Biological Psychology 91 (2012) 376–382

Contents lists available at SciVerse ScienceDirect

Biological Psychology

journal homepage: www.elsevier.com/locate/biopsycho

Higher luteal progesterone is associated with low levels of premenstrual aggressive behavior and fatigue

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ARTICLE INFO

Article history:
Received 5 January 2012
Accepted 2 August 2012
Available online 10 August 2012

Keywords:
Progesterone
Mood symptoms
PMS
Luteal phase

ABSTRACT

Contradictory findings show both positive and negative effect of progesterone on the premenstrual mood changes in women. Here we present the study investigating this relationship on the large sample of premenstrual women. 122 healthy, reproductive age women collected daily morning saliva samples and recorded intensity scores for the mood symptoms: irritability, anger, sadness, tearfulness, insomnia, and fatigue. Saliva samples were assayed for progesterone concentrations and mood intensity scores were used to calculate behavioral indices. Women with low Aggression/Irritability and Fatigue had consistently higher progesterone levels during the luteal phase than women with high Aggression/Irritability and Fatigue. Additionally, Aggression/Irritability and Fatigue correlated negatively with maximal progesterone value during the luteal phase. Our results demonstrated a negative effect of low progesterone level on the premenstrual mood symptoms such as aggressive behavior and fatigue in healthy reproductive age women. This supports a previously proposed model of biphasic action of progesterone metabolites on mood.

1. Introduction

There is a common notion that certain mood symptoms in reproductive age women depend on the phase of the menstrual cycle. In particular, such psychological symptoms as irritability, anger, mild depression, tearfulness, anxiety, fatigue and insomnia are suggested to be more pronounced in the end of menstrual cycle. These negative changes in behavior are widely studied and, in the clinical literature, defined as premenstrual syndrome (PMS) (American College of Obstetricians and Gynecologists, 2000; Campagne and Campagne, 2007; Halbreich et al., 2007; Perez-Lopez et al., 2009). Their most severe form is defined as premenstrual dysphoric disorder (American Psychiatric Association, 1994). Prevalence of the PMS in reproductive age women varies from 75 to 80%, if diagnosed based on a single symptom, through 10–15% when medical assistance is required, to 2–8% when social activity is severely disturbed (Perez-Lopez et al., 2009). This pattern of occurrence is universal for the most of studied populations worldwide (Reiber, 2008).

Despite many studies and years of research there is still no agreement about the relationship between levels of reproductive steroid hormones and premenstrual syndrome. Although the temporal relationship between peak luteal progesterone and occurrence of mood changes is obvious (Bäckström et al., 2003), results of clinical case–control studies are inconsistent. Many studies reported no significant differences in levels of estradiol and progesterone between women who are affected by premenstrual syndrome and those who are not (review in Bäckström et al., 2003; Andreen et al., 2009; Rapkin et al., 2011). In other studies, PMS patients had either decreased (Dennerstein et al., 1984; Munday et al., 1981) or increased (Eriksson et al., 1992; Redei and Freeman, 1995) levels of progesterone. Corpus luteum formation was found to be necessary condition for premenstrual syndrome development, because in anovulatory cycles, when corpus luteum is not formed, women do not suffer from cyclical changes of mood (Hammarback and Bäckström, 1988; Hammarback et al., 1991 but see Adamopoulos et al., 1972).

Further, there is no agreement among studies when comes to the direction of the relationship between severity of negative mood changes and levels of progesterone in women diagnosed with PMS (Bäckström and Carstensen, 1974; Eriksson et al., 1992; Halbreich et al., 1986; Hammarback et al., 1989; Redei and Freeman, 1995; Wang et al., 1996). In several studies, increased levels of progesterone in the luteal phase were related to the increased intensity of premenstrual complaints (Eriksson et al., 1992; Halbreich et al.,

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http://dx.doi.org/10.1016/j.biopsycho.2012.08.001

1986; Hammarback et al., 1989; Redei and Freeman, 1995), while in other studies decreased progesterone levels were found to be related to more pronounced negative mood changes (Bäckström and Carstensen, 1974; Dennerstein et al., 1984; Munday et al., 1981). Further support for the effect of progesterone on mood comes from clinical trials showing that application of progesterone compared to placebo reduced frequency of premenstrual syndrome complaints in women clinically diagnosed with PMS (Rapkin et al., 1987; Dennerstein et al., 1985), although in several other studies the effect of progesterone was questioned (review in Wyatt et al., 2001).

