. Backwards searching of reference lists and forward searching via Google Scholar was conducted for included studies. A supplementary grey literature search was conducted using the term “premenstrual exacerbation mental disorder” in OpenGrey, Google Scholar and ResearchGate.

**Data Extraction (selection and coding)**

Database references were exported into Endnote for deduplication and imported into Rayyan. Titles and abstracts were independently screened by two reviewers to identify those potentially meeting inclusion criteria; all were screened by LN and a subset (20%) by a second reviewer. A Cohen’s kappa statistic of 0.46 was achieved suggesting a moderate level of agreement. Disagreements were resolved through discussion. For grey literature, only the title and abstract of the first one-hundred papers of each source were screened for inclusion by one author (LN).

The full text papers were then assessed for eligibility and any reasons for exclusion were coded. Study data was extracted into a pre-specified table. A subset (10%) of data extraction was crosschecked and no errors were found. Information extracted includes author/s, publication year, title, study design, setting, sample size, age, primary diagnosis, diagnostic criteria, comorbidities, medication/s, measurement tool/s, measurement of MC (e.g., self-report, hormonal assay), definition of cycle phases, study duration, and key findings (including means, standard deviation, and p-values for relevant outcomes).

**Risk of Bias (quality) assessment**

To assess risk of bias for individual studies, a modified version of the Newcastle-Ottawa Scale (NOS) was applied (Wells et al., 2008; Appendix B). A maximum of eight points was available and full details of scoring is available from supplemental material in Appendix B. Scoring was conducted by LN and a subset (10%) were cross-checked by a second reviewer with no disagreements. The authors agreed to interpret an overall score of ≥5 across all domains as ‘low risk of bias’ and studies scoring <5 as ‘high risk of bias’ (Luchini et al., 2017).

**Data analysis**

A meta-analysis was not possible due to considerable heterogeneity amongst studies, including lack of consistent measurement timepoints, outcome measures and definitions of MC phases (Reilly et al., 2020). Therefore, a narrative synthesis was conducted (Popay et al., 2006). Studies were arranged into subgroups according to their category of mental disorder: Severe Mental Disorders (Psychosis and Bipolar Disorder), Common Mental Disorders (Panic, Anxiety and Depression), Eating Disorders and Personality Disorders. Findings were tabulated and outlined with consideration of the following variables:

* Measurement of menstrual phase – hormonal verification versus self-report
* Use of medications – hormonal contraception, psychotropic medication, both, or none.
* Setting – inpatient, outpatient, or community.
* Study quality – low or high risk of bias.

These are potential effect modifiers, and findings should be interpreted in light of these. Firstly, psychotropic medication (e.g., antipsychotics) can profoundly disrupt hormonal fluctuations (Dickson et al., 2000). Hormonal contraception may prevent ovulation and thus, removes the natural hormonal fluctuations of exposure variable (Cooper & Mahdy, 2021). Inpatient settings often involve acute illness and are vulnerable to ‘treatment effect’ of new medication (e.g., Bergemann et al., 2007). Self-report does not allow for verification of ovulation (i.e., exposure variable). Finally, low quality studies limit confidence, such that the “true effect” might be substantially different from the estimate of the effect (Balshem et al., 2011).

**Fig. 1 PRISMA diagram of search strategy**

**Identification of studies via other methods**

**Identification of studies via databases and registers**

Records identified from:

Google (n=100), Research Gate (n=100) OpenGrey (n=0)

Article reference lists (n=42)

Records identified from Electronic Databases MEDLINE, EMBASE, PsycINFO and CINAHL (n = 629)

Records removed *before screening*:

Duplicate records removed (n = 95)

**Identification**

Records excluded

(n = 492)

Study design

Non-clinical samples

Records screened

(n = 534)

Reports not retrieved

(n = 196)

Reports sought for retrieval

(n = 46)

Reports sought for retrieval

(n = 42)

Reports not retrieved

(n = 0)

**Screening**

Reports excluded (n=36\*)

Study design (n = 17)

Non-Clinical sample (n=11)

Non-specific symptoms (n=4)

Duplicate (n= 2)

Publication type (n=1)

Menopause included (n=1)

\*Reasons not mutually exclusive

Reports excluded: (n=17)

Non-clinical sample (n=6)

Study design (n=4)

Non-specific symptoms (n=3)

Other language (n=2)

Menopause included (n=2)

Reports assessed for eligibility

(n = 46)

Reports assessed for eligibility

(n = 42)

Studies included in review

(n = 35)

**Included**

**Results**

The initial database search yielded 629 records and an additional 46 papers were identified through grey literature and hand-searching. The search results are detailed in Figure 1 PRISMA flow chart (Moher et al., 2009).

**Study characteristics**

The 35 studies included a total of 992 participants (range 5 to 125) with a diagnosis of the following disorders: Schizophrenia, Schizoaffective Disorder, Brief Psychotic Disorder, Delusional Disorder, Bipolar Disorder, Panic Disorder, Generalised Anxiety Disorder, Bulimia Nervosa, Binge Eating Disorder and Borderline Personality Disorder. All studies are prospective Cohort Studies, and the majority (33/35) did not include an unexposed comparison, that is, subjects without a menstrual cycle (e.g., male controls). Study characteristics are outlined in the sections below and detailed in table 2 to table 5.

**Risk of bias (quality) assessment**

A quality score was ascertained for all studies (N=35) at the individual study level according to Modified NOS criteria (Reilly et al., 2020). All studies were categorised as either ‘high risk of bias’ or ‘low risk of bias’. Most studies (21/35) were classified ‘high risk of bias’. The mean total score was 4.17 and range is 2 to 6. See supplementary material Appendix C for details.

**Severe Mental Disorders**

***Psychotic disorders***

Ten individual studies examining psychosis symptoms across the MC were included (Table 2). Seven exclusively included Schizophrenia and three included Schizophrenia plus other psychotic disorders. All studies included subjects on psychotropic medication (including antipsychotics), three with fixed doses (i.e., administered during the study at a standard dose) and seven uncontrolled (i.e., unknown doses). None of the studies included individuals on hormonal contraception.

