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Higher Depressive Symptoms in Irregular Menstrual Cycles: Converging Evidence from Cross-Sectional and Prospective Assessments

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Keywords
Menstrual cycle · Depressive disorders · Mood disorders · Longitudinal studies · Women's health

Abstract
Background: Menstrual cycle regularity is an important marker of reproductive health and associated with physiological and psychological illnesses, as well as experiencing stress. We hypothesized that individuals with irregular menstrual cycles report higher depressive symptom severity, after controlling for stress occurrence. ***Methods:*** The hypothesis was examined through two measurement approaches: a cross-sectional and a prospective, longitudinal study. In the cross-sectional study, participants (n = 394) reported depressive symptoms and their overall menstrual cycle regularity. In the longitudinal study, participants (n = 77) completed questionnaires on depressive symptoms and stress during the mid-follicular and periovulatory phase of one menstrual cycle. Depressive symptoms were compared between participants with regular and irregular cycles through a Welch t test and an ANCOVA. ***Results:*** Participants with irregular menstrual cycles reported more depressive symptoms in the cross-sectional analysis. Similarly, in the longitudinal analysis, the group with a current irregular menstrual cycle reported more depressive symptoms after controlling for stress occurrence. When including only complete data sets without multiple imputation (n = 52), the direction of the effects remained but did not reach statistical significance. ***Conclusions:*** The results indicate an association between depressive symptoms and menstrual cycle irregularity. Limitations were that although we investigated the menstrual cycle prospectively, it would have been more precise to include two or more cycles and daily sex hormone measurements. Further limitations were the suboptimal statistical power and the data collection during the COVID pandemic. We give recommendations on how to incorporate the association of depressive symptoms and cycle irregularity in future study designs on women's mental health.

Introduction

Menstrual cycle characteristics are highly important markers of female reproductive health [1, 2]. Typical menstrual cycles approximately last 25–35 days with

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substantial variation in length between women[1] [3, 4]. Deviation in cycle length stems from differences in the follicular phase (onset of menses to ovulation). The luteal phase (ovulation to onset of next menses) has a more consistent length, determined by the life span of the corpus luteum [5]. Above interindividual differences in average length, intraindividual regularity of length has been associated with a higher risk for some somatic and mental illnesses [6–9]. Influencing factors of cycle regularity are age [10, 11], night work [12], jet lag [13], excessive exercise [14], and stress [15–17]. Psychological symptoms related to menstrual cycle irregularity have been investigated by Nillni et al. [18], who estimated a 63% greater prevalence of irregular menstrual cycles for pregnancy-planners reporting severe depressive symptoms. Similarly, Yu et al. [19] found an increased chance of irregular menstrual cycles in adolescents who reported depressive symptoms within the previous 12 months. Importantly, neither study assessed severity of depressive symptoms continuously. Moreover, Yu et al. [19] investigated exclusively adolescent participants, which show unique menstrual cycle characteristics (e.g., high rate of anovulatory and/or cycles, lower progesterone concentrations) and can therefore differ compared to an adult population [20, 21].

This study aims to investigate the association between menstrual cycle irregularity and depressive symptoms by incorporating a cross-sectional and longitudinal design in adult female humans. Thereby, we either controlled for or eliminated other influencing factors of menstrual cycle regularity, specifically stress occurrence, age, jet lag, and night work. We hypothesized that women with an irregular menstrual cycle report higher depressive symptom severity than participants with a regular menstrual cycle. Further, this study contributes to the foresighted planning of future studies by discussing how to address menstrual cycle irregularity when assessing depressive symptoms.

Methods

The hypothesis was investigated with two approaches: a cross-sectional and a longitudinal study. In both, depressive symptoms were compared between participants with and without irregular menstrual cycles. Depressive symptoms were defined by the criteria for major depressive episode (MDE) in the diagnostic and statistical manual of mental disorders (DSM V) [22]. Data for both studies were collected between January 2020 and May 2021.

This is a secondary analysis of a study on depression and stress in the menstrual cycle. It is preregistered on ClinicalTrials.gov (NCT04086316) and approved by the Institutional Review Board at the Department of Psychology and Educational Science at Freie Universität Berlin (ID:003.2019). Written consent was given twice, once for the cross-sectional and once for the longitudinal study.

