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

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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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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.

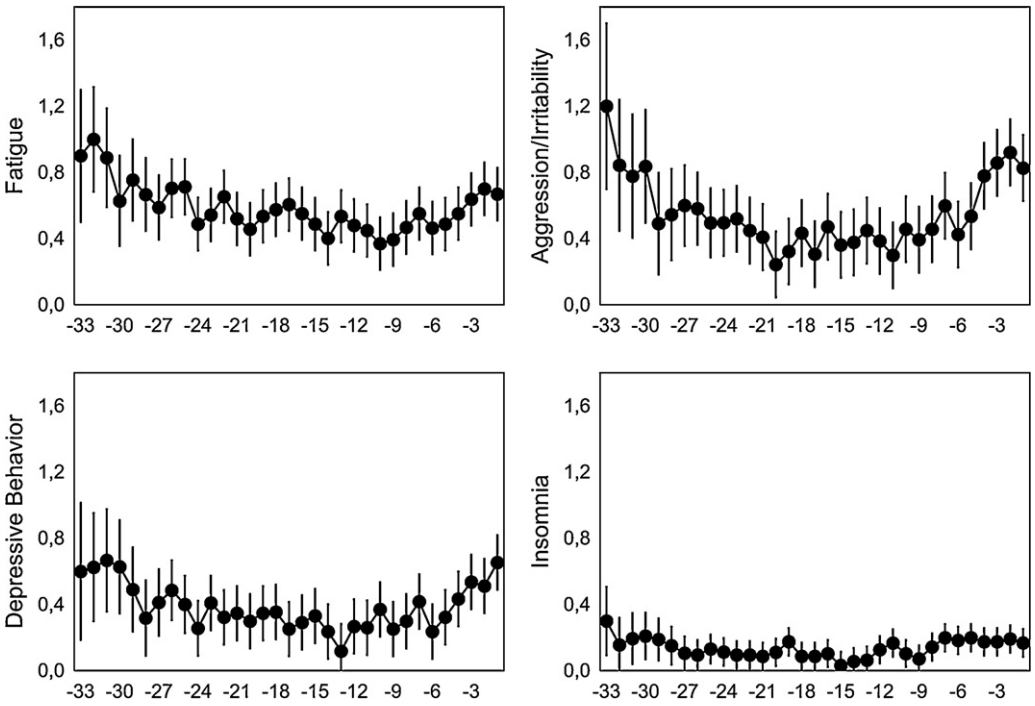

Fig. 1. Fatigue, Aggression/Irritability (AI), Depressive Behavior (DB) and Insomnia during the menstrual cycle. Reversed cycle day represents the day of the menstrual cycle calculated backward (day −1 represents the last day of the menstrual cycle). Values on *y*-axis represent average intensity ratings for the symptoms.

3. Results

3.1. Mood changes during the menstrual cycle

More than 80% of women reported negative mood symptoms during the luteal phase of menstrual cycle. Among them 75% had elevated AI, 61% elevated DB, 72% elevated fatigue and 40% elevated insomnia.

Women who reported mood symptoms occurring during the luteal phase did not differ from women who did not report such changes either in age, body height, body weight, BMI, body fat percentage, parity, education or in progesterone levels (Table 1).

Symptoms intensity distribution with respect to AI, DB, fatigue, and insomnia during the menstrual cycle is presented in Fig. 1. As revealed by the analysis of variance significant changes in the intensity of symptoms were present for AI ($F_{32,3568} = 2.88$, $p < 0.001$), fatigue ($F_{32,3568} = 1.50$, $p = 0.006$) and DB ($F_{32,3568} = 1.74$, $p = 0.003$). There were no differences in the average intensity ratings for insomnia ($F_{32,3600} = 1.23$, $p = 0.18$).