Four out of ten studies reported statistically significant symptom exacerbation during the perimenstrual phase (Ray et al., 2020; Riecher-Rossler et al., 1994; Akhonzadeh et al., 2005; Choi et al., 2001). Two of which found a significant correlation between oestrogen levels and symptoms (Akhonzadeh et al., 2005; Riecher-Rossler et al., 1994). Three of ten studies reported significant symptom exacerbation during other phases including the follicular, periovulatory and menstrual phase (Bergemann et al., 2007; Harris, 1997; Rubin et al., 2011).

The remaining three studies found no evidence of exacerbation of psychotic symptoms across the MC (Thompson et al., 2000; Hallonquist et al., 1993; Huber et al., 2004).

Table 2. Characteristics of studies measuring symptoms of Psychotic Disorders across the menstrual cycle

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Diagnosis** | **Sample size** | **Medication** | **Study setting** | **Number of menstrual cycles** | **Menstrual cycle phase definition** | **Measurement of Menstrual cycle phase** | **Measurement of PME** | **Key findings[[1]](#footnote-1)** |
| **Akhonzadeh et al. (2005)** | Schizophrenia | N=30 | Psychotropic (fixed) | Inpatient | One | **Follicular phase** (14 days after menses onset), **Ovulation** (day 14), **Luteal phase** (day +15 to -1) **Premenstrual phase** (up to day +3) | Hormone assay | Positive and Negative Syndrome Scale (PANSS) | PANSS total and subscales significantly higher at day 3 than day 13 (p<0.001). This corresponded with Oestrogen and Progesterone levels (p<0.001). |
| **Bergemann et al. (2007)** | Schizophrenia | N=125 | Psychotropic | Inpatient | One | **Follicular phase** (day +2 to +4) **Periovulatory phase** (day +10 to +12) **Luteal phase** (day +20 to +22) | Hormone assay | PANSS and Brief Psychiatric Rating Scales (BPRS) | Significant *improvement* in psychotic symptoms during the luteal phase, compared with periovulatory phase (p<0.01) and follicular phase (p<0.001) |
| **Choi et al. (2001)** | Schizophrenia | N=24 | Psychotropic (fixed) | Inpatient | One | **Premenstrual phase** (days -7 to -1) **Postmenstrual phase** (7 days after menses cessation) | Hormone assay | BPRS | BPRS total significantly higher in the premenstrual phase compared with postmenstrual phase (p<0.01). NSD in psychotic symptom subscales |
| **Hallonquist et al. (1993)** | Schizophrenia | N=5 | Psychotropic | Outpatient | Two | **Early follicular phase** (days +4 to +8) **Midluteal phase** (days -5 to -12) | Self-report | Symptom Checklist Abbreviated (SCL-A) | Total scores significantly higher during the early follicular compared to mid-luteal phase (p<0.05). NSD in psychotic subscales |
| **Harris (1997)** | Schizophrenia | N=39 | Psychotropic | Inpatient | One | **Premenstrual phase** (days -5 to -1) **Postmenstrual phase** (5 days after menses onset) | Self-report | BPRS | No significant exacerbation of symptoms in premenstrual phase. Subscales Grandiosity (p<0.05) and Hostility (p<0.01) scores significantly higher in the postmenstrual and menstrual phase |
| **Huber et al. (2004)** | Schizophrenia, Schizoaffective Disorder, Brief Psychotic Disorder, Delusional Disorder | N=27 | Psychotropic | Inpatient | One | None defined | Hormone assay | BPRS and Clinical Global Impression Scale (CGI) | No correlation between BPRS or CGI scores and oestradiol levels overall. |
| **Ray et al. (2020)** | Schizophrenia | N=40 | Psychotropic (fixed) | Inpatient | Two | **Premenstrual phase** (-7 to -1 days) **Postmenstrual phase** (7 days after menses cessation) | Self-report | PANSS | Total score higher in premenstrual phase than menstrual phase (p=0.002) and higher in the menstrual phase than postmenstrual phase in both cycles (both p<0.01). PANSS positive subscale was higher in the premenstrual than menstrual phase (p=0.013) |
| **Riecher-Rössler et al. (1994)** | Schizophrenia | N=32 | Psychotropic | Inpatient | One | Not explicitly defined. **Menstrual phase** (days +2 to +7) **Ovulatory phase** (days +13 to +14) **Premenstrual phase** (day +21 to +28) | Hormone assay | 1. BPRS  2. Nurses Observation Scale for Inpatient Evaluation (NOSIE)  3. Paranoid-Depressive Scale (PDS)  4. Befindlichkeits Skala (BFS) | Significant inverse correlation between oestrogen levels and total BPRS score (M=-.25 SD=.41 p=0.002) PDS Paranoid scale (M=-.17 SD=.42 p=0.029), NOSIE total score (M=.25 SD=.49 p=0.004), BFS score (M=-.20 SD=.43 p=0.032)  [reported as correlation coefficients] |
| **Rubin et al. (2011)** | Schizophrenia, Schizoaffective Disorder | N=23 | Psychotropic | Outpatient and Residential Facilities | One | **Early Follicular phase** (days +2 to +4) **Midluteal Phase** (days +20 to +22) | Hormone assay | PANSS | Total, Positive and General Psychopathology scores were significantly higher during the early follicular phase versus midluteal phase (p<0.01) |
| **Thompson et al. (2000)** | Schizophrenia, Bipolar, Schizoaffective illness, Depression with psychotic features, Schizophreniform Disorder | N=29 | Psychotropic | Inpatient and Outpatient | One | **Follicular phase** (first 14 days after menses onset), **Luteal phase** (days +14 to +28) | Hormone assay | PANSS | No significant difference in PANSS total or subscale between the follicular and luteal phase |

***Bipolar Disorder***

Six studies examining bipolar disorder were included (Table 3). All studies included psychotropic medication (including mood stabilisers) and four included hormonal contraceptives (HC). Five studies used self-report to determine cycle phase. All were community or outpatient settings.

One study found evidence for exacerbation ofmood symptoms during the perimenstrual phase, however, only in subjects not taking hormonal contraception (Rasgon et al., 2003). Three studies found significant exacerbation of mood symptoms during other phases including the menstrual and follicular and phase, but no mood-direction or phase was consistently implicated (Rasgon et al., 2005; Robakis et al., 2015; Leibenluft et al., 1999). Two of six studies found no evidence of symptom fluctuation across the MC (Shivakumar et al., 2008; Sit et al., 2011).

