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Exacerbation of Psychosis During the Perimenstrual Phase of the Menstrual Cycle: Systematic Review and Meta-analysis

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Psychotic disorders can be exacerbated by the hormonal changes associated with childbirth, but the extent to which exacerbations occur with the menstrual cycle is unclear. We addressed this issue by conducting a systematic review. Embase, Medline, and PsychINFO databases were searched for studies that measured exacerbations of psychotic disorders in relation to the menstrual cycle. We extracted exacerbation measure, definition of menstrual cycle phase, and measurement of menstrual cycle phase. Standard incidence ratios were calculated for the perimenstrual phase based on the observed admissions during this phase divided by the expected number of admissions if the menstrual cycle had no effect. Random effects models were used to examine pooled rates of psychiatric admission in the perimenstrual phase. Nineteen studies, comprising 1193 participants were eligible for inclusion. Eleven studies examined psychiatric admission rates, 5 examined symptoms scores, 2 examined self-reported exacerbation, and 1 examined both admission rates and symptom scores. A random effects model demonstrated the rate of admissions during the perimenstrual phase was 1.48 times higher than expected (95% CI: 1.31–1.67), with no significant heterogeneity detected. Four of six symptom score studies reported perimenstrual worsening, but lack of consistency in timepoints precluded meta-analysis. Two studies examining self-reported menstrual exacerbations reported prevalences ranging from 20% to 32.4%. Psychiatric admission rates are significantly higher than expected during the perimenstrual phase. There is some evidence that a worsening of psychotic symptoms also occurs during this phase, but further research with more precise measurement of the menstrual cycle and symptomatology is required.

Key words: schizophrenia/psychotic disorders/bipolar disorder/menstrual cycle/menstruation/menstruation disturbances

Introduction

Since the turn of the 19th century, there have been over 27 confirmed and 200 possible cases of "menstrual psychosis," whereby brief psychotic episodes occur in synchrony with the menstrual cycle, with complete inter-episode remission.[1] Hormonal treatments can be used to prevent recurrences,[2] suggesting a causative pathophysiological mechanism involving fluctuating levels of female sex hormones. This raises the possibility that among female patients with psychosis, there may be a subgroup in which the disorder is particularly related to hormonal fluctuations. Alternatively, there may be more subtle menstrual cycle-related changes in mental state universally in women with psychosis.

The estrogen hypothesis states that estrogen is protective for psychosis and that a reduction in estrogen can worsen or precipitate psychosis.[3] The putative neuro-protective effect of estrogen is thought to underlie the later age of onset of psychotic disorders in women than men, the rise in incidence of psychosis in women post-menopause (following decline in estrogen levels), and the greater severity of psychotic symptoms in late-onset psychosis in women than in men.[4] Moreover, various interventions associated with estrogen withdrawal can precipitate episodes of psychosis. These include termination of pregnancy, removal of a hydatidiform mole, withdrawal of estrogen medication, administration of estrogen receptor antagonists, and administration of gonadotropin-releasing hormone agonists which inhibit estrogen release.[5] Similarly, the period following childbirth results in an abrupt drop in estrogen and progesterone levels and carries a 23-fold increase in relative risk for affective psychotic episodes.[6]

Levels of estrogen vary throughout the menstrual cycle, typically peaking around the time of midcycle

and declining before the start of menses.[7] The estrogen protection hypothesis predicts that psychotic disorders worsen at times in the cycle when estrogen is low, around menstruation[8] and several narrative reviews assert this is indeed the case.[3,4,9,10] A recent meta-analysis pooling data across studies of women with psychiatric diagnoses (psychotic disorders, affective disorders, drug-related disorders) and those with no specific diagnosis (patients presenting with self-harm or suicidal behaviors) demonstrated worse mental health outcomes around the time of menstruation.[11] However, this study examined a sample of women with different psychiatric disorders; the extent to which this relationship is evident in those with psychotic disorders is not known. In the present study, we sought to address this issue by conducting a systematic review of the evidence for menstrual exacerbation of psychotic disorders and synthesizing the evidence by meta-analysis.

Methods

The study protocol was pre-registered with PROSPERO http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018105320. PRISMA reporting guidelines were followed.[12]

Search Strategy

The search was conducted in duplicate by 2 independent researchers (T.J.R. and V.C.S.), using Medical Subject Headings (MeSH) and text words. Medline, Embase, and PsychINFO were initially searched using Ovid (Wolters Kluwer) from inception to July 2018 with the following combinations of subject headings:

- (Schizophrenia OR Bipolar Disorder OR Psychotic Disorders) AND
- (Menstruation OR Menstrual Disturbances OR Estrogens OR Receptors, Estrogen OR Estradiol OR Progesterone OR Follicle Stimulating Hormone OR Luteinizing Hormone)

A PubMed search was then performed using the following textwords:

- ((psychosis OR psychotic OR schizophr* OR schizoaffective OR bipolar) AND
- (menstrua* OR catamenia* OR estrogen OR oestrogen OR estradiol OR oestradiol OR estrus OR oestrus OR monthly OR cyclical OR menses OR periodical OR periodic OR luteal OR follicular OR ovulation))

Reference lists of previous reviews[3,9–11,13] were manually examined to identify additional papers of relevance.