Procedure

The cross-sectional study was carried out through an online questionnaire (Questback GmbH, 2020 [23]), in which participants reported demographics, cycle characteristics, and depressive symptoms, as described below. For the longitudinal study, a subset of participants from the cross-sectional study, that fulfilled additional inclusion criteria, was selected. Across one menstrual cycle, they reported daily if menstrual bleeding occurred and additional ovulation tests were carried out to determine menstrual cycle phase. Furthermore, participants completed a set of questionnaires on current depressive symptoms and stress occurrence at two time points: once in the mid-follicular phase (T1) and once in the periovulatory phase (T2). For more details, see Menstrual Cycle Assessment.

Participants

Cross-Sectional Study

Participants for the cross-sectional study were recruited on social media platforms, via the university's official website, and its outpatient clinic. Participants with and without depressive disorder were recruited to retrieve a broad variance of depressive symptom intensity and to enable group comparisons for research questions addressed in other manuscripts of the parental study (Klusmann et al., submitted). This preregistered study required a sample of approximately equal group sizes for participants with and without depressive disorders. Participants were not informed that the topic of the current study was the menstrual cycle to avoid possible biases regarding cycle effects. Rather, they received study information entailing that either mood in general or the etiology for depression was investigated and were informed that factors such as the menstrual cycle were controlled for. Exclusion criteria were male sex, shift work, age <18 or >45 years, menopause, hormonal contraception use, pregnancy in the last year, current breastfeeding, psychotropic medication in the past 6 months, lifetime diagnosis of bipolar disorders, psychotic disorders, substance-related disorders, or eating disorders, and current diagnosis of chronic diseases, that could influence the hypothalamic-pituitary-gonadal-axis and thereby ovarian hormones and menstrual cycle characteristic or the hypothalamic-pituitary-adrenal-axes (for a list of excluded chronic diseases see online suppl. Material A; for all online suppl. material, see https://doi.org/10.1159/000535565).

Longitudinal Study

Participants for the longitudinal study consisted of a subgroup of the cross-sectional study. All participants that fulfilled the previously reported inclusion criteria, reported to have a regular cycle and agreed to participate in the longitudinal study were invited for further participation. Once the required number of participants without depressive disorder, as required by the parental study, was reached, only participants with depressive

[1]The term "women" is often incorrectly restricted to individuals with the female biological sex instead of gender. In the following text, we will use a more precise description of the designated group, wherever possible.

disorder were invited for study participation. Due to the necessity to plan assessments in specific cycle phases, a self-reported regular menstrual cycle between 26 and 30 days was an additional inclusion criterion. Participants who planned to travel to a destination with more than 1 h time difference were excluded to account for potential jet lag. Furthermore, individuals that reported moderate to severe suicidal ideation were excluded and referred to a psychotherapist.

Menstrual Cycle Assessment

Cross-Sectional Study

General menstrual cycle characteristics were assessed by self-report for both studies in the cross-sectional questionnaire, including average menstrual cycle length, dates of previous and next expected menses and mean cycle length. There is no uniform definition of the range of days in variability that is considered regular and irregular [24]. Standard deviations of mean menstrual cycle length vary greatly, depending on age range and included cycle lengths but are typically estimated between 2 and 4 days [5, 10, 25]. We chose a rather strict approach and defined a cycle range of more than 5 days, i.e., variations of more than +/− 2 days around the expected onset of menstruation, as irregular. Survey participants self-reported their menstrual cycle as either regular or not, whereas the definition of regular as +/− 2 days was provided.

Longitudinal Study

In the longitudinal study, ovulation and menstrual cycle phase were assessed to ensure that the questionnaires would fall into the mid-follicular (T1) or periovulatory phase (T2). Following the guidelines of Schmalenberger et al. [26], the mid-follicular phase was defined as days +4 to +7 after the onset of menstruation. The periovulatory phase was defined as days −2 to +1 around a positive ovulation test or, if no valid test was available, days −15 to −12 before onset of the next menstruation.

On five consecutive days, scheduled based on self-reported cycle length, participants were asked to perform a commercially available LH-test to determine ovulation (One+ step® ovulation test). They were prompted to send a photo of the test strip 10 min after taking the test. Ovulation was confirmed, as soon as a positive test result was followed by a negative test result. A daily question provided via smartphone app (mobileQ; [27]) was used to assess current menstrual bleeding. Thereby, the exact length of the investigated menstrual cycle was determined from the first indicated menstrual bleeding up to the second time when menstrual onset was confirmed.

Participants were assigned to the irregular cycle group if the length of the longitudinally investigated menstrual cycle fell into a range of 5 days, i.e., variations of +/− 2 days, around their self-reported cycle length. All other participants were assigned to the regular menstrual cycle group.