Table 3. Characteristics of studies measuring symptoms of Bipolar Disorder across the menstrual cycle

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Diagnosis** | **Sample size** | **Medication** | **Study setting** | **Number of menstrual cycles** | **Menstrual cycle phase definition** | **Measurement of Menstrual cycle phase** | **Measurement of PME** | **Key findings** |
| **Leibenluft et al. (1999)** | Rapid Cycling Bipolar Disorder | N=25 | Psychotropics | Outpatient | Three | **Premenstrual phase** (days -7 to -1) **Postmenstrual phase** (7 days after menses onset) | Self-report | Daily Mood Ratings | 44% of subjects exhibited statistically a significant relationship between menstrual cycle phase and mood, but not specific to premenstrual phase (p<.05).  None of the group analyses showed a significant effect of menstrual cycle on mood. |
| **Rasgon et al. (2003)** | Bipolar Disorder | N=17 | Psychotropics and Hormonal Contraception | Outpatient | Three | Not defined. In analysis: **Premenstrual phase** (days -7 to -1) **Menstrual phase** (7 days after menses onset) | Self-report | ChronoSheet | Mood scores significantly higher in premenstrual phase compared to menstrual phase (p=0.015) for subjects not taking hormonal contraception but no significant effect for subjects taking contraception. |
| **Rasgon et al. (2005)** | Bipolar Disorder | N=31 | Psychotropics and Hormonal Contraception | Outpatient | Three | Not defined. In analysis: **Premenstrual phase** (days -7 to -1) **Menstrual phase** (7 days after menses onset) | Self-report | ChronoSheet | 17 of 31 subjects (54.8%) had significant mood changes across the cycle (p<0.05). This was not specific to the premenstrual phase. |
| **Shivakumar et al (2008)** | Bipolar Disorder, Schizoaffective-Bipolar type, Rapid Cycling | N=41 | Psychotropics and Hormonal Contraception | Outpatient | Three | **Early Follicular** (days 0 to +7) **Late Follicular** (day +8 to +14) **Early Luteal** (day +15 to +22) **Late Luteal** (day +23 to +28) | Self-report | NIMH-Life Chart Method | No significant effect of the menstrual cycle on Depression (p=0.18) or Mania (p=0.92) |
| **Sit et al (2011)** | Bipolar Disorder | N=11 | Psychotropics | Outpatient | Three | **Early Follicular** (day +3 to +8) **Late Follicular** (day +9 to +14) **Early Luteal** (day -14 to -7) **Late Luteal** (day -6 to -1) | Hormonal assay | 1. Hamilton Depression Rating Scale 2. Mania Rating Scale 3. NIMH-prospective life chart 4. Perceived Stress Scale 5. Short-Form Health Survey | No significant effect of the menstrual cycle on depression, mania, perceived stress or psychosocial functioning |
| **Robakis et al. (2015)** | Bipolar Disorder | N=72 | Psychotropics and Hormonal Contraception | Outpatient and Community | Two | **Luteal phase** (days -7 to -1) **Follicular phase** (menses cessation until -8 days) **Menstrual phase** (menses) | Self-report | ChronoSheet | Mood scores in premenstrual phase not significantly different from other phases. Significantly higher in the follicular phase compared to menstrual phase (p=0.033) |

**Common Mental Disorders**

***Panic Disorder***

Six individual studies examining panic disorder across the MC were included (Table 4). Two included psychotropic medication (including Benzodiazepines) and none included HC, although one study did not record medication use (Haigh et al., 2018). All studies used self-report to determine cycle phase and were community or outpatient settings.

Two out of six studies found evidence for PME of panic attack *frequency,* but not severity (Kaspi et al., 1994; Haigh et al., 2018). In contrast, Cameron et al. (1988) found a significant change in panic attack intensity but not frequency across the cycle, however, the phase was not specified. One study found evidence of exacerbation in fear-rating scores during the menstrual phase compared to the premenstrual and midluteal phase (Brambilla et al., 2003). Finally, two studies found no evidence for exacerbation of panic attack symptoms (Cook et al., 1990; Stein et al., 1989).

***Anxiety and Mood Disorders***

Three individual studies measuring Generalised Anxiety Disorder were included (Table 4). None included psychotropic medication or HC. All studies used self-report to determine cycle phase. All were community settings.

One study by McLeod et al. (1993) found that anxiety symptoms were significantly worse during the premenstrual phase compared to follicular phase. The remaining two studies found no evidence of anxiety exacerbation at any phase of the cycle (Li et al., 2020; Li, Lloyd et al., 2020).