3.2. Aggression/Irritability and progesterone level during luteal phase

Table 2 presents descriptive characteristics for all women participating in the study and for groups of women differing with respect to their AI during the luteal phase. Low AI women had significantly higher level of progesterone when compared to high AI women (mean luteal progesterone 4.84 vs. 4.59, $t_{120} = 2.69$, $p = 0.008$, mean midluteal progesterone 5.08 vs. 4.82, $t_{120} = 2.47$, $p = 0.01$, maximal progesterone 5.51 vs. 5.22, $t_{120} = 2.81$, $p = 0.006$). Those two groups did not differ significantly with respect to mean age, parity, education and anthropometric characteristics (Table 2). In addition, repeated analysis of variance of salivary luteal progesterone profiles showed that women with low AI had consistently higher progesterone levels during the whole luteal phase of menstrual cycle ($F_{1,120} = 7.17$, $p = 0.008$) (Fig. 2).

Results of Spearman rank correlations confirmed relationships between AI and progesterone level in the luteal phase. Significant negative correlation was observed between the intensity of AI and the maximal daily luteal progesterone ($r_s = -0.21$, $p = 0.02$).

Table 1
Descriptive statistics and progesterone indices by total and divided by no mood vs. any mood changes. Standard deviations or quartile ranges in parenthesis.

	All women $N = 122$	Any mood changes $N = 110$	No mood changes $N = 12$	*p*
Age	29.6 (3.37)	29.7 (3.34)	28.3 (3.50)	0.16
Education (years spent at school)	15.3 (3.38)	15.4 (3.32)	14.4 (3.90)	0.36
Parity (yes)	47.6%	47.3%	52.8%	0.86
Number of children	0.0 (0.00–2.00)	0.0 (0.00–2.00)	0.5 (0.00–1.00)	0.41
Height (cm)	162.9 (6.53)	162.7 (6.42)	164.0 (7.90)	0.52
Weight (kg)	61.3 (10.70)	61.3 (10.77)	60.6 (9.91)	0.85
Body fat %	27.1 (7.45)	27.1 (7.45)	26.1 (7.71)	0.66
BMI (kg/m^2)	23.1 (3.87)	23.1 (3.97)	22.5 (2.73)	0.56
P luteal (ln)	4.71 (0.533)	4.71 (0.531)	4.75 (0.518)	0.79
P midluteal (ln)	4.95 (0.573)	4.95 (0.575)	4.98 (0.577)	0.87
P maximal (ln)	5.36 (0.592)	5.37 (0.593)	5.39 (0.591)	0.89

Table 2
Descriptive statistics, Aggression/Irritability and progesterone indices for women characterized by low and high AI during the luteal phase of the menstrual cycle. Standard deviations or quartile range in parenthesis.

	All women $N = 122$	Low luteal AI Below median $N = 61$	High luteal AI Above median $N = 61$	p
Age	29.6 (3.37)	29.3 (3.36)	29.9 (3.39)	0.37
Education (years spent at school)	15.3 (3.38)	15.4 (3.51)	15.3 (3.27)	0.87
Parity (yes)	47.6%	51.6%	43.5%	0.37
Number of children	0.0 (0.00–2.00)	0.5 (0.00–2.00)	0.0 (0.00–2.00)	0.69
Height (cm)	162.9 (6.53)	163.6 (6.34))	162.2 (6.71)	0.28
Weight (kg)	61.3 (10.70)	60.7 (8.81)	62.0 (12.36)	0.48
Body fat %	27.1 (7.45)	26.7 (7.20)	27.5 (7.74)	0.53
BMI (kg/m^2)	23.1 (3.87)	22.7 (3.23)	23.5 (4.42)	0.24
Aggression/Irritability	0.31 (0.00–0.80)	0.04 (0.00–0.15)	0.80 (0.50–1.15)	<0.001
P luteal (ln)	4.71 (0.533)	4.84 (0.451)	4.59 (0.572)	0.008
P midluteal (ln)	4.95 (0.573)	5.08 (0.467)	4.82 (0.642)	0.010
P maximal (ln)	5.36 (0.592)	5.51 (0.514)	5.22 (0.631)	0.006

Furthermore, differences in summarized AI scores for women from consecutive quartiles of maximal progesterone distribution showed a trend toward significance ($F_{3,118} = 1.68$, $p = 0.17$). Women from the first quartile of progesterone distribution had higher summarized AI scores when compared to women from third ($p = 0.06$) and fourth quartile ($p = 0.05$) (Fig. 3).