Recently, Gailliot et al. (2010) proposed that premenstrual mood swings occur as the results of the impairment of the self-control caused by the insufficient energy resources during the luteal phase when the energy demands are increased due to intensive metabolic changes in the reproductive tracts. Here we propose that insufficient energy resources result in decreased progesterone levels and through that decreased levels of neuroactive progesterone metabolites such as allopregnanolone. Levels of these metabolites were found to influence mood and behavior in women (Andreen et al., 2009). They correlate positively with progesterone levels during menstrual cycle and were demonstrated to be lower in PMS patients in a case–control study (Rapkin et al., 1997). Andreen et al. (2009) proposed a model of biphasic action of progesterone metabolites on mood. According to this model low concentration of allopregnanolone via $GABA_A$ system increases negative mood changes such as irritability and aggression, whereas high concentration has calming effect on mood. Direct evidence supporting this model in reproductive age women are yet scarce.

The aim of our study was to investigate the relationship between levels of progesterone and the intensity of the psychological symptoms such as irritability, anger, sadness, tearfulness, insomnia, and fatigue during one menstrual cycle in the large sample of reproductive age women. In line with the model of biphasic effect on mood, we hypothesized that lower level of progesterone is related to the higher intensity of the studied negative psychological symptoms. Based on the daily mood ratings that women recorded during the entire menstrual cycle we created 4 indices representing the above mood symptoms. Aggression/Irritability (AI) was defined as the sum of the intensity of symptoms such as anger and irritability, and Depressive Behavior (DB) was defined as the sum of the intensity of symptoms such as sadness and tearfulness. Fatigue and insomnia represented the intensity of these symptoms during the menstrual cycle.

2. Material and methods

2.1. Study participants

186 healthy Polish women of reproductive age participated in the study investigating influence of life style factors on levels of ovarian steroid hormones during the entire menstrual cycle (Jasienska et al., 2006). The recruitment criteria for the study were: age between 24 and 37 years old, self-reported regular menstrual cycles not shorter than 25 and not longer than 35 days, no diagnosed fertility problems, and gynecological and endocrinological disorders, not taking hormonal oral contraceptives or other hormonal medications for the period of 6 months prior to the recruitment, and not being pregnant or lactating during the 6 months prior to the recruitment. Each woman was informed about the study aims and signed a written consent for participation. Study protocol was approved by the Jagiellonian University Bioethical Committee.

126 women returned Menstrual Cycle Mood Calendar documenting daily behavioral changes across the menstrual cycle. Three women were excluded from the analysis because we were unable to assess the ovulation day and thus follicular and luteal phase length. Additionally, we excluded one woman who reported unusually high intensity of mood symptoms (over two standard deviations in every mood symptom). The final size of the study group consisted of 122 women.

2.2. Mood changes assessment

Women collected the information about their mood symptoms for one entire menstrual cycle. Menstrual Cycle Mood Calendar was used to assess the occurrence and intensity of the mood symptoms around the menstrual cycle. The calendar was constructed based on the American College of Obstetricians and Gynecologists criteria for PMS diagnosis (ACOG, 2000). It consists of different types of symptoms such as: anger, irritability, depressed mood, tearfulness, fatigue and insomnia. Depressed mood, anger and irritability were defined for the participants by additional adjectives to ensure that women rated the intensity of the same or very similar mood. Depressed mood was thus described as feeling sad, depressed or hopeless, irritability as feeling annoyed and touchy, and anger as feeling aggressive and irascible. Daily scores for symptoms were recorded using four-grade scale. In this scale 0 represented not experiencing the symptom, 1 – experiencing mild symptom, 2 – experiencing moderate symptom, 3 – experiencing severe symptom.