One study measuring Major Depression was included (Table 4; Hartlage et al., 2004). The majority (58%) of subjects reported significant worsening of one or more depressive symptoms during the premenstrual phase and this was associated with deterioration in general functioning.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study**  Table 4. Characteristics of studies measuring symptoms of Common Mental Disorders across the menstrual cycle | **Diagnosis** | **Sample size** | **Medication** | **Study setting** | **Number of menstrual cycles** | **Menstrual cycle phase definition** | **Measurement of Menstrual cycle phase** | **Measurement of PME** | **Key findings** |
| **Brambilla et al. (2003)** | Panic Disorder, Agoraphobia | N=25 | None | Outpatient | One | **Follicular phase** (day +7) **Midluteal phase** (day +22) **Premenstrual phase** (day +27) | Self-report | 1. Panic-associated symptom scale (PASS) frequency 2. Fear questionnaire total scores (Fqtot) 3. State-trait anxiety inventory (STAI) | Fear questionnaire total scores decreased significantly from the early follicular to the midluteal phase (p=0.0004) and premenstrual phase (p=0.001). |
| **Cameron et al. (1988)** | Panic Disorder, Agoraphobia with Panic Attacks | N=10 | None | Outpatient | One | **Perimenstrual phase** (7 days after menses onset) **Premenstrual phase** (days -7 to -1) **Midcycle phase** (7 days closest to mid-cycle) | Self-report | 1. Panic attack diary. 2. Self-report severity of DSM panic symptoms. 3. Sheehan Anxiety Scale. 4. Hamilton Anxiety Scale. 5. Marks-Sheehan Fear and Avoidance scale. 6. Symptom Checklist-90-Revised (SCL-90-R) | Severity of full situational panic attacks (P <0.02) and 'muscle tension' (P<0.04) changed significantly between phases. |
| **Cook et al. (1990)** | Panic Disorder | N=19 | Psychotropics (includes benzos) | Outpatient | One | **Premenstrual phase** (days -5 to -1) **Postmenstrual phase** (5 days after menses ends) | Self-report | 1. Panic Attack diary. 2. Short Anxiety Symptom Checklist 3. Global assessment of anxiety severity | Panic attack frequency and anxiety symptoms did not differ significantly across the MC |
| **Haigh et al. (2018)** | Panic Disorder | N=20 | None noted (not measured) | Community | One | **Menstrual phase** (days 1 to 7) **Follicular phase** (days 8 to 20) **Premenstrual phase** (days 21 to 28) | Self-report | Daily Symptom Checklist | Panic attack frequency increased significantly in the premenstrual phase (M=1.93 SD=1.67) compared to the menstrual phase (M=1.27 SD=1.71) (p=.04, d=.60), and follicular phase (M=.27 SD=.59) (p<.001 d=.70). Anxiety symptoms significantly more severe in the premenstrual phase (p=0.001) |
| **Kaspi et al. (1994)** | Panic Disorder with and without Agoraphobia | N=24 | Psychotropics (includes benzos and others) | Community | Two | **Premenstrual phase** (days -5 to -1) **Postmenstrual phase** (5 days following menses cessation) | Self-report | Daily Diary (frequency and severity of panic attacks, severity of agoraphobic avoidance, severity of anticipatory anxiety) | Panic attack frequency was significantly higher in the premenstrual phase (M= .40 SD=.59) versus postmenstrual phase (M=.25 SD=.65) (p<.035). |
| **Stein et al. (1989)** | Panic Disorder with and without Agoraphobia | N=20 | None | Community | Two | **Late luteal** (days -7 to -1) **and Mid-follicular** (days +5 to + 11) | Self-report | State-Trait Anxiety Inventory - State version  NIMH Panic Attack Scale | No significant change in anxiety rating or frequency of panic attacks across the menstrual cycle |
| **Li, Denson et al. (2020)** | Generalised Anxiety Disorder | N=40 | None | Community | One | Not defined. **Early Follicular phase** (days -14 to -6), **Mid-follicular phase** (days -7 to -1), **ovulation** (day 0), and M**id-luteal phase** (days +1 to +7) | Hormone assay and Self-report | 1. Generalised Anxiety Disorder 7 (GAD-7) 2. Penn State Worry Questionnaire 3. Repetitive Thinking Questionnaire-10 (RTQ-10) 4. Negative Affect Scale-negative affect subscale (PANAS-N) 5. Worry Behaviours Inventory Short Form (WBI-SF). | Repetitive negative thinking (p=0.039) and negative affect (p=0.047) increased significantly in midluteal versus early follicular phase. NSD in GAD symptoms across the MC. |
| **Li, Lloyd et al. (2020)** | Generalised Anxiety Disorder | N=18 | None | Community | One | **Early follicular** (days +10 to +14 before ovulation) **Mid-luteal phases** (+5 to +10 days after ovulation) | Hormone assay and Self-report | Fatigue and Energy Scale  Patient Health Questionnaire-9 | Symptoms did not differ significantly across the menstrual cycle |
| **McLeod et al. (1993)** | Generalised Anxiety Disorder | N=41 | None | Community | One | **Premenstrual phase** (days -7 to -1) **Follicular phase** (7 days following menses cessation) | Self-report | Hamilton Anxiety Rating Scale (HARS) - psychiatrist rated.  Hopkins Symptom Checklist-90 (HSCL90) | Anxiety rated significantly greater during premenstrual versus follicular phase (p=0.001). Significantly higher scores in HSCL-90 in all anxiety subscales in premenstrual versus follicular phase (p<0.0001). |
| **Hartlage et al. (2004)** | Major Depressive Disorder (MDD), Bipolar Disorder with MDD episode, Dysthymia. | N=58 | Psychotropics and Hormonal Contraception | Community | One | **Follicular phase** (days +5 to +10) **Premenstrual phase** (days -7 to -1) | Hormonal assay | Daily Symptom and Mood Questionnaire | 58% of depressed participants had at least one symptom significantly exacerbated during the premenstrual phase. This was associated with deterioration in General Functioning (p<.001). |

**Eating Disorders**

Six studies examining eating disorders were included – five measuring Bulimia Nervosa (BN) and one measuring Binge Eating Disorder (BED) (Table 5). One study included psychotropic medication with HC and five included neither. Five studies used self-report to determine cycle phase and one used hormonal assay. All were community or outpatient settings.

Five studies reported significant exacerbation of binge and/or purge symptoms during the premenstrual phase (Gladis & Walsh, 1987; Price et al., 1987; Lester et al., 2003; Schoofs et al., 2011). One of which noted a significant correlation between oestradiol and binge frequency (Edler et al., 2007). One study measuring BN found no significant change in binge or purge symptoms across the cycle (Leon et al., 1986). No studies found evidence of symptom exacerbation at other phases of the cycle.

