



Progesterone and women's anxiety across the menstrual cycle

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ABSTRACT

Animal models and a few human investigations suggest progesterone may be associated with anxiety. Progesterone naturally fluctuates across the menstrual cycle, offering an opportunity to understand how within-person increases in progesterone and average progesterone levels across the cycle correspond to women's anxiety. Across two longitudinal studies, we simultaneously modeled the between- and within-person associations between progesterone and anxiety using multilevel modeling. In Study 1, 100 Polish women provided saliva samples and reported their anxiety at three phases of the menstrual cycle: follicular, peri-ovulatory, and luteal. A significant between-person effect emerged, revealing that women with higher average progesterone levels across their cycles reported higher levels of anxiety than women with lower progesterone cycles. This effect held controlling for estradiol. In Study 2, 61 American women provided saliva samples and reported their attachment anxiety during laboratory sessions during the same three cycle phases. A significant between-person and within-person association emerged: women with higher average progesterone levels reported higher levels of attachment anxiety, and as women's progesterone levels increased across their cycles, so too did their attachment anxiety. These effects held controlling for cortisol. In sum, both studies provide support for a link between menstrual cycle progesterone levels and subjective anxiety.

1. Introduction

Women's bodies undergo an important set of physiological changes over the course of each menstrual cycle. After ovulation, the ovaries release the steroid hormone progesterone to prepare the uterus for a possible pregnancy. Beyond causing physical changes across the menstrual cycle, progesterone has also been linked to changes in psychological states that may be functional in preparing for possible pregnancy. For example, research on both animals and humans is beginning to uncover a relation between progesterone and anxiety (Wirth, 2011), an emotion that functions to keep organisms vigilant to signs of danger (see Marks and Nesse, 1994). The current investigation examined how cyclical increases in progesterone across the menstrual cycle, as well as between-person differences in average cyclical progesterone levels, correspond to women's anxiety. We prospectively measured anxiety and progesterone three times over the course of one menstrual cycle in two samples of women. In Study 2, we extended our examination to a specific facet of anxiety—attachment anxiety.

1.1. Progesterone and anxiety

Research suggests a complex and potentially cyclic relationship between progesterone, stress, and anxiety (see Wirth, 2011 for a review). In rodents, for example, progesterone and its metabolites (e.g., allopregnanalone) rise in response to stressors, such as foot shock and swim stress (Barbaccia et al., 1996; Purdy et al., 1991). Progesterone's conversion to allopregnanalone, in turn, decreases anxiety and behaviors reflecting stress (Reddy et al., 2005; Rhodes and Frye, 2001). When progesterone is administered directly, rodents exhibit fewer anxiety behaviors (Toufexis et al., 2004).

Most investigations of humans have uncovered a positive association between progesterone and anxiety (but see Le Mellédo et al., 2001). Many of these studies reveal that progesterone increases in response to stressors (Childs et al., 2010; Droogleever Fortuyn et al., 2004; Maner et al., 2010; Roca et al., 2003; Seidel et al., 2013; Wirth and Schultheiss, 2006). For example, Wirth and Schultheiss (2006) demonstrated that fear of social rejection increased progesterone levels.

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Some research also suggests that directly administering progesterone predicts increased anxiety (Klatzkin et al., 2006; Roca et al., 2003; Van Wingen et al., 2007). For example, Roca et al. (2003) demonstrated that direct administration of progesterone augmented women's hormonal stress response to a treadmill stressor, suggesting that absolute levels of progesterone can increase the intensity of the stress response. This positive association between progesterone and anxiety may have implications for how anxiety fluctuates across the menstrual cycle.

Progesterone concentrations naturally shift across the menstrual cycle, and this cyclical pattern offers a unique opportunity to explore how changes in progesterone correspond to changes in anxiety. Indeed, several investigations have provided evidence suggestive of a positive association between cyclical increases in progesterone and anxiety (Gonda et al., 2008; Nilni et al., 2012). In one study, for example, women prone to experience anxiety (compared to women less prone) exhibited a stronger cognitive panic response during their luteal phase, when progesterone levels are elevated, compared to their follicular phase, when progesterone levels are lower (Nilni et al., 2012). A similar pattern appears to emerge among nonclinical populations. In another study, women reported higher anxiety and interpersonal sensitivity in the luteal phase compared to the follicular phase of their cycle (Gonda et al., 2008). Although such findings are suggestive, they are limited by their comparisons between cycle phases, rather than directly estimating the association between circulating progesterone levels and anxiety.