Selection Criteria

Inclusion Criteria. (1) original research of human participants; (2) English language; (3) sample sizes of 10 or more; (4) studies of any psychotic disorder including: schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorder not otherwise specified, bipolar disorder with psychotic symptoms, depressive disorder with psychotic symptoms (with no restrictions on the diagnostic classification system used); and (5) studies measuring phase of menstrual cycle in relation to exacerbation of the disorder.

Exclusion Criteria. (1) case reports, case series, conference abstracts, and reviews; (2) studies which only measured menstruation abnormalities rather than exacerbation of the disorder; (3) studies measuring only premenstrual tension symptoms; and (4) studies exclusively of healthy volunteers.

Data Extraction

The following variables were extracted from each study: author, year of publication, setting, study population, sample size, ethnicity, age, study design, diagnosis, diagnostic instrument, measurement of psychosis exacerbation, measurement of menstrual cycle, definition of menstrual cycle phases. Study design was determined for the outcome of interest (which may differ from the study design of the overall study). For studies measuring symptom scores, we extracted symptom rating scale and the timepoints of assessment. For studies measuring self-reported exacerbation, we extracted method of self-report. Data were extracted independently by 2 researchers (T.J.R. and V.C.S.) with disagreements discussed with a senior researcher (A.E.C.).

Definition of Menstrual Cycle Phase

Consistent with previous meta-analyses[14] we standardized to a 28-day cycle where day 1 was defined as the first day of menstruation and day 24–day 5 was pre-specified as the perimenstrual phase. While we initially intended to analyze the premenstrual phase (day 24–day 28) and menstrual phase (day 1–day 5) separately, as per Jang and Elfenbein,[11] this was not possible because only 3 studies distinguished between these phases.

Risk of Bias Assessment

Studies were assessed independently for quality using a modified version of the Newcastle-Ottawa Scale[15] by 2 study authors (T.J.R. and V.C.S.) with disagreement resolved by a senior author (A.E.C.). This measure provides separate assessment criteria for cross-sectional, case-control, and cohort studies. Consistent with previous meta-analyses by our group,[16] scoring criteria were amended such that the maximum score available for each study design was 8 to facilitate comparison across study designs, see supplementary material.

Data Synthesis

We planned separate meta-analyses for 3 outcomes of interest identified by pilot searches: (1) rate of psychiatric admissions during the perimenstrual phase relative to the non-perimenstrual phase; (2) change in symptom measures across menstrual cycle phases; and (3) point prevalence of self-reported menstrual exacerbation of psychotic symptoms. Meta-analysis was performed for outcomes reported in 5 or more studies, which meant we were only able to examine hospital admissions.

Consistent with previous meta-analyses,[11] the rate of psychiatric admissions during the perimenstrual phase relative to the non-perimenstrual phase was examined using pooled standardized incidence ratios (SIR). The SIR was defined as the observed count of admissions during the phase of interest (O) divided by the expected number of admissions during that period (E), where it is assumed that expected probability of admission on any given day of the menstrual cycle is uniform if there is no association between menstrual phase and admission. Prior to analyses, individual study data were standardized to a pre-defined phase definition (perimenstrual: day 24–day 5 and non-perimenstrual: day 6–day 23), using the procedure described by Jang and Elfenbein.[11] Specifically, for studies that examined more than 2 phases, this involved aggregating data across phases so that the phase definitions approximated those used in the current study (ie, day 24–day 5 vs day 6–day 23). As this standardization procedure did not always generate phases that corresponded exactly with our pre-defined phases of interest, we computed a deviance score for each study representing the difference in days between the pre-defined phases of interest and those employed in the original study. For example, a study examining admissions between day 25–day 4 vs day 5–day 24 would have a deviance score of 2 on account of the fact that day 26 and day 5 were not included in the phase of interest, but instead included in the non-perimenstrual phase. Deviance scores were absolute values based on the rationale that effect sizes would be attenuated regardless of whether the phase definitions used in the original study was longer or shorter than our pre-defined perimenstrual phase. Meta-regression analysis was then used to examine the effect of these scores. SIRs and associated standard errors were computed for the perimenstrual phase where ratios greater than 1 indicate a greater rate of the outcome than would be expected in that phase. SIRs and standard errors were log transformed prior to performing meta-analyses to produce a pooled SIR for the perimenstrual phase with 95% CI used to determine whether SIRs significantly differ from 1.

Meta-analysis

Meta-analyses were performed on data extracted from papers examining admission rates across the perimenstrual phase; all analyses were performed in Stata 15.[17] We used the "meta" command to perform random-effects meta-analyses on log-transformed SIRs.[18] This command uses inverse-variance weighting and has the advantage of enabling analyses to be conducted for user-defined effect sizes (in this case, SIRs). The influence of individual studies was estimated using the "metainf" command which omits each study in turn from the meta-analysis to determine the effect on the pooled SIR. We then conducted meta-regression to determine the effect of the following variables: (1) year of study; (2) deviance score (described above); (3) study quality score; and (4) diagnosis (comparing schizophrenia with a more broadly inclusive psychosis spectrum diagnoses).