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| **Study**  Table 5. Characteristics of studies measuring symptoms of eating disorders across the menstrual cycle | **Diagnosis** | **Sample size** | **Medication** | **Study setting** | **Number of menstrual cycles** | **Menstrual cycle phase definition** | **Measurement of Menstrual cycle phase** | **Measurement of PME** | **Key findings** |
| **Edler et al. (2007)** | Bulimia Nervosa | N=9 | None | Community | One | **Ovulatory phase** (days -12 to -15) **Midluteal phase** (days -9 to -5) **Premenstrual phase** (days -3 to +1) **Follicular phase** (days +3 to +7) | Hormonal assay | Daily diary | Binge and purge frequency significantly higher in mid-luteal (M=.61 SD=.33) and premenstrual phase (M=-.08 SD=.35) compared to follicular (M-.30 SD=.35) and ovulatory phases (M=-0.37 SD=.21) (p<0.001). [presented as Z-scores]  Binge frequency was negatively correlated with oestradiol (p=0.02) and progesterone (p=0.04) |
| **Gladis & Walsh (1987)** | Bulimia Nervosa | N=15 | None | Community | Two | **Menstrual phase** (5 days after menses onset) **Premenstrual phase** (days -15 to -1 in three segments) **Postmenstrual phase** (+6 to +20 days) | Self-report | Daily diary | Binge frequency significantly higher 5 days preceding menses (M=.61 SD=.73) compared to all postmenstrual phases (p <0.05) [Presented as Z scores] |
| **Leon et al. (1986)** | Bulimia Nervosa | N=45 | Psychotropics and  Hormonal Contraception | Community | Two | **Premenstrual period** (days -3 to -1), **Menstrual period** (3 days after menses onset) **Ovulation period** (days -13 to -15) | Self-report | Daily diary | No significant differences in any symptoms across the cycle. |
| **Lester et al. (2003)** | Bulimia Nervosa | N=8 | None | Community | One | **Ovulatory phase** (days -12 to -15) **Midluteal phase** (Days -9 to -5) **Premenstrual phase** (days -3 to +1) **Follicular phase** (Days +3 to +10 or -16) | Self-report (did assays but not of E2 or PG) | Daily diary | Significant exacerbation of binge frequency in premenstrual phase (M=.41 SD=.37) compared to other phases (p<0.05). Significant exacerbation of binging (M=.35 SD=.70) and purging frequency in the midluteal and premenstrual phase combined (p<0.001).  [Presented as Z scores] |
| **Price et al. (1987)** | Bulimia Nervosa | N=10 | None | Community | Two | **Menstrual phase** (days 0 to +14), **Premenstrual Period** (days +15 to +30) | Self-report | Weekly diary | Significant exacerbation in binge frequency in the premenstrual phase (M=6.65 SD=1.87) compared to the menstrual phase (M=4.1 SD=.66) (p>0.001) |
| **Schoofs et al. (2011)** | Binge Eating Disorder (with comorbid bipolar disorder in remission) | N=15 | None | Outpatient | Three | Not defined. | Self-report | Daily diary | The frequency of binge episodes was significantly higher in the week prior to menses (M=6 SD=3) compared to all other weeks (M=3 SD=1 p≤0.01). |

**Personality Disorders**

Three individual studies measuring symptoms of borderline personality disorder were included (Table 6). One included psychotropic medication, and none included HC. Two studies used hormonal assay and one used self-report to determine cycle phase.

Two studies reported significant exacerbation of symptoms (e.g., anger, irritability, hopelessness) during the perimenstrual phase (Eisenlohr-Moul et al., 2018; Peters et al., 2020). The remaining study found no significant change in symptoms, although the majority of subjects reported worsening of at least one symptom (Ziv et al., 1995).

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Diagnosis** | **Sample size** | **Medication** | **Study setting** | **Number of menstrual cycles** | **Menstrual cycle phase definition** | **Measurement of Menstrual cycle phase** | **Measurement of PME** | **Key findings** |
| **Eisenlohr-Moul et al.** (2018) | Borderline Personality Disorder | N=15 | None | Community | One | **Ovulatory phase** (days -12 to -15) Perimenstrual **phase** (days -4 to +3). **Midluteal phase** (days between ovulatory and perimenstrual phase). **Follicular phase (**days between perimenstrual and ovulatory phase) | Hormonal assay | 1. State Shame and Guilt Scale 2. The Anger Rumination Scale 3. Daily Record of Severity of Problems | All BPD symptoms significantly worse in perimenstrual phase compared to other phases (e.g., shame, hopelessness p<0.001) |
| **Peters et al. (2020)** | Borderline Personality Disorder | N=15 | None | Community | One | **Ovulatory phase** (days -1 to +2 of Luteinizing Hormone Surge) **Perimenstrual phase** (days -4 to +3) **Midluteal phase** (days between ovulatory and perimenstrual phase). **Follicular phase** (days between perimenstrual and ovulatory phase) | Hormonal assay | 1. Daily Record of Severity of Problems 2. State‐Trait Anger Expression Inventory 3. Reactive‐Proactive Aggression Questionnaire | BPD symptoms *Anger/Irritability* and *Anger-in* were significantly worse in the perimenstrual phase than all other phases (p<0.001 and p<0.05).  Proactive aggression and Reactive Aggression significantly worse during other phases. |
| **Ziv et al. (1995)** | Borderline Personality Disorder | N=14 | Psychotropic | Inpatient | Two | **Follicular phase** (days 5 to 10), **Luteal phases** (days -6 to -1) | Self-report | Daily log of impulsive behaviours, urges and affective states | No significant change in symptoms across the cycle. 11 of 14 subjects did experience 30%> worsening of at least one symptom during premenstrual phase |

Table 6. Characteristics of studies measuring symptoms of personality disorders across the menstrual cycle

**Discussion**

**Summary of evidence**

A majority of studies included in this review found evidence for perimenstrual exacerbation (PME) of symptoms of Psychotic Disorders, Panic Disorder, Eating Disorders and Borderline Personality Disorder. Just one study examined depression, finding evidence for PME. Less strong links between the perimenstrual phase and symptom exacerbation were found in Generalised Anxiety Disorder and Bipolar Disorder.

The findings relating to Psychotic Disorders are in line with prior reviews suggesting a strong link between the menstrual cycle and symptom exacerbation (Reilly et al., 2020; Brzezinksi-Sinai & Brzezinski, 2020). The studies that analysed hormone levels found mixed evidence for an inverse correlation between oestrogen levels and psychotic symptoms (Akhonzadeh et al., 2005; Huber et al., 2004; Riecher-Rossler et al., 1994). Contrary to the oestrogen protection hypothesis of psychosis, this might suggest the link between hormone levels and symptom exacerbation is indirect (i.e., mediated through other factors surrounding menstruation), but more likely reflect methodological and participant factors of included studies obscuring the ability to detect this relationship (e.g., medication use, hypoestrogenism amongst participants). Findings for panic disorder were consistent with prior reviews and support the theory that rapidly falling ovarian hormone levels may reduce GABAnergic neurosteroid levels and change the anxiolytic profile of GABAa receptors (Green & Graham, 2021; Nillni et al., 2021; Rasmusson et al., 2017). For Eating Disorders, findings support a breadth of prior research implicating decreasing ovarian hormones during the luteal phase in exacerbating eating and binging behaviour (Hirschberg, 2012; Altabe & Thompson, 1990; Klump et al., 2008). Notably, the study with the largest sample size found no evidence of eating disorder symptom exacerbation, suggesting that the findings of less powered studies might be false discoveries (i.e., were not powered to detect the true effect or lack thereof) (Leon et al., 1986; Button et al., 2013). This was also the only eating disorder study including subjects taking hormonal contraception (HC) and psychotropic medication, offering the additional explanation that HC and/or medication was effective in obscuring or reducing premenstrual symptom exacerbations in Bulimia Nervosa. The consistency and otherwise similar methodology in the remaining studies suggest eating disorder symptoms are susceptible to PME. Studies relating to Personality Disorders were of highest methodological quality and provide promising preliminary evidence that symptoms (e.g., hopelessness) worsen premenstrually. This is consistent with reviews highlighting changes in suicide risk across the MC (Saunders and Hawton, 2006; Jang & Elfenbein 2019). For Depression, there was a general paucity of research, with just one study included in the current review. Nevertheless, this study by Hartlage et al (2004) provides methodologically sound evidence for PME, with almost 60% of subjects affected. Notably, this study included subjects on HC, and it remains unclear if findings can be extrapolated to individuals with natural cycles.

