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Negative affect is unrelated to fluctuations in hormone levels across the menstrual cycle: Evidence from a multisite observational study across two successive cycles

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ABSTRACT

Background: Female sex hormones may play a crucial role in the occurrence of cycle-related mood disorders. However, the literature is inconsistent and methodologically stringent observational studies on the relationship between sex hormones and negative affect are lacking.

Methods: In this longitudinal multisite study from Hannover, Germany, and Zurich, Switzerland, we examined oestrogen, progesterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone serum levels in association with negative affect as measured with the Positive and Negative Affect Schedule (PANAS). Negative affect and hormone assays were collected at four consecutive time points comprising menstrual, pre-ovulatory, mid-luteal and premenstrual phase across two cycles (n = 87 and n = 67 for the first and second cycles). The Beck Depression Inventory (BDI) was assessed once prior to the first cycle and included as a secondary measure.

Results: Mean negative affect scores did not significantly fluctuate across both cycles and there was in particular no symptom increase premenstrually. No sex hormone consistently related to repeated measures of negative affect across two consecutive cycles. The BDI sum-score assessed at baseline was not related to hormone levels across the first cycle.

Conclusions: This is the first multisite longitudinal study on the association between negative affect and sex hormone levels encompassing two consecutive menstrual cycles. Negative affect did not fluctuate across the cycle and there was no direct and uniform association between sex hormones and self-reported negative affect. These findings suggest that moderators such as personality traits and epigenetics should be considered in future research.

1. Introduction

A commonly purported belief is that fluctuations in sex hormones across the menstrual cycle contribute to women's emotion processing and experience of negative affect such as irritability, nervousness, anger, depression and anxiety [1–3]. Gender differences in psychopathology, characterised by an increased prevalence of externalising disorders in men and a higher prevalence of internalising disorders in women, originate simultaneously with hormonal changes during childhood/puberty [4]. However, the specific contribution of sex hormones to cycle-related negative affect is largely unknown [3,5]. Severe affective disorders related to the menstrual cycle that may require

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psychiatric treatment include premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) [5,6]. Both conditions relate by definition to specific menstrual stages, but, most importantly, no consistent pattern emerged with respect to their association with sex hormone levels and hormone fluctuations across the cycle.

1.1. Negative affect related to hormone levels

An increased individual sensitivity to cyclic variations in ovarian hormones has been discussed as a trigger for mood symptoms across the menstrual cycle, but the efficacy of treatments with combined oral contraceptives for PMS/PMDD is inconclusive and at best modest [7–9]; see review by Halbreich [10]. Conversely, mood symptoms disappear in natural or medically induced anovulatory cycles [3]. Though a few small-sample studies reported associations of either oestrogen or progesterone with cycle-related negative affect [11], most studies, including adequately powered analyses with $n > 50$ women, did largely fail to replicate such associations [12–16]; for comprehensive reviews, see [3,5]. In addition to the premenstrual rise of progesterone, the period of the transition to menopause has also been suggested to increase the risk for depression [17]. However, findings are largely inconsistent and inconclusive [18,19], which is in part attributable to methodological biases and inadequate statistical modelling [20]. Accordingly, the literature indicates no clear association between sex hormones and the onset of depression during the transition to menopause [19,21].

1.2. Negative affect related to cycle phases

There is a long history of empirical work focused on mood alterations in healthy reproductive women [15,22,23], but these studies produced inconsistent associations with cycle phases. For instance, it has been shown that some mood symptoms fluctuate across the cycle, but others do not [24,25]. Very recently, a longitudinal study by Kiesner and colleagues [26] suggested that null-associations between menstrual cycle and mood symptoms in healthy women reported in earlier studies (e.g. [15]) could be due to inadequate statistical modelling of within-subject effects. Though the authors found modest variability in within-subject variance, they also reported significantly increased negative affect around menstruation [26]. Another longitudinal study likewise reported slight worsening of mood symptoms premenstrually in healthy women, but these changes were statistically not significant. There was neither an association between mood scores and length of the luteal phase [16]. Because both Harvey et al. [16] and Kiesner et al. [26] aggregated within-subject data from several cycles, here we will focus on two consecutive cycles separately, as fluctuations in negative affect could be variable.