Symptoms of anger and irritability, and depressed mood and tearfulness were grouped into two indices, because pairs of these moods represent the changing intensity of similar emotions. The intensity ratings of anger and irritability were used to calculate the Aggression/Irritability. This was done by summing up the intensity grades for symptoms from each day of the luteal phase of the cycle and calculating average intensity of symptoms for luteal phase and the entire cycle. Similarly, from symptoms of depressed mood and tearfulness the Depressive Behavior was calculated. Spearman–Brown split half coefficient for DB was 0.7 and for AI was 0.8. Average intensity of insomnia and fatigue were also calculated for the luteal phase and for the entire cycle.

2.3. Demographic and anthropometric data

A general questionnaire requesting information about place of birth, age, education, marital status, reproductive history, use of hormonal medication and tobacco consumption was distributed to the study participants. Height, weight and body fat percentage were measured by a trained anthropologist at the beginning of the study, randomly with respect to phase of the menstrual cycle. Body height was measured using standard methods. Body mass and body fat percentage was assessed using the TANITA scale (model TBF 551), with a measurement accuracy of 0.1 kg and 0.1% respectively.

2.4. Salivary sample collection and progesterone assay procedure

Women collected morning saliva samples at home, daily, for one entire menstrual cycle according to previously established collection protocols developed at the Reproductive Ecology Laboratory at Harvard University, USA (Lipson and Ellison, 1996).

Saliva samples from 14 days (reverse cycle day −1 to −14) of each cycle were analyzed for the concentration of progesterone (P) by radioimmunoassay. P measurements were made using an I-125 based radioimmunoassay kit (#3400, Diagnostic Systems Laboratories, Webster, TX, USA) with the following modifications: standards were prepared in assay buffer and run at six concentrations from 2 to 200 pg/ml. Samples were added in 100 μl amounts together with 100 μl of assay buffer. Antibody was diluted in the ratio of 1:4. Antibody and labeled steroid were added to each tube in 100 μl amounts to yield a total reaction volume of 400 μl per tube. After overnight incubation at 4 °C, 500 μl of second antibody was added to each reaction tube. Reaction tubes were subsequently centrifuged for 45 min; after aspiration of the supernatant, tubes were counted in a gamma counter for 2 min.

Based on the acquired values three progesterone indices were calculated: mean luteal progesterone (the average P level for day −1 to −14), mean midluteal progesterone (the average P level for day −5 to −9) and maximal daily luteal progesterone (the highest P concentration day between −1 to −14).

2.5. Statistical analysis

Spearman correlation was used to assess the relationship between average levels of progesterone and AI, DB, fatigue and insomnia during luteal phase and entire menstrual cycle due to skewed distribution of these indices. Progesterone levels during the luteal phase were log-transformed to ensure normality of the distribution. Further, based on the median value, women were assigned to the low intensity or high intensity group of particular mood indices. Differences between those groups in median mood indices and median number of children were tested by Mann–Whitney *U* test due to their nonparametric distribution. Differences in mean log-hormone levels, demographic data and anthropometrics were tested using Student's *t*-test and two-way ANOVA. One-way ANOVA with the cycle day as the categorical predictor was conducted to assess differences in mood symptoms intensity during the menstrual cycle. The same analysis was used to compare differences in summarized Aggression/Irritability scores in the consecutive quartiles of progesterone concentration. Significance of the differences between quartiles was tested using the least significant difference post hoc test. Repeated measure analysis of variance was used to test differences in salivary profiles in progesterone levels during the luteal phase between groups of women with high and low mood indices.