For GAD, evidence for perimenstrual worsening of symptoms is lacking, with just one study demonstrating premenstrual worsening of symptoms. This is inconsistent with a breadth of prior literature implicating ovarian hormones in anxiety symptomology (e.g., Van Veen et al., 2009; Borrow & Handa, 2017). This finding likely reflects the limited number of prospective studies examining PME in anxiety despite its overlap with PMS symptoms (Lester et al., 2003; Green & Graham, 2021).

Exacerbation of symptoms during phases other than the perimenstrual phase was observed in particular for Bipolar Disorder and to a lesser extent, Psychotic Disorders. This finding is consistent with prior reviews suggesting a periovulatory, rather than perimenstrual, exacerbation in Bipolar Disorder symptoms (Teatero et al., 2013; Kuehner & Nayman, 2021). The persistence of this finding in the current review, which was limited to studies of higher methodological quality (e.g., prospective, and within-subjects design) supports the suggestion of a further pathophysiological mechanism for symptom exacerbation across the menstrual cycle in Bipolar Disorder – that is, of periovulatory exacerbation of symptoms (Teatero et al., 2013). Nevertheless, findings should be viewed with consideration for methodological factors. Firstly, the majority of bipolar disorder studies included individuals on hormonal contraception - this directly alters the exposure variable of interest (i.e., natural hormonal fluctuations) which might have considerably influenced findings. For example, Rasgon et al (2003) found exacerbation of symptoms in HC-free subjects only, suggesting its possible influence in obscuring symptom variability. Importantly, unlike all other disorders investigated in this review, studies relating to bipolar disorder and psychotic disorders included a majority of subjects on psychotropic medication. Interpreting findings in the context of a variable with unclear influences on menstrual cycle symptom exacerbation is difficult. For example, where symptom exacerbation is found in the context of medication, to what extent this reflects the effects of the MC on pharmacokinetic processes such as drug absorption and metabolism (e.g., reduction in serum medication levels during the luteal phase) rather than absolute symptom exacerbation, is unknown (Damoiseaux et al., 2014; Carmassi et al., 2019).

Taken together, PME appears to be a transdiagnostic phenomenon, and the variability in findings likely reflect that a sub-group of menstruators are more sensitive to hormone fluctuations than others. Certain disorders and symptoms appear to be more vulnerable to PME and it may be that distinct neurological and psychological mechanisms underly menstrual exacerbation of symptoms within each disorder. This, combined with methodological and participants factors unique to some disorders (e.g., medication and hormonal contraception) suggests the need to consider each disorder and its relationship to the menstrual cycle separately.

**Strengths and Limitations**

***Strengths***

This review used a systematic search strategy utilising electronic databases, grey literature and handsearching of reference lists to find studies. The broad sourcing of studies improves the comprehensiveness of results. Additionally, this is the first review to solely include prospective studies which are more reliable thereby affording more confidence that reporting of symptoms across the cycle is accurate and not subject to recall bias. Further, few restrictions were placed the sample (e.g., age, comorbidities), increasing representation of this heterogeneous population within this review.

***Limitations***

There are several important limitations to address. Firstly, substantial inconsistencies in how MC phases are defined in included studies is a major issue in comparing their results and interpreting findings in relation to the ‘perimenstrual’ phase. For example, Bergemann et al. (2007) found worsening of psychotic symptoms during the follicular phase (days 2-4) compared to the luteal phase (days 20-22) which might be interpreted as follicular phase exacerbation. However, this follicular phase definition overlaps with Akhonzadeh et al’s (2005) definition of premenstrual phase (days 1 to +3), illustrating how lack of operationalisation of phases adds difficulty to interpreting data and answering the current research question. Increased consistency would reduce phase misclassification, improve the reproducibility of studies, and facilitate cross-study comparisons and meta-analyses.

Moreover, confounding factors are not well controlled for amongst studies and it remains unclear which aspects of the MC are responsible for any observed symptom exacerbation. Whilst hormones are often implicated in outcomes associated with the MC, it is unclear how *direct* this link is to symptomology. This association could be mediated through factors such as menstrual pain, negative affect and/or shame and stigma i.e., exacerbation resulting from the additional ‘burden’ imposed by menstruation (Eisenlohr-Moul et al., 2018; Edler et al., 2007).

Further, whilst lenient inclusion criteria widened the scope of this review, it permitted studies with subjects taking hormonal contraception. Although this applied to a small minority of studies (i.e., six of thirty-five), it adds difficulty in extrapolating results beyond the sample and drawing conclusions on the impact natural MCs on symptoms. The study quality was generally poor and there were no stringent exclusion criteria controlling for this, reducing confidence that findings are generalisable (Sterne et al., 2019). Further, this review was restricted to English language papers, and we may have excluded relevant insights and context (Walpole, 2019).

**Research implications**

This review highlights the lack of methodologically robust evidence into premenstrual exacerbation of mental disorders. This has likely contributed to the mixed findings of this review. Recent best-practice recommendations have been proposed to advance methodological rigour in measurement of the MC (Schmalenberger et al., 2021). These include: (1) use of standardised menstrual phase definitions (2) hormonal assays to verify cycle phase (including Luteinizing Hormone) (3) minimum observation period of three menstrual cycles (4) within-subjects design (5) consideration of demand characteristics (6) prospective symptom measurement (7) characterising reproductive status (e.g., naturally cycling, pregnant, menopausal) (8) sufficiently powered sample sizes (9) accounting for medication use. In light of the current review, we further suggest: (10) measurement and adjustment for potential covariates (e.g., pain, affect, shame, treatment effects) – in line with a biopsychosocial approach to mental health.