Results

After screening for eligibility, 19 full-text articles including 1193 participants met inclusion criteria (supplementary material). Eleven studies examined admission rates,[19–29] 5 symptom scores,[30–34] 2 self-reported exacerbation,[35,36] and 1 examined both admission rates and symptoms scores.[37] When categorized according to the outcome of interest, 14 studies were cross-sectional[19–29,35–37] and 5 were prospective cohort studies.[30–34]

Admission Rates

Characteristics of the 12 studies examining admission rates are shown in table 1. All were cross-sectional, with 1 providing data for 2 independent samples.[20] Half of the studies examined schizophrenia specifically, with the remainder employing a broader psychosis spectrum diagnosis (including affective psychosis, delusional disorder, and brief psychotic disorder). Sample characteristics were not well defined; 4 studies provided no information on participant age (mean age range: 30.8 to 37.0 y) and none reported ethnicity.

Inclusion criteria meant that many women experiencing menstrual irregularity or dysfunction, or those unable to give a comprehensive menstrual cycle history were not eligible. Eight studies included only women with regular menstrual cycles or cycles of typical length[19,22,23,26–29,37] and 4 specifically excluded women who could not provide accurate details on their last menstrual cycle.[20–22,37] Ascertainment of menstrual cycle phase was generally poor. Six studies used self-report (with or without the aid of an interview) alone, as their method of ascertaining menstrual phase,[19,21,23,27–29] 2 used a combination of self-report and observation,[20,26] 2 used a combination of self-report and hormone assays to determine phase,[24,37] 1 study used self-report, observation and hormone assays,[25] and 1 did not report measurement method of menstrual phase.[22]

Eleven of the 12 studies examining admissions data (1 including 2 independent samples), provided data that

Table 1. Characteristics of Studies Examining Admission Rates Across the Menstrual Cycle

Study	Number of Participants	Mean Age	Diagnosis	Diagnostic Criteria	Measurement of Menstrual Cycle	Definition of Menstrual Cycle Phases	Number of Phases	Summary of Results
Abramowitz et al. 1982	76	33.7	Schizophrenia	DSM-II	Interview by gynecologist	Paramenstrual phase: day 25–day 4	2	28 (36.8%) admitted in the paramenstrual phase nonsignificant
Bergemann et al. 2002	115	32.1	Schizophrenia	DSM-IV and ICD-10	Self-report and observation	Perimenstrual phase: day 26–day 4	2	43 (37.4%) admitted in the perimenstrual phase $P = .002$
	170	37.0	Schizophrenia	DSM-IV and ICD-10	Self-report and observation	Perimenstrual phase: day 26–day 4	2	54 (31.8%) admitted in the perimenstrual phase $P = .028$
Dalton et al. 1959	114	Not reported	Schizophrenia	Not reported	Self-report	Phase 1 (menstrual): day 1–day 4; phase 2: day 5–day 8; phase 3: day 9–day 12; phase 4 (ovulatory): day 13–day 16; phase 5: day 17–day 20; phase 6: day 21–day 24; phase 7 (premenstrual): day 25–day 28	7	54 (47.4%) admitted in the premenstrual or menstrual phase, no statistical test performed
Gattaz et al. 1994	65	31.2	Schizophrenia	DSM-III-R	Not reported	Premenstrual/menstrual phase: day 22–day 7; inter-menstrual phase day 8–day 21	2	40 (61.5%) admitted in the premenstrual/menstrual phase $P = .11$
Glass et al. 1971	20	Not reported	Schizophrenia and affective psychosis	DSM-II	Self-report	Menstrual phase: day 1–day 7; midcycle phase: day 8–day 21; premenstrual phase: day 22–day 28	3	16 (80%) admitted in the premenstrual/menstrual phase $P < .01$
Herceg et al. 2018	31	35.2	Schizophrenia	DSM-V	Self-report and hormonal assay	Follicular phase: day 1–day 14; luteal phase day 15–day 28	2	21 (67.7%) admitted in the luteal phase $P = .0068$
Huber et al. 2001	28	35.8	Schizophrenia, brief psychotic disorder, schizoaffective disorder, delusional disorder	DSM-IV and ICD-10	Self-report and hormonal assay	Perimenstrual phase: day 26–day 7	2	20 (71.4%) admitted in the perimenstrual phase, no statistical test performed
Huber et al. 2004	27	35.0	Schizophrenia, brief psychotic disorder, schizoaffective disorder, delusional disorder	DSM-IV and ICD-10	Self-report, hormonal assay and observation	Perimenstrual phase: day 26–day 7	2	19 (70.4%) admitted in the perimenstrual phase, no statistical test performed
Lande et al. 2002	19	Not reported	Schizophrenia	DSM-IV	Self-report and observation	Late luteal / early menstrual phase: day 25–day 3; follicular phase: day 4–day 13; ovulatory phase: day 14–day 15; luteal phase: day 16–day 24	4	12 (63.2%) admitted in the late luteal / early menstrual phase, no statistical test performed