3.3. Fatigue and progesterone level during luteal phase

Table 3 presents descriptive statistics for the entire study sample and for the groups of women who differ with respect to intensity of reported fatigue during the luteal phase. Women reporting higher fatigue during the luteal phase had lower levels of luteal (4.62 vs. 4.81, $t_{120} = 2.01$, $p = 0.047$), midluteal (4.82 vs. 5.08, $t_{120} = 2.47$, $p = 0.015$) and maximal daily luteal progesterone (5.25 vs. 5.48, $t_{120} = 2.12$, $p = 0.036$) than women who did not report increased fatigue. They were also significantly older (30.5 vs. 28.7, $t_{120} = -3.17$, $p = 0.002$) and shorter (161.5 vs. 164.3, $t_{120} = 2.40$, $p = 0.018$). In contrast, there was no difference in education, parity, number of children, body weight and body fat between groups of women with low and high fatigue.

To adjust for potentially confounding effect of age and body height on the relationship between levels of luteal phase progesterone and fatigue we performed non-parametric Spearman correlation analysis. Result of this analysis showed a significant positive relationship between age and fatigue ($r_s = 0.26$, $p = 0.004$) and no correlation between body height and fatigue. Thus, participants' age was included as additional factor into further analysis.

After including participants age into the model of repeated measure ANOVA, women with higher fatigue during the luteal phase had lower salivary progesterone profile during this menstrual cycle phase ($F_{1,121} = 3.88$, $p = 0.05$) (Fig. 4). Age did not have significant effect in this model ($F_{1,121} = 0.02$, $p = 0.89$).

This relationship was further confirmed by results of Spearman rank correlation. Significant negative correlation was found between intensity of fatigue and levels of midluteal ($r_s = -0.19$, $p = 0.03$) and maximal daily luteal progesterone ($r_s = -0.19$, $p = 0.04$).

3.4. Other symptoms and progesterone level during luteal phase

Table 4 presents level of progesterone in groups of women characterized by low and high intensity of DB and insomnia. Groups did not differ significantly with respect to any of the luteal phase progesterone indices. We also did not find any statistically significant correlations between DB or insomnia intensity and any of the progesterone indices during the luteal phase of the menstrual cycle.

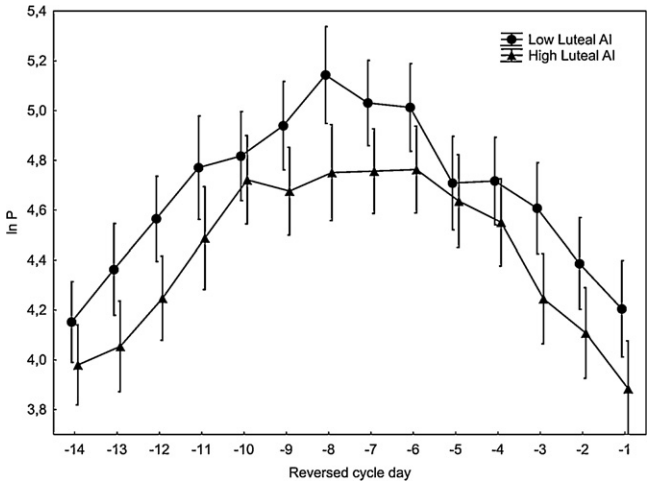

Fig. 2. Salivary luteal progesterone (daily means with 95% confidence interval) in menstrual cycle of groups of women differing in Aggression/Irritability (AI). Differences in progesterone profiles are significant at $p = 0.008$. Reversed cycle days represent last 14 days of the menstrual cycle.