Research would also benefit from confirmation that standard outcome measures (e.g., PANSS for schizophrenia) are valid for measuring PME. One concern is that for individuals with severe symptoms at baseline, such measures might be subject to ceiling effects (Hartlage et al., 2004). Moreover, research would benefit from co-production, working *with* menstruating individuals and clinical staff to better understand experiences of PME and how any recommendations can be effectively implemented. Future research might benefit from incorporating widely-used cycle-tracker apps into data collection.

Beyond treatment recommendations, diagnostic clarity is important for early identification of hormone-sensitive individuals, allowing for planning around pregnancy and menopausal transition. It would also be a conceivable next step that ‘Premenstrual Exacerbation’ is added as a diagnostic specifier in manuals such as DSM and ICD. This is an important and practical addition given how integral knowledge of PME is to risk management and treatment.

Finally, recognition of the interactive relationships between hormones, medication and symptomology are often acknowledged insofar as excluding and under-representing women in clinical trials (Ravindran et al., 2020). In research that does include menstruating people, there remains a lack of consideration for the MC. Whilst random allocation avoids confounding bias (i.e., would randomly assign menstrual phases), imbalance is possible and even if it is statistically non-significant – it can impact the type I error rate and power in ‘marginal’ intervention effect estimates (Ciolino et al., 2019). Thus, consideration of the MC as a prognostic variable is likely to benefit reliability and validity of trials on treatment efficacy and research more generally.

**Clinical practice and policy implications**

Despite the importance of addressing the impact of the MC on existing mental health conditions, there are several barriers to this including stigma and inattention to physical health in mental health services (Young et al., 2017; Johnston-Robledo, 2013). It is therefore recommended that clinical staff are trained to recognise and pay attention to this issue and develop pathways for referring to a Gynaecologist or General Practitioner, if premenstrual disorders are identified.

In line with prior recommendations, MC phase should be routinely recorded during psychiatric assessment – this will help frame disorder severity at the time of assessment (Blumenthal & Nadelson, 1988). It may also be useful to recommend cycle-tracking apps such as Clue or Flo. This information can be integrated into existing psychological interventions such as Cognitive Behavioural Therapy to manage PME (Ussher et al., 2017).

Finally, symptom exacerbation across the cycle in context of stable pharmacological treatment was common. This is important and demonstrates a potential inadequacy of current pharmacological treatment regimens for menstruating individuals. Together, this suggests provision of flexible and individually tailored treatment regimens to manage PME of psychiatric symptoms.

**Conclusions**

Upon review of the prospective literature, this review found mixed evidence for perimenstrual exacerbation of mental disorders, which is partly explained by methodological limitations. Nevertheless, the MC has been shown in the majority of studies to exacerbate psychiatric symptoms and PME appears to be an unrecognised feature of many mental health disorders. Variations in our findings might reflect that a sub-group of people are more sensitive to hormone fluctuations across the cycle. The influence of the menstrual cycle is not restricted to the premenstrual phase and its role in symptom exacerbation should be considered separately for distinct disorders. More research is required into the impact of psychotropic medication and/or concomitant use of hormonal contraception and how these might obscure or otherwise impact observed symptom exacerbations. The influence of hormonal fluctuations in the MC should be routinely considered in mental health clinical practice and research.

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**Appendix A**

**Medline search terms (n = 139)**

Menstrual Cycle/

(Menstrual Cycle OR Premenstrual Exacerbation OR perimenstrual exacerbation OR menstrual exacerbation OR perimenstrual symptoms OR menstrual related OR reproductive cycle OR menstrual fluctuation OR EstrogensOR Estradiol OR Progesterone OR Follicle Stimulating Hormone OR luteinizing hormone).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]  
  
exp Mental Disorders/

(Mental Disorder OR mental illness OR mental health condition OR mental health symptoms OR psychiatric OR symptom severity OR Psychological Tests).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

**Embase search terms (n = 145)**

Menstrual Cycle/

exp Mental Disease/

(Premenstrual Exacerbation or PME or perimenstrual exacerbation or menstrual exacerbation or perimenstrual symptoms or menstrual related or reproductive cycle or menstrual fluctuation OR EstrogenOR Estradiol OR Progesterone OR Follicle Stimulating Hormone OR luteinizing hormone).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

(Mental Health Disorder or mental illness or mental disorder or mental health condition or mental health symptoms or psychiatric or symptom intensity or symptom severity OR Psychological Rating Scale).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

**PsycINFO search terms (n= 105)**

Menstrual Cycle/

(Menstrual Cycle OR Premenstrual Exacerbation OR perimenstrual exacerbation OR menstrual exacerbation OR perimenstrual symptoms OR menstrual related OR reproductive cycle OR menstrual fluctuation OR EstrogensOR Estradiol OR Progesterone OR Follicle Stimulating Hormone OR luteinizing hormone).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

exp Mental Disorders/

(Mental Disorder OR mental illness OR mental health condition OR mental health symptoms OR psychiatric OR symptom severity OR Psychological Tests OR psychological assessment).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

**CINAHL search terms (n= 240)**

Menstrual Cycle

AND

Mental Disorders+

**Appendix B**

**Risk of Bias Scoring using the Modified Version of Newcastle Ottawa Scale**

Supplementary Scoring Table. Adapted from Reilly et al. (2020)

|  |  |
| --- | --- |
| *Cohort Studies* | *Max Score* |
| Representativeness of exposed cohort | 1 |
| Method used to ascertain exposure | 1 |
| Exposed and unexposed are matched or adjustment for confounding factors? | 2 |
| Assessment of outcome | 2 |
| Follow-up period was sufficiently long for outcomes to occur | 1 |
| Loss to follow-up | 1 |

Further details of scoring are outlined below. For ‘*Representativeness of exposed cohort’*, one point was awarded for sufficient sample size (with power calculations), selection methods and consideration for representativeness. For ‘*Method to ascertain exposure’* one point was only awarded if hormonal assays (e.g., urine tests, blood/saliva samples) were used. For ‘*Exposed and unexposed matched or adjustment for confounding*’ one point was awarded for within-subject designs, and one additional point was awarded for sufficient consideration of confounds (e.g., medication, stressful events, negative affect, carry-over effects). For ‘*Assessment of outcome’*, one point was allocated for assessment process (i.e., prospective) and one point for robustness of measurement tool (i.e., validated scale). For ‘*Follow-up period was sufficiently long for outcome to occur’* one point was only awarded if a minimum of two menstrual cycles was observed, this length is standard for establishing diagnosis of other premenstrual disorders (e.g., PMDD). For ‘*loss to follow-up*’ one point was awarded if attrition rate was reported, was low (<30%), and the same in exposed and non-exposed (where applicable). A maximum of eight points was available, this differs from the original seven points as ‘*Assessment of outcome*’ criterion was allocated two points rather than one.