Table 1. *Continued*

Study	Number of Participants	Mean Age	Diagnosis	Diagnostic Criteria	Measurement of Menstrual Cycle	Definition of Menstrual Cycle Phases	Number of Phases	Summary of Results
Luggin et al. 1984	38	Not reported	Psychotic illness	ICD-8	Self-report	Phase 1 (menstrual): day 1–day 7; phase 2: day 8–day 14; phase 3: day 15–day 21; phase 4 (premenstrual) day 22–day 28	4	22 (57.9%) admitted in the premenstrual/menstrual phase, no statistical test performed
Targum et al. 1991	19	30.8	Schizophrenia, schizoaffective disorder	DSM-III-R	Self-report	Paramenstrual phase: day 25–day 5	2	10 (52.6%) admitted in the paramenstrual phase, no statistical test performed
Zola et al. 1979	51	34.0	Psychotic depression, schizophrenia, acute psychoses of uncertain type	DSM-II	Self-report	Premenstrual/menstrual phase: day 23–day 4	2	21 (41.2%) admitted in the premenstrual/menstrual phase, no statistical test performed

Note: DSM, Diagnostic Statistical Manual of Mental Disorders; ICD, International Classification of Diseases.

could be examined by meta-analysis. One study,[37] which reported a significantly higher rate of admissions during the luteal phase (day 15–day 28) relative to the follicular phase (day 1–day 14), could not be converted to our phase of interest (day 24–day 5) and so was not included in the meta-analysis. The forest plot of the 11 studies included in the meta-analysis is shown in figure 1. A random-effects meta-analysis yielded an overall SIR of 1.48 (95% CI: 1.31–1.67), indicating an excess of admissions during the perimenstrual phases compared with the expected rate. There was no significant effect of heterogeneity, Cochran's Q = 13.846. Meta-regression analyses indicated that year of study, deviance from our pre-specified definition perimenstrual phase, study quality or diagnosis were not associated with effect sizes ($P > .05$ for all). The influence analysis ("metainf") indicated that none of the studies had a substantial influence on the overall effect size (ie, omitting any one of the studies would not change the SIR derived).

Risk of bias for each study is reported in table 2. Scores ranged from 2 to 7 with a mean of 4.7. Most studies (10/12) scored full marks for representativeness, using consecutive psychiatric admissions as the study sample. No study reported a power calculation and only Bergemann et al[20] had a large enough total sample size ($n = 285$) to suggest that a power calculation was not required. Only one cross-sectional study[19] scored a point for nonresponders, describing participants who were potentially eligible but did not take part in their study. Most studies (8/12) scored no points for assessment of exposure (that is to say, menstrual cycle phase), due to reliance on self-report of last menstrual period. All bar one study used record-linkage to measure admission rates, and so scored maximum points for assessment of outcome (11/12), while most reported outcomes appropriately (8/12).

Symptom Scores

Studies reporting symptom scores, with a total of 262 participants, are shown in table 3. Mean age of the samples ranged from 29.1 to 36.1. Four studies used a narrow diagnosis of schizophrenia while 2 also included affective psychoses. Five studies used the Positive and Negative Syndrome Scale (PANSS) and one used the Brief Psychiatric Rating Scale (BPRS). Four studies reported repeated measures of symptom scores from different timepoints in the cycle, as illustrated in figure 2. As shown, there was little consistency in the time-points examined, precluding a meta-analysis. Herceg et al[37] compared mean symptom scores of participants admitted in the follicular phase (day 1–day 14) to those admitted in the luteal phase (day 15–day 28), while Bergemann et al[31] reported regression coefficients for changes in PANSS scores only, rather than mean symptom scores.

Four studies reported higher symptom scores perimenstrually[30–33] while 2 reported no effect.[34,37] Akhondzadeh
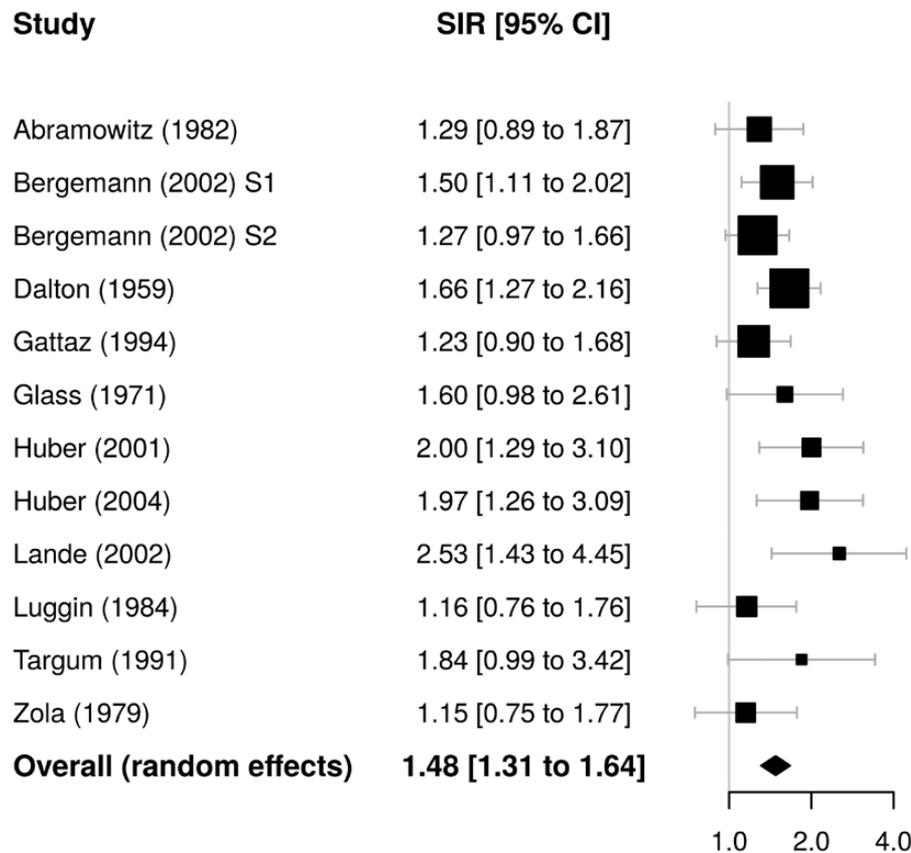
Fig. 1. Pooled standard incident ratios (SIR) of observed/expected rates of psychiatric admissions during the perimenstrual phase (day 24–day 5) of a 28-day cycle.