1.3. Methodological issues

Most work aimed at associations between negative affect and sex hormones used dichotomous mood disorder categories. However, negative affect is a dimensional construct and even treatment-relevant disorders such as PMS and PMDD are simply extreme manifestations along this continuum [3]. Because mental disorders and most somatic diseases are dimensional traits rather than discrete taxa by nature [27,28], limiting research to dichotomous disorders with arbitrary diagnostic boundaries severely compromises the yield of psychopathological research and may even undermine the validity of research findings [29–31]. Therefore, in accordance with newly developed dimensional approaches to psychopathology [32,33], it is necessary to study dimensional behavioural phenotypes that cut through arbitrary diagnostic categories [27,29]. In addition, most previous studies relied on small samples of $n < 50$ women. Though it is well established that small-sample studies increase the rate of false-negative findings (i.e. β-errors), it is less known that these underpowered studies also produce inflated effect sizes and false-positive results (i.e. α-errors) [34]. That is, the smaller the sample size, the higher the probability that study results are flawed [34,35]. Observational studies with larger samples are therefore required to provide unbiased findings on associations between menstrual cycle phases, sex hormones, and negative affect.

1.4. The present study

Because exploratory studies are particularly prone to false positives [36], we applied a stringent design that minimises the probability of false-positive findings. Firstly, we propose that statistical modelling should not merely rely on overall associations between negative affect and hormone levels across the cycle, but also specifically consider inter-individual differences in intra-individual change across the cycle [26]. Secondly, significant associations found across a first index cycle should be replicated using data from a second menstrual cycle. And thirdly, associations that replicated across both cycles should not only meet statistical significance, but also demonstrate practical significance, that is, an effect size that is sufficiently large to have implications for clinical practice [37,38]. Because this was an exploratory study at the outset we did not specify hypotheses prior to data analysis. However, data from the second cycle will be used to confirm possible associations explored in the first cycle. To the best of our knowledge, such a rigorous testing involving direct replication has not yet been applied to observational studies focusing on associations between negative affect and hormones. Specifically, we are not aware of any study that linked progesterone, oestrogen, LH, FSH and testosterone to negative affect at four consecutive measurements across two menstrual cycles.

2. Methods

2.1. Procedure and participants

The study was designed as a prospective observational study investigating serial measurements of hormonal and neurocognitive parameters in healthy women and women with endocrine disorders aged 18–40 years in up to two menstrual cycles. During a baseline visit women were interviewed to verify inclusion and exclusion criteria and a physical examination was performed to exclude medical conditions which might influence hormone levels or cognitive performance except for endometriosis, PCOS or hyperprolactinemia. Women were excluded if they were using oral contraceptives, had been pregnant or breastfeeding within the past six months, were using medication or had surgery which might interfere with endocrine parameters, had severe psychiatric or general somatic diseases (such as schizophrenia or cancer), worked irregular shifts, had menstrual or ovulation disorders except those investigated in the study (endometriosis, PCOS and hyperprolactinemia) and if they showed any additional abnormality in hormonal parameters (LH, FSH, estradiol, progesterone, testosterone, prolactin, fasting glucose, fasting insulin, and thyroid stimulating hormone) taken at cycle days 2–5 following the baseline examinations. Current and lifetime somatic and mental disorders were carefully evaluated at baseline examination within an anamnestic clinical interview based on ICD-10 criteria. Specifically, no women met diagnostic criteria for PMS/PMDD, although it is worth noting that some women reported subthreshold premenstrual complaints. Participants who were included in the study were then assessed four times across the menstrual cycle for two consecutive cycles. All hormone assays, questionnaires and other measures were taken at the same points in time (see Fig. 1). For every completed cycle, participants received 600 Swiss Francs (at Zurich study site) or 500 Euros (at Hannover study site). This study followed the guidelines of the World Medical Association Declaration of Helsinki 1964, updated in October 2013, and was conducted after approval by the Swiss and the Hannover Ethics Committee for investigations involving human subjects. All participants provided written informed consent. Women were compensated for their expenditures associated