Two criteria from the original ‘selection’ domain are excluded: “*selection of non-exposed cohort*” and “*outcome of interest was not present at start of study*”. The former is redundant given that within-person comparisons (i.e., within exposed cohort only) are most relevant to the review. The latter criterion is unnecessary given the purpose of this review was to establish the outcome (PME) which is assumed to be pre-existing.

**Appendix C**

Table 1. Quality Scores for individual studies using a Modified Version of the Newcastle-Ottawa Scale

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Cohort Study | **Representativeness of subjects (max 1)** | | **Ascertainment of Exposure (max 1)** | **Comparability - design and/or adjustment of confounding (max 2)** | **Assessment of Outcome (max 2)** | **Follow-up period (max 1)** | **Adequacy of follow-up of cohort (max 1)** | **Total score (max 8)** |
| **Severe Mental Disorders** |  | |  |  |  |  |  |  |
| Akhonzadeh et al. (2005) | 0 | | 1 | 1 | 2 | 0 | 0 | **4** |
| Bergemann et al. (2007) | 0 | | 1 | 2 | 2 | 0 | 0 | **5** |
| Choi et al. (2001) | 0 | | 1 | 2 | 2 | 0 | 1 | **6** |
| Hallonquist et al. (1993) | 0 | | 0 | 1 | 1 | 1 | 0 | **3** |
| Harris (1997) | 0 | | 0 | 2 | 2 | 0 | 0 | **4** |
| Huber et al. (2004) | 0 | | 1 | 1 | 2 | 0 | 0 | **4** |
| Leibenluft et al. (1999) | 0 | | 0 | 2 | 1 | 1 | 0 | **4** |
| Rasgon et al. (2003) | 0 | | 0 | 2 | 1 | 1 | 1 | **5** |
| Rasgon et al. (2005) | 0 | | 0 | 2 | 1 | 1 | 1 | **5** |
| Ray et al. (2020) | 0 | | 0 | 1 | 2 | 1 | 1 | **5** |
| Riecher-Rössler et al. (1994) | 0 | | 1 | 1 | 2 | 0 | 0 | **4** |
| Robakis et al. (2015) | 0 | | 0 | 2 | 1 | 1 | 1 | **5** |
| Rubin et al. (2011) | 0 | | 1 | 2 | 2 | 0 | 0 | **5** |
| Shivakumar et al. (2008) | 0 | | 0 | 1 | 2 | 1 | 0 | **4** |
| Sit et al. (2011) | 0 | | 1 | 1 | 2 | 1 | 0 | **5** |
| Thompson et al. (2000) | 0 | | 1 | 1 | 2 | 0 | 0 | **4** |
| **Common Mental Disorders** | |  |  |  |  |  |  |  |
| Cameron et al. (1988) | 0 | | 0 | 1 | 1 | 0 | 1 | **3** |
| Brambilla et al. (2003) | 0 | | 0 | 1 | 1 | 0 | 0 | **2** |
| Cook et al. (1990) | 0 | | 0 | 1 | 1 | 0 | 1 | **3** |
| Haigh et al. (2018) | 0 | | 0 | 1 | 1 | 0 | 1 | **3** |
| Kaspi et al. (1994) | 0 | | 0 | 2 | 1 | 1 | 0 | **4** |
| Li, Denson et al. (2020) | 1 | | 1 | 2 | 1 | 0 | 0 | **5** |
| Li, Lloyd et al. (2020) | 0 | | 1 | 2 | 1 | 0 | 0 | **4** |
| McLeod et al. (1993) | 0 | | 0 | 1 | 1 | 0 | 0 | **2** |
| Stein et al. (1989) | 0 | | 0 | 1 | 1 | 1 | 0 | **3** |
| Hartlage et al. (2004) | 0 | | 1 | 2 | 1 | 1 | 0 | **5** |
| **Eating Disorders** |  | |  |  |  |  |  |  |
| Edler et al. (2007) | 0 | | 1 | 2 | 1 | 0 | 1 | **5** |
| Gladis & Walsh (1987) | 0 | | 0 | 1 | 1 | 1 | 0 | **3** |
| Leon et al. (1986) | 0 | | 0 | 1 | 1 | 1 | 1 | **4** |
| Lester et al. (2003) | 0 | | 0 | 1 | 1 | 0 | 1 | **3** |
| Price et al. (1987) | 0 | | 0 | 2 | 1 | 1 | 1 | **5** |
| Schoofs et al. (2011) | 0 | | 0 | 1 | 1 | 1 | 1 | **4** |
| **Personality Disorders** |  | |  |  |  |  |  |  |
| Eisenlohr-Moul et al. (2018) | 0 | | 1 | 2 | 2 | 0 | 1 | **6** |
| Peters et al. (2020) | 0 | | 1 | 2 | 2 | 0 | 1 | **6** |
| Ziv et al. (1995) | 0 | | 0 | 1 | 2 | 1 | 0 | **4** |

**Compliance with Ethical Standards**

**Disclosure of potential conflicts of interest**

None.

**Research involving human participants and/or animals**

Not Applicable – systematic review conducted

**Informed consent**

Not Applicable – systematic review conducted

**Funding**

None.

1. Means and Standard Deviations are not provided for scores on outcome measures. Given the large range of outcome measures, these would be largely arbitrary values. Means and Standard Deviation are detailed for all other outcomes (e.g., frequency data). [↑](#footnote-ref-1)