et al[30] found significantly higher scores in all PANSS subscales and lower levels of estrogen and progesterone menstrually (day 3), compared with midcycle (day 13) in patients with chronic schizophrenia. Choi et al[32] reported higher total BPRS scores in the premenstrual phase and lower levels of estradiol and progesterone, compared with the menstrual and post-menstrual phases. However, they found no correlation between change in estradiol and change in total BPRS scores. Rubin et al[33] reported higher total PANSS scores in the early follicular phase (day 2–day 4) compared with the mid-luteal phase (day 20–day 22), but estradiol was not significantly associated with change in symptom scores in regression models. Both Herceg et al[37] and Thompson et al[34] reported no differences in total PANSS scores between the follicular phase (day 1–day 14) and luteal phase (day 15–day 28). Interestingly, Herceg et al[37] found higher estradiol levels in the follicular phase, while Thompson et al[34] found higher levels in the luteal phase, despite both studies using the same days to define these phases. This discrepancy may be attributable to the long sampling period of 14 days. Herceg et al[37] found no correlation between estradiol and total PANSS scores.

Bergemann et al[31] was by far the largest study of symptom ratings (*n* = 125). They reported significant improvement in PANSS scores in the luteal phase (day 20–day 22), compared with both the menstrual phase (day 2–day 4) and the peri-ovulatory phase (day 10–day 12). Estradiol levels were lowest in the menstrual phase and showed a statistically significant inverse correlation with PANSS Positive scores ($P < .05$).

Only one study systematically measured premenstrual tension symptoms, using the daily rating form (DRF).[32] They found a significant correlation between total BRPS score and total DRF score in the premenstrual phase (Pearson's correlation coefficient 0.44, $P = .05$).

The quality of symptom studies was higher than the admission studies (table 2); ranging from 4 to 7, with a mean of 5.7, from a maximum of 8. None of the 5 cohort studies of symptom scores scored marks for representativeness as they tended to be selected, nonconsecutive samples. As they used repeated measures for symptom scores at different timepoints with participants effectively acting as their own controls, all scored maximum marks for matching of exposed and unexposed groups. Most (3/5) measured exposure adequately, most (4/5) used blinded assessment of outcome and most (4/5) had sufficient time (1 full menstrual cycle) for the outcome to occur. Less than half (2/5) of these studies described participants lost to follow-up adequately. The single cross-sectional study of symptom scores[37] lost marks only

Table 2. Quality Rating Scores for Included Studies Using a Modified Version of the Newcastle-Ottawa Scale

Quality Assessment for Cross-sectional Studies

Study	Outcome of Interest	Representativeness (Max 2)	Sample Size (Max 1)	Description of Nonresponse (Max 1)	Exposure (Max 1)	Assessment of Outcome (Max 2)	Reporting of Outcome (Max 1)	Total Quality Score (Max 8)
Abramowitz et al. 1982	Admission rate	2	0	1	0	2	1	6
Bergemann et al. 2002	Admission rate	2	1	0	1	2	1	7
Dalton et al. 1959	Admission rate	2	0	0	0	2	0	4
Gattaz et al. 1994	Admission rate	2	0	0	0	2	1	5
Glass et al. 1971	Admission rate	2	0	0	0	2	1	5
Huber et al. 2001	Admission rate	2	0	0	0	2	0	4
Huber et al. 2004	Admission rate	2	0	0	1	2	0	5
Lande et al. 2002	Admission rate	0	0	0	1	2	0	3
Luggin et al. 1984	Admission rate	2	0	0	0	2	0	4
Targum et al. 1991	Admission rate	2	0	0	0	2	1	5
Zola et al. 1979	Admission rate	1	0	0	0	1	0	2
Herceg et al. 2018	Admission rate and Symptom score	2	0	0	1	2	1	6
Gleeson et al. 2016	Self-report	0	0	0	0	0	1	1
Hsiao et al. 2004	Self-report	2	0	0	0	0	1	3