Other research suggests a positive association between increases in progesterone across the cycle and anxiety using more socially relevant indicators (Conway et al., 2007; Derntl et al., 2013; Van Veen et al., 2009). For example, women diagnosed with generalized social anxiety disorder retrospectively reported that their social anxiety symptoms worsened over the course of the menstrual cycle, as progesterone levels typically increase (van Veen et al., 2009). In a non-clinical sample, women perceived fearful faces as particularly intense at times during their cycles when progesterone levels were heightened compared to when progesterone levels were lower (Conway et al., 2007). Relatedly, women's cyclical progesterone levels predicted their attention to social stimuli (Maner and Miller, 2014) and desire for social affiliation (Schultheiss et al., 2003). Taken together, these findings demonstrate that cyclical increases in progesterone correspond to heightened social sensitivity, which might reflect heightened levels of anxiety in social domains, such as interpersonal anxiety.

1.2. Current investigation

The current investigation tested whether within-person cyclical increases in progesterone were associated with anxiety by prospectively measuring women's progesterone and anxiety at three time points over the course of one menstrual cycle in two independent samples: community Polish women (Study 1) and American undergraduate women (Study 2). We examined these relations using both a measure of general anxiety (Study 1) and, given the studies finding an association between progesterone and social sensitivity, one specific, interpersonal form of anxiety: attachment anxiety (Study 2). Analyses also simultaneously estimated the between-person associations between average levels (across the cycle) of anxiety and progesterone.

Although previous research suggests a positive association between progesterone and anxiety, we are aware of no studies that have simultaneously examined the association between progesterone and anxiety both between women and within-women's menstrual cycles in nonclinical samples. Although progesterone rises over the course of each menstrual cycle, recent evidence suggests that average cyclical progesterone levels can vary from cycle to cycle within the same woman, suggesting both intra- and inter-cycle variation in progesterone (Eisenlohr-Moul and Owens, 2016; Jasienska et al., 2017; Jasienska and Jasienski, 2008). It is important then to understand how both sources of variance in progesterone –within cycle increases and average cycle

levels –are associated with anxiety. The current investigation therefore employed multilevel modeling to examine whether within-person changes in progesterone and between-person differences in average progesterone levels are associated with anxiety. To better isolate the independent effects of progesterone, we also controlled for estradiol, another steroid hormone that varies across the menstrual cycle (Study 1), and cortisol, which is often associated with anxiety (Study 2; Dickerson and Kemeny, 2004; Mantella et al., 2008).

2. Study 1

Study 1 relied on a sample of community Polish women to examine whether within-person cyclical variation in progesterone and between-person average progesterone levels were associated with self-reported anxiety. During three lab sessions, occurring at the follicular, peri-ovulatory, and luteal phases of their menstrual cycles, participants provided saliva samples that were assayed for progesterone and estradiol, and reported their levels of anxiety. We controlled for women's estradiol levels because estradiol also varies across the menstrual cycle (Gilbert, 2000; Jasienska et al., 2017). Furthermore, some research indicates an association between estradiol and anxiety (e.g., Kajantie and Phillips, 2006), making it important to disentangle the association between progesterone and anxiety from any association with estradiol.

2.1. Method

2.1.1. Participants

Women were recruited through mailing lists, social media, and word of mouth in the Malopolska region of Poland. Women were eligible to participate if they had no history of diabetes, no diagnosed reproductive problems, regular menstrual cycles (consecutive cycles of similar length—within ± 5 days), and had not been pregnant, breastfed, or used hormonal contraception within three months prior to participation. We recruited participants and collected data for 12 months. Of the 110 participants recruited, 102 attended all planned meetings. Because we could not assess hormone levels from any of the three samples of two women (one for progesterone and one for estradiol), our final sample included 100 women. Of the 300 possible assessments (100 participants \times 3 assessments), we had corresponding assessments between progesterone and anxiety for 262 assessments and between progesterone, anxiety, and estradiol for 259 assessments. Participants were just under 30 years old on average ($M_{\text{age}} = 28.82$, $SD = 4.6$, age range: 18–37 years), all were Caucasian, and 71 (69.6%) were in long-term relationships (at least 6 months in length).

2.1.2. Procedure

Analyses focused on salivary progesterone and estradiol levels from the days women visited the lab, during which they also reported their level of anxiety (see below). These lab sessions were scheduled in the early follicular phase (between the 2nd and 8th day after menstrual onset), at peri-ovulatory phase [no later than 72 h after a luteinizing hormone (LH) surge or if the tests did not indicate an LH surge, on the 20th day of the cycle] and in mid-luteal phase (about one week after ovulation or participants' second session). To detect ovulation, participants were given LH ovulation kits, urine cups, and written instructions for conducting urine tests. LH typically surges one to two days prior to ovulation (Testart and Frydman, 1982) and luteinizing tests have been shown to be highly accurate in detecting ovulation (Guermendi et al., 2001). Women were asked to conduct LH tests from days 10–20 of their cycles or until a test indicated a positive result. Sixty-seven (65.7%) participants had a confirmed LH surge.

At each laboratory session, women completed a large survey packet presented in Polish. A section of the packet asked about their current mood. Particularly relevant to the investigation's primary hypothesis, one item asked women to indicate the extent to which they agreed with the statement “I feel anxious today” on a 7-point Likert scale

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