Measures

Sociodemographic and Health-Related Information

Sociodemographic for sample description (biological sex, age, relationship status, occupation) and health-related information for determining inclusion (chronic diseases, medication, hormonal contraception, menopausal status, psychological disorders, specifically psychotic, bipolar, substance-related, and eating disorders) were assessed by self-developed items in the cross-sectional questionnaire.

Cross-Sectional Study: Assessment of Depressive Symptoms

Patient Health Questionnaire-8 (PHQ-8). To assess symptoms of depressive disorders, the eight-item version of the PHQ-9 (PHQ-8) was used [28, 29]. This version excludes the item for suicidal ideation [30, 31]. Each item assesses one symptom of a major depressive episode (MDE) on a 4-point Likert-Scale (0 = not at all, 3 = nearly every day). As a marker for overall depressive symptoms, a sum score ranging from 0 to 24 is calculated.

Longitudinal Study: Assessment of Depressive Symptoms and Stress

Structured Clinical Interview for DSM-5 Disorders (SCID-5 CV, German Version). The SCID-CV [32] was used to determine current affective disorders and to confirm absence of exclusion criteria. The following modules were administered by professionally trained, certified researchers: affective episodes (Module A), psychotic and associated symptoms (Module B), substance-related disorders (Module E), and screening questions for eating disorders (from Module I). Reliability of the SCID-5 CV is ≥0.70 but may vary depending on study design, interviewer training and sample population [32].

IDAS-Based Symptom Measure of Depression (IDAS-b; Modified Version). This scale aims to represent individual symptoms of depressive disorders as latent variables. Items were in part translated and adapted from the Inventory of Depression and Anxiety Symptoms [33–35] and complemented by additional items. Participants rated how often they experienced described emotions or behaviors on that day, using a rating scale from not at all (0) to extreme (4). Depressive symptom severity was estimated by the mean of all responses, ranging from 0 to 4. Validation of the scale is in progress.

Weekly Hassles Scale (WHS). The WHS [36] consists of 30 items that list stressors. They are rated once regarding their occurrence in the last week (yes/no) and, if they occurred, rated for severity of perceived stress on a five-point Likert scale. Sum scores are calculated for frequency of occurred stressors (WHS_{occur}) and experienced intensity of the occurred stressors (WHS_{intens}).

Statistical Analysis

Statistical analyses were conducted with R (v.4.0.2).

Cross-Sectional Study

For the cross-sectional sample, a Welch *t* test for independent groups was conducted with overall menstrual cycle regularity as group variable and PHQ-8 score as dependent variable. Only complete datasets were included. To account for group differences in age and differing sample sizes, a subsequent covariate matching using optimal matching with one matching partner in each group was applied with the MatchIt package [37].

Longitudinal Study

For the longitudinal study, a covariance analysis (ANCOVA) was conducted with the IDAS-b sum score as the dependent variable and WHS_{occur} and menstrual cycle regularity as predictors. Depression and stress scores were averaged over T1 and T2 to be represented in a single score.

Missing data in the longitudinal analysis were estimated with the mice package [38] which applies an algorithm for multiple imputations. For further analyses, the estimated parameters and confidence intervals were pooled [39]. Twenty-seven of 77 records

Table 1. Demographic characteristics by group for both studies

Variable	Cross-sectional study						Longitudinal study					
	regular menstrual cycle (*N* = 311)			irregular menstrual cycle (*N* = 83)			regular menstrual cycle (*N* = 59)			Irregular menstrual cycle (*N* = 18)		
	M	SD	%	M	SD	%	M	SD	%	M	SD	%
Age	28.02	6.32		26.50	5.73		27.92	6.91		28.55	7.04	
Menstrual cycle length	28.49	1.59		29.27	2.12		28.31	1.22		28.44	0.92	
PHQ score	10.23	5.32		11.81	5.31		9.39	5.96		13.3	5.73	
Permanent relationship[ab]			54.66			56.63			54.24			72.22
Children[ac]									10.2			22.1
Student[a]			58.71			62.65			67.80			61.11
Chronic disease[a]			2.57			1.20			6.78			5.56

[a]The percentage indicates the proportion of participants to whom the status applies. [b]Dichotomous variable summarizing any current permanent partnership irrespective of legal status (e.g., marriage). [c]Percentage of participants with one or more children.

were incomplete (35.06%). For T1, eight surveys were unavailable because timepoints were missed (5 surveys) or retrospectively excluded because they did not fall in the mid-follicular phase (3 surveys). For T2, 19 surveys were unavailable because timepoints were missed (8 surveys) or retrospectively excluded because they did not fall in the periovulatory phase (11 surveys).