Quality assessment for cohort studies

Study	Outcome of Interest	Representativeness (max 1)	Ascertainment of exposure (max 1)	Exposed and unexposed matched or adjustment for confounding (max 2)	Assessment of outcome blinded or record linkage (max 2)	Follow-up period was sufficiently long for outcomes to occur (max 1)	Loss to follow-up (max 1)	Total quality score (max 8)
Akhondzadeh et al. 2005	Symptom score	0	1	2	2	1	1	7
Bergemann et al. 2007	Symptom score	0	0	2	2	0	0	4
Choi et al. 2001	Symptom score	0	0	2	2	1	1	6
Rubin et al. 2010	Symptom score	0	1	2	2	1	0	6
Thompson et al. 2000	Symptom score	0	1	2	1	1	0	5

Table 3. Characteristics of Studies Examining Symptom Ratings Across the Menstrual Cycle

Study	Country	Design	Sample Description	Number	Mean Age	Diagnosis	Diagnostic Tool	Measurement of Menstrual Cycle Phases	Scale	Summary of Result
Akhondzadeh et al. 2005	Iran	Cohort	Inpatient	30	29.1	Schizophrenia	DSM-IV	Questionnaire, observation and hormonal assay	PANSS	More severe symptoms during menstruation compared with midcycle, $P < .001$
Bergemann et al. 2007	Germany	Cohort	Inpatient	125	35.0	Schizophrenia	DSM-IV	Self-report and hormonal assay	PANSS	Improvement in symptoms during the luteal phase compared with menstrual ($P < .001$) and peri-ovulatory ($P < .01$) phases
Choi et al. 2001	South Korea	Cohort	Inpatient	24	36.1	Schizophrenia	DSM-IV	Not defined, however, hormonal assays taken	BPRS	More severe symptoms in premenstrual phase compared with menstrual and post-menstrual phases, $P < .05$
Herceg et al. 2018	Croatia	Cross-sectional	Inpatient	31	35.2	Schizophrenia	DSM-V	Self-report and hormonal assay	PANSS	No difference between the follicular and luteal phases, $P = .4707$
Rubin et al. 2010	USA	Cohort	Outpatients	23	30.7	Schizophrenia, Schizoaffective disorder depressed type	DSM-IV	Self-report and hormonal assay	PANSS	More severe symptoms in follicular phase compared with luteal phase, $P < .01$
Thompson et al. 2000	Australia	Cohort	Inpatient and outpatient	29	30.7	Schizophrenia, Bipolar disorder with psychotic symptoms, schizoaffective disorder, depression with psychotic symptoms, schizophreniform disorder	DSM-IV	Menstrual Cycle Questionnaire and hormonal assay	PANSS	No difference between the follicular and luteal phases, $P = .146$

Note: DSM, Diagnostic Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; PANSS, Positive and Negative Syndrome Scale; BPRS, Brief Psychiatric Rating Scale.
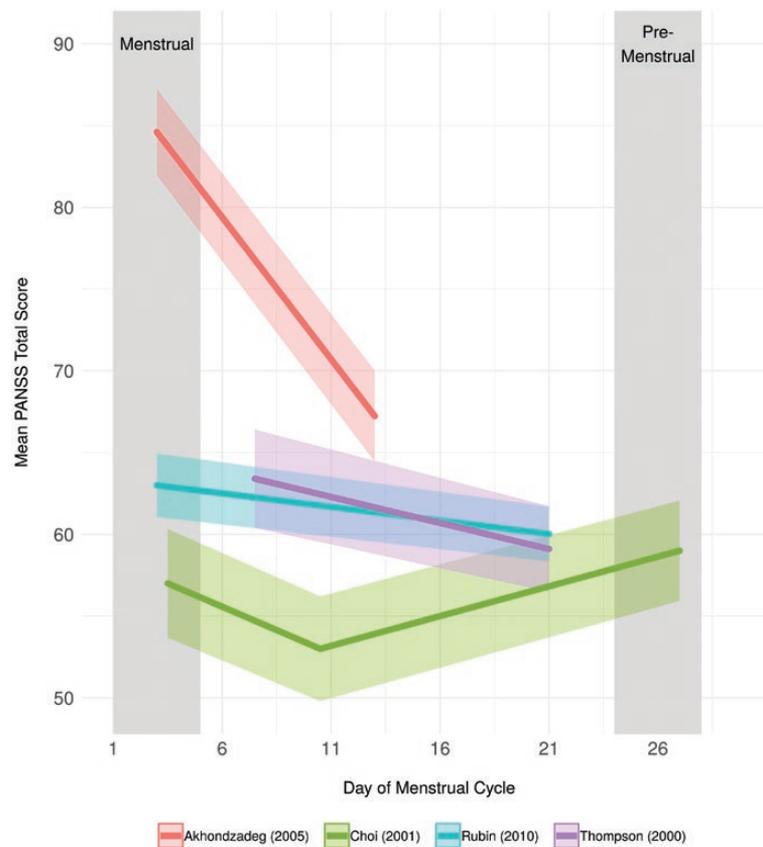
Fig. 2. Mean Positive and Negative Syndrome Scale (PANSS) total scores with standard errors from studies reporting symptom scores at more than one timepoint.

through lacking a power calculation for the sample size and description of nonresponders, scoring a total of 6.