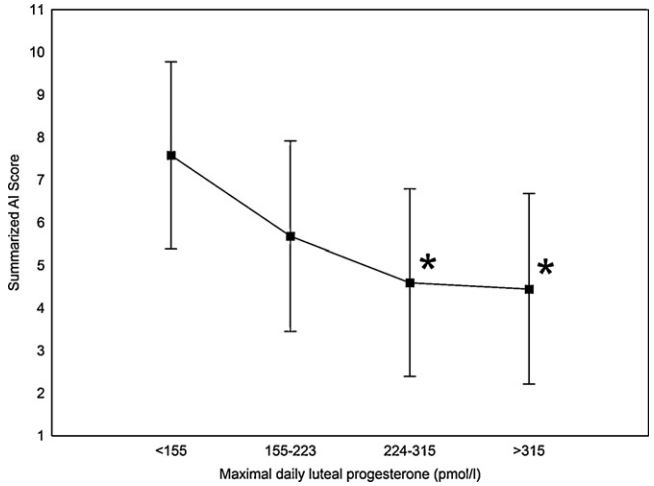

Fig. 3. Summarized Aggression/Irritability (AI) scores (means with 95% confidence interval) in women from consecutive quartiles of maximal daily luteal progesterone concentration. Asterisked differences in summarized scores between first and third and first and fourth quartile significant at $p = 0.05$.

Table 3
Descriptive statistics, fatigue and progesterone indices for groups of women characterized by low and high fatigue intensity during the luteal phase of the menstrual cycle. Standard deviations or quartile ranges in parenthesis.

	All women $N = 122$	Low luteal fatigue Below median $N = 61$	High luteal fatigue Above median $N = 61$	p
Age	29.6 (3.37)	28.7 (3.21)	30.5 (3.29)	0.002
Education (years spent at school)	15.3 (3.38)	15.6 (3.26)	15.1 (3.50)	0.48
Number of children	0.0 (0.00–1.00)	0.0 (0.00–1.00)	1.0 (0.00–2.00)	0.15
Parity (yes)	47.1%	44.8%	53.8%	0.32
Height (cm)	162.9 (6.53)	164.3 (6.50)	161.5 (6.32)	0.018
Weight (kg)	61.3 (10.70)	61.8 (10.72)	60.9 (10.74)	0.71
Body fat %	27.1 (7.45)	27.0 (7.84)	27.2 (7.13)	0.88
BMI (kg/m^2)	23.1 (3.87)	22.9 (3.84)	23.3 (3.92)	0.50
Fatigue	0.33 (0.00–0.79)	0.00 (0.00–0.14)	0.76 (0.50–1.21)	<0.001
P luteal (ln)	4.71 (0.533)	4.81 (0.503)	4.62 (0.540)	0.047
P midluteal (ln)	4.95 (0.573)	5.08 (0.539)	4.82 (0.583)	0.015
P maximal (ln)	5.36 (0.592)	5.48 (0.573)	5.25 (0.593)	0.036

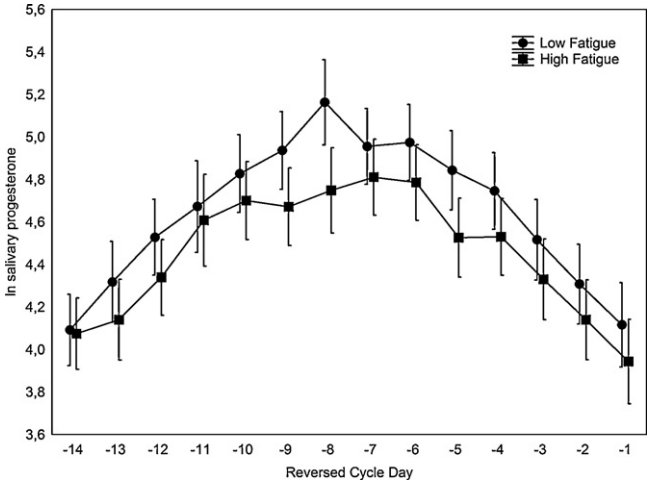

Fig. 4. Salivary luteal progesterone (daily means with 95% confidence interval) in menstrual cycle of women differing in Fatigue intensity. Differences in progesterone profiles significant at $p = 0.05$. Reversed cycle days represent last 14 days of the menstrual cycle.