Results

Sample Characteristics

Cross-Sectional Study

Three hundred ninety-four participants were included into the cross-sectional analysis. Of those, 83 (21.07%) reported an irregular menstrual cycle and were assigned to the irregular cycle group. Three hundred eleven participants were assigned to the regular cycle group. The two groups were mostly comparable but differed significantly in age and menstrual cycle length (age: t (140.05) = 2.11, p = 0.04; cycle length: t (140.61) = −3.09, p = 0.003). Table 1 summarizes further group characteristics.

Longitudinal Study

Seventy-seven participants were included into the longitudinal analysis. Eighty participants started the study, but two dropped out because their menstrual cycle did not start within 7 weeks after their previous menses and one dropped out due to unknown reasons. Of the remaining 77 participants, 18 (23.38%) had an irregular menstrual cycle and 59 (76.62%) a regular menstrual cycle. The two groups did not differ significantly in age nor any other examined sociodemographic characteristic, as measured by a t test (for continuous numeric variables) or χ^2 test (for categorical variables). The mean PHQ score at enrollment was significantly higher in the irregular group (p = 0.018). Table 1 summarizes further sample characteristics.

Results of the Cross-Sectional Study

In the irregular cycle group, the mean depression score (PHQ-8) (M = 11.81, SD = 5.31) was significantly higher (t [130.33] = −2.57, p = 0.006) than in the regular cycle group (M = 10.23, SD = 5.32). The effect size estimate was small (d = −0.32, 95% CI [−∞; −0.11]). Because the groups differed significantly in age, a matching procedure was applied, which showed similar results (t [164.0] = −1.91, p = 0.029, d = −0.30, 95% CI [−∞; −0.05]). The comparison is visualized in Figure 1.

Results of the Longitudinal Study

An ANCOVA was fitted as a linear model with menstrual cycle irregularity as categorical predictor and stress occurrence as continuous predictor. In the imputed-data analysis (n = 77), the pooled model estimate for the unstandardized regression weight of menstrual cycle irregularity was significantly different from zero (b = 0.30, t [65.04] = 2.04, p = 0.045), indicating that, irrespective of stress occurrence, depressive symptoms were higher in women with menstrual cycle irregularities. In the complete-case analysis (n = 52), the unstandardized regression weight for menstrual cycle irregularity was estimated at b = 0.38 (t [49] = 1.83, p = 0.07, $\eta 2p$ = 0.06). The direction of effect was equivalent to the estimation based on the imputed data set but did not reach statistical

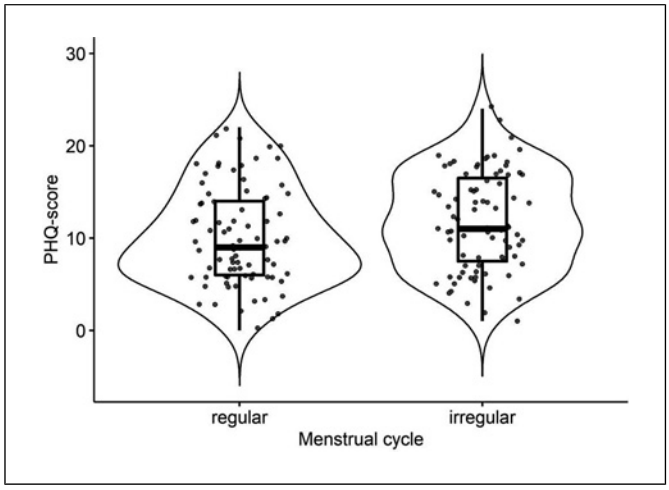

Fig. 1. Violin plots of depression scores (PHQ-8) by group (regular menstrual cycle vs. irregular menstrual cycle) in age-matched samples (N = 166). The plot depicts a standard box-plot, the observed data and the kernel probability density of the data at different values [47].

significance, presumably due to the smaller sample and the loss of statistical power. Figure 2 visualizes the values of the model for complete cases.

Discussion

Summary of Results

Evidence from a cross-sectional and longitudinal study consistently showed that women with an irregular menstrual cycle reported significantly higher depressive symptom severity than regularly cycling women. We further showed that the association between cycle irregularities and depressive symptoms was also present when controlling for relevant influencing factors, specifically stress occurrence (by including it as covariate), age (through matching), shift work and jet lag (by excluding affected participants).