Self-Report

Only 2 studies provide data on self-reported menstrual exacerbation. Hsiao et al[36] asked participants or their families to report exacerbation in relation to the premenstrual phase and to rank symptoms as mild, moderate or severe. Of 50 participants diagnosed with schizophrenia, 7 (14.0%) had mild exacerbation, 2 (4.0%) had moderate exacerbation, and 1 (2.0%) had severe exacerbation. Gleeson et al[35] found 45 of 139 (32.4%) participants diagnosed with a schizophrenia-spectrum disorder reported fluctuation of severity across their cycle at any timepoint.

The quality of self-report studies was low (table 2). Gleeson et al[35] used baseline data from a clinical trial, which was not likely to be representative of the wider patient population, whereas Hsiao et al[36] used a random sample of women presenting to outpatient services. Neither study justified sample size nor described nonresponders. Neither study used a valid measurement of menstrual cycle phase or exacerbation; both simply asked participants if they experienced menstrual worsening of their illness. Thus, Gleeson et al[35] scored a total of 1 and Hsiao et al[36] scored 3.

Discussion

This is the first meta-analysis to demonstrate perimenstrual exacerbation in women diagnosed with a psychotic disorder. Specifically, we found evidence of a clear excess of psychiatric admissions during the perimenstrual phase relative to the non-perimenstrual phase. There was also some evidence from studies examining symptoms at multiple time-points of perimenstrual worsening of psychotic symptoms, but this was not consistent across all studies and was not amenable to meta-analysis. Prevalence of self-reported exacerbation was only reported by 2 studies, ranging from 20% to 32.4%. Our findings lend support to the estrogen protection hypothesis by showing a worsening of psychosis at times in the cycle when estrogen levels are low.

As an outcome measure, admission to psychiatric hospital is likely to have a low risk of bias as it uses record linkage of routine clinical data. Hospitalization has validity as an outcome measure as it is associated with poorer quality of life and severity of psychopathology in patients with psychosis.[38] Admission due to psychotic relapse is a key driver of mental health costs,[39] so factors affecting admission rates have important health economic implications. Our results are consistent with Jang and Elfenbein[11] who report increased rate of psychiatric admissions

during the premenstrual and menstrual phase irrespective of diagnosis. Their study reports a smaller SIR of 1.20 (CI: 1.08–1.33) during the menstrual phase (day 1–day 5) and 1.13 (CI: 1.01–1.26) during the premenstrual phase (day 24–day 28), relative to the expected admission rate. The higher SIR reported in our study might imply that women with psychotic disorders are particularly vulnerable to the effects of the menstrual cycle, more so than women with other mental disorders. It also suggests that the robust finding of worst mental health outcomes around the time of menstruation across psychiatric diagnosis could be driven by poor outcomes in the subgroup of women diagnosed with psychotic disorders.

There was some overlap in the studies used for each meta-analysis, with 7 admissions papers being used for both Jang and Elfenbein[11] and ours.[19,21,23,26–29] Jang and Elfenbein[11] also report a small but statistically significant increase in completed suicides and suicide attempts in the menstrual phase. None of our included studies reported these outcomes, therefore we are unable to confirm whether this also holds for psychotic disorders.

Admission to psychiatric hospital is not synonymous with relapse or exacerbation of psychosis; worsening of psychotic symptoms will not always result in a hospital admission, unless particularly severe. Thus, admissions data potentially captures more extreme variation in psychotic symptomatology. While symptom rating scales may be a more sensitive and direct measure of illness exacerbation, most studies of symptom ratings examined inpatient samples, with only one being exclusive of outpatients. Inpatients would be expected to have more severe psychotic symptoms than community populations. This reduced variability may hinder the ability to detect fluctuations in symptoms across the menstrual cycle.

Unfortunately, heterogeneity in the 6 studies measuring symptoms ratings, precluded meta-analysis of these data. Both the definition of perimenstrual phase and the comparison time-points varied between studies. Of the studies that reported symptom ratings, all compared the symptom scores of participants at one time-point with one or 2 other time-points. This method of comparing symptom scores is a crude measurement which is not sensitive to the marked individual inter-cycle variability, present even in those women reporting regular cycles.[40] Indeed, both Herceg et al[37] and Thompson et al[34] compared an average of symptom ratings of day 1–day 14 to day 15–day 28, which is almost certainly too long to interpret whether there are menstrual fluctuations, potentially missing exacerbation over shorter time-periods.

Despite the lack of any cross-study synthesis, there is some evidence that menstrual exacerbation of psychotic symptoms occurs; 4 of the 6 studies report statistically significant changes in symptoms scores across the cycle. It is likely that more precise research methodology in tracking both menstrual cycle phase and symptoms of psychosis over time will uncover the underlying relationship.

Worsening of psychotic disorders around the time of menstruation, when estrogen levels are low, is supportive of the estrogen protection hypothesis.[41] However, only 2 studies of admission rates confirmed menstrual cycle phase by hormonal assay,[25,37] so it is not known whether estradiol was indeed low during the perimenstrual phase. Studies of symptom scores did measure estradiol levels according to menstrual cycle phase and in 4 of 6 studies found more severe symptoms in low estrogen phases. Three studies failed to find a correlation of estradiol levels and symptoms scores,[32,33,37] though this may be attributable to small sample sizes (mean $n = 26$). The largest study of symptom scores,[31] with a sample size of 125, did detect a significant inverse correlation between estradiol and PANSS Positive scores. Moreover, inverse correlations between psychotic symptoms and estradiol levels over time have been reported by 3 studies,[42–44] which did not meet our inclusion criteria as they did not report exacerbation of psychosis in relation to menstrual cycle phase. It may be that absolute values of estrogen are less relevant than the magnitude of decline in estrogen levels over a cycle. Only one study, Choi et al,[32] examined this and showed no significant correlation between change in estradiol and change in BPRS scores (Pearson's correlation coefficient −0.21, $P = .30$). Likewise, they reported no correlation between symptoms and the ratio of estradiol/progesterone. Nevertheless, the effect of fluctuations in estrogen at an individual level warrants further investigation in larger studies.

It is difficult to draw firm conclusions from the 2 low-quality studies of self-reported menstrual exacerbation. Although both report that a minority of participants experience worsening of psychosis menstrually, it is possible that participants incorrectly ascribe premenstrual dysphoric symptoms to an exacerbation of their psychotic illness.[9] Conversely, a substantial number of women with a psychotic disorder may lack insight that their symptoms are worsening.[45] Thus, self-report is likely to be an unreliable measure of true exacerbation of psychotic illness.

Limitations

There are important limitations to our review. Firstly, there was no consistent definition of premenstrual or menstrual phases across studies, necessitating the creation of a perimenstrual phase ranging from day 24 to day 5 based on a 28-day cycle. One study[37] could not be included in the meta-analysis because their definition of menstrual cycle phases (day 1–day 14 and day 15–28) could not be converted into our phase of interest. The time-points were largely calculated by the self-report of last menstrual period, which is prone to bias.[46] Estimation of cycle phase may be particularly fallible in women who are experiencing an acute relapse in mental state, who are prescribed medication that interferes with their cycle or

who have irregular cycles; factors relevant to our study population.

Most studies (12/19) specifically excluded women with irregular cycles, which aids the standardization of data to a 28-day cycle. However, as menstrual dysfunction is commonplace in psychotic disorders where up to 40% report irregular cycles,[35] excluding such patients reduces the generalizability of results. Another limitation is the use of participants with established psychotic disorders, rather than those presenting specifically with their first episode of psychosis who would be minimally treated. In patients taking regular antipsychotic medication, menstruation may be affected because of a reduction in the dopaminergic inhibition of prolactin.[47] Nonetheless, hyperprolactinemia has also been reported in antipsychotic naïve patients with schizophrenia,[48] suggesting dysfunction of the hypothalamic-pituitary-gonadal axis is present at illness onset.

We initially planned to include studies of bipolar affective disorder with psychotic symptoms. Although we identified several studies examining bipolar disorder in relation to menstrual exacerbation,[49–61] none specified whether psychotic symptoms were present. One-third of women with bipolar disorder experience a relapse postpartum,[62] suggesting a vulnerability to hormonal fluctuations that merits a further review of the existing research on menstrual exacerbation. The only systematic review of this topic to date did not conduct a meta-analysis.[13]

Further Research

Future research should take advantage of widely used and scientifically validated menstrual tracking Smartphone apps.[63] These offer more detailed assessment of menstrual cycles which do not rely simply upon self-report of last menstrual period. This could be done in conjunction with validated Smartphone measures of psychotic symptoms[64] to provide standardized phases of the menstrual cycle. Larger sample sizes, of women who are early in their illness, either antipsychotic naïve or minimally treated would further reduce the effect of confounding factors associated with chronic psychosis. The impact of premenstrual tension symptoms should be considered as well as individual variation in sex hormones, including estrogen, progesterone, and testosterone. Not only would this allow for a more sensitive measure of menstrual exacerbation at a greater temporal resolution that does not rely on standardization to a 28-day cycle, but individual correlations for each participant could also be used to identify women prone to menstrual exacerbation of psychosis. This subgroup may thus be more prepared to self-manage monthly exacerbations in their illness and could benefit from slight increases in antipsychotic doses during times of increased vulnerability. They may also be suitable for trials of novel targeted hormonal therapy, utilizing emerging estrogen treatments

in schizophrenia.[65,66] A similar strategy has already been employed for women whose epilepsy has been shown to be menstrually exacerbated.[67] Furthermore, identifying whether women whose psychotic illness is vulnerable to menstrual fluctuations are subsequently at increased risk of relapse postpartum and postmenopausal (times of declining estrogen levels) could provide impetus for novel preventative treatments.

Conclusion

This systematic review and meta-analysis provides robust evidence of an excess in admissions for psychotic disorders perimenstrually, in keeping with the estrogen protection hypothesis. Further research is needed to characterize the effect of the menstrual cycle on the symptomatology of psychosis, whether there is a subgroup of women who individually have a strong correlation between psychotic symptoms and menstrual cycles, and whether this subgroup is amenable to intervention in the form of hormonal therapy.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

Acknowledgment

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