Interpretation of Results

The observed higher depressive symptom severity in irregular cycles complements findings from Nillni et al. [18] and Yu et al. [19], who predicted menstrual cycle regularity from depressive symptom severity. In previous studies on depression-related conditions, such as premenstrual dysphoric disorder (PMDD), hormone fluctuation has been shown to influence affective symptoms in some hormone-sensitive individuals [40]. Our results suggest that, beyond the regular fluctuation of sex hormones, the deviation from regular, predictable cycles could be a relevant factor in the development of depressive symptoms. Of note, other factors such as low or vigorous physical activity [1, 2], smoking [3], higher BMI or and increased age at menarche [2] are associated with higher menstrual cycle irregularity.

Furthermore, our study results give more insights into the accuracy of self-reported cycle lengths. Previous studies have investigated the accuracy of self-reported length and irregularity with mixed results [10, 41, 42]. In the current sample, a substantial number of participants (22.5%) had irregular cycles by our definition, after self-reporting to have a regular one. Our results show that depressive symptoms are associated with cycle regularity and therefore might be a factor influencing differences between self-report and actually observed menstrual cycles. This is highly relevant when planning studies with cycling participants.

Strengths and Limitations

The major strength of these studies is the interlocking of two methodological approaches that ideally complement each other: The results from a large, cross-sectional study that relied on self-reported cycle irregularities were validated in a longitudinal study with a smaller sample but objective methodology for cycle assessment. We applied prospective assessments to associate cycle irregularities with depressive symptoms, and further considered stress, which has been identified as an important correlate of both, cycle irregularities and depressive symptoms [15–17]. Further, as depressive symptoms were assessed across the follicular and ovulatory phase, potential cycle phase effects on depressive symptom severity were controlled for.

A limitation of our longitudinal study is the suboptimal statistical power (25.33% for the estimated effect of f = 0.21), which is due to the fact that our a-priori power analysis was not based on this secondary analysis. Further, to investigate menstrual cycle irregularities even more precisely, two or more consecutive cycles as well as daily hormone measurements would be an excellent addition for future studies on the topic.

It has to be noted that both study periods were affected by the COVID-19 pandemic. Preliminary evidence indicates that the pandemic impacted menstrual cycle characteristics [43, 44]. Although we were not able to eliminate this problem, we tackled it by asking women to report any pandemic-related stressors they experienced. Including pandemic-related stressors did not change the results of the analyses (see online suppl. Material B). We controlled for important aspects of cycle irregularity that

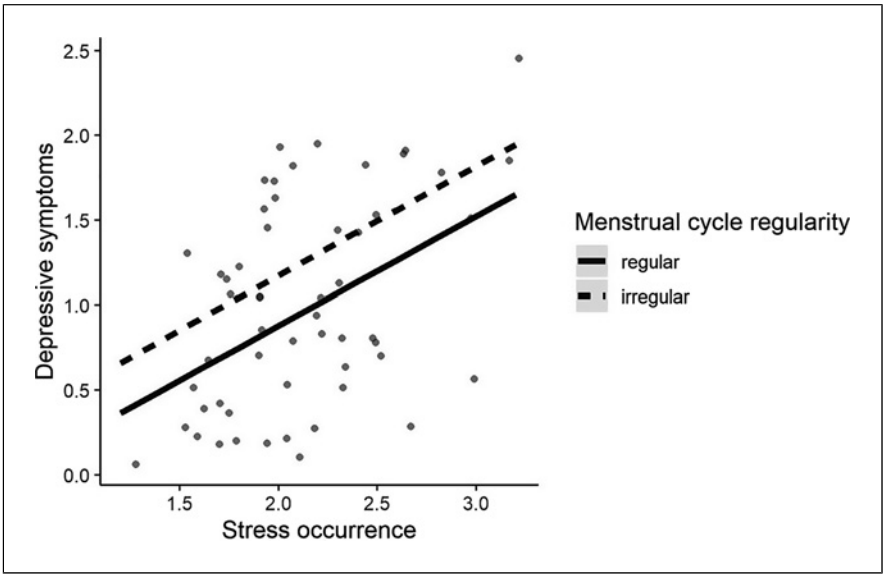

Fig. 2. Group difference of depressive symptoms (IDAS-b) between participants with a current regular or irregular menstrual cycle after adjusting for stress occurrence (Weekly Hassles Scale). *x* axis is number of reported stressful events, *y* axis is mean of all items of the IDAS-b, ranging from 0 ("not at all") to 4 ("extreme").

can influence cycle irregularity by either accounting for these factors in the analyses, e.g., stressful life events, or through exclusion criteria, e.g., shift work or substance abuse. However, some other factors that can contribute to menstrual cycle irregularity were not assessed or controlled for, e.g., physical activity or smoking status. Furthermore, as this was a remote study in which participants did not come into the laboratory and therefore a medical examination of the discussed exclusion criteria was not possible and they relied on self-report. Acknowledging these limitations and also the strengths of our two studies, their results provide evidence for an association between cycle irregularities and depressive symptoms and lay a foundation for future studies on the topic.

Implications for Future Research

Notably, our results demonstrated that 22.5% of women who reported to have a regular menstrual cycle did not fulfill this criterion in the longitudinal study. This is highly relevant for future studies that depend on predictable lengths of hormonal patterns within the menstrual cycle. Oftentimes, psychoneuroendocrinological studies investigate depressive symptoms related to the menstrual cycle, e.g., within premenstrual dysphoric disorder (PMDD). Thereby, it is important to account for menstrual cycle irregularities, which can be more common with higher depressive symptoms, as our results show. To enable a reliable study design and assessment planning, we suggest taking the following practical measures when conducting a study related to the menstrual cycle: the precise definition of menstrual cycle regularity, including a defined cycle range, is essential when aiming to include regularly cycling participants, as otherwise the term "regular" may be defined differently by different people. We suggest including a cycle range of at least 7 days to account for variability more common in participants with higher depressive symptoms. This follows the definition of cycle irregularity as determined in the Stages of Reproductive Aging Workshop [45]. A further step to determine regularity is to assess the start days of the last three menses (as suggested by Schmalenberger et al. [26]) and to inquire how often an irregular cycle appeared within the last year. All these measures aim to identify people with regular menstrual cycles. However, it is essential to be prepared for possible irregularities, e.g., through incorporating additional assessment days before and after the expected onset of menses when using daily measures.

In general, the aim should not be to exclude irregularly cycling participants from research, but instead to further investigate psychological and physiological influencing factors. Additionally, studies are warranted that investigate a broad range of cycle irregularity with larger sample sizes to be able to inspect irregularity intensity and depressiveness in a continuous approach. Other symptoms of mental disorders commonly co-occurring with depression, e.g., anxiety symptoms [46], are another promising topic for future research. The exact biological mechanisms of these interactions and a future investigation of the causational direction of the association between depression and menstrual cycle

regularity deserve attention in further studies. This is not only relevant to conduct precise and predictable studies but also for cycling individuals with depressive symptoms, interested in natural contraception, family planning, or individualized treatment options for their symptoms.

Conclusions

Female reproductive health is important for all women and thus, half of the world population. The menstrual cycle is an important indicator of female reproductive health. As our studies showed, its impact goes beyond physical health, but might influence women's mental health, too. Given that cycle irregularities have been associated with depressive symptom severity, irregular cycling women might have an elevated long-term risk to develop a depressive disorder. This needs to be elaborated in further studies. Further sex-sensitive mental health research holds the potential to transform women's mental and physical health care by developing and researching appropriate and specifically tailored prevention and treatment options.

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Statement of Ethics

This is a secondary analysis of a study on depression and stress in the menstrual cycle. It is preregistered on ClinicalTrials.gov (NCT04086316) and approved by the Institutional Review Board at the Department of Psychology and Educational Science at Freie Universität Berlin (ID: 003.2019). Written informed consent was given twice, once for the cross-sectional and once for the longitudinal study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Hannah Klusmann: conceptualization, project administration, funding acquisition, software, writing – original draft, writing – review and editing, and visualization. Claudia Kapp: conceptualization, methodology, software, formal analysis, writing – original draft; Sinha Engel: conceptualization, writing – original draft, writing – review and editing; Tabea Schumacher: writing – original draft and writing – review and editing; Elise Bücklein: software, writing – original draft, and writing – review and editing; Christine Knaevelsrud: supervision, funding acquisition, andwriting – review and editing; Sarah Schumacher: conceptualization, supervision, funding acquisition, writing – review and editing, and project administration.

Data Availability Statement

The data that support the findings of this study are not publicly available due to ethical and legal data protection requirements. Data contain information that could compromise the privacy of research participants. Further inquiries can be directed to the corresponding author.

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