4. Discussion

Results of our study support a relationship between progesterone levels and changes in woman's mood during the luteal phase of the menstrual cycle. To our knowledge, for the first time, based on the large sample of healthy, reproductive age women who were never clinically diagnosed with premenstrual syndrome, it was demonstrated that lower levels of progesterone in luteal phase of menstrual cycle coincide with the higher intensity of aggressive behavior and fatigue during this phase. We showed that women characterized by low premenstrual symptoms had about 20% higher level of mean luteal progesterone and about 25% higher level of maximal progesterone when compared to those with high premenstrual symptoms.

Our findings are supported by results of some previous studies. First of all, the prevalence of mood changes during the luteal phase of the menstrual cycle was similar to frequencies of mood changes reported by others (Campbell et al., 1997; Hylan et al., 1999; Johnson et al., 1988). In the study by Johnson et al. (1988) the overall lifetime prevalence of premenstrual syndromes was 87%, while in our study more than 80% women reported any mood changes during the luteal phase. Similar prevalence was also reported by Hylan et al. (1999) and Campbell et al. (1997). Hylan et al. (1999), reported the occurrence of particular mood symptoms in women from three countries (United States, United Kingdom and France) and results obtained in our study are in agreement with those reported. The occurrence of irritability/anger in their study ranged from 79% in UK to 81% in US (in our study 75%) and occurrence of depressed mood ranged from 51% in France to 70% in UK (in our study 61%).

The negative effect of low progesterone (or its metabolite allopregnanediol) on premenstrual mood symptoms found in our study was also demonstrated in previous works. Bäckström and Carstensen (1974) found decreased level of progesterone during the days preceding menstruation in women whose main symptom of premenstrual tension was anxiety. Similar results were found by Bäckström et al. (1976), Munday et al. (1981) and Dennerstein et al. (1984) where levels of progesterone or progesterone metabolite pregnanediol were lower in women reporting premenstrual tension then in controls. Additionally, in study by Wang et al. (1996) symptoms severity in PMS women were negatively related to some of the progesterone metabolites levels, but not to progesterone itself.

In contrast, studies by Redei and Freeman (1995), Hammarback et al. (1989), Halbreich et al. (1986) and Eriksson et al. (1992) found positive relationship between occurrence of negative mood changes and progesterone level, while others reported no significant relationships between levels of steroid hormones and mood changes (Adamopoulos et al., 1972; Rapkin et al., 2011; Rosenfeld et al., 2008). It should be noted that most of the studies reported in this research area are plagued by very low numbers of participants. For instance, study by Redei and Freeman (1995) was conducted on 10 PMS diagnosed women and 8 controls, study by Rosenfeld et al. (2008) on 9 PMS diagnosed women and 9 controls, and study by Rapkin et al. (2011) on 12 PMDD women and 12 controls. Thus, the estimated power of the statistical analysis for these studies

Table 4
Average values of progesterone indices in groups of women characterized by low and high intensity of Depressive Behavior (DB) and insomnia during luteal phase of the menstrual cycle.

	DB		p
	Low intensity $N = 61$	High intensity N = 61	
P luteal (ln)	4.72 (0.522)	4.71 (0.539)	0.93
P midluteal (ln)	4.95 (0.559)	4.95 (0.591)	0.95
P max (ln)	5.40 (0.606)	5.33 (0.580)	0.53
	Insomnia		p
	Low intensity $N = 74$	High intensity $N = 48$	
P luteal (ln)	4.77 (0.514)	4.63 (0.544)	0.16
P midluteal (ln)	5.00 (0.551)	4.89 (0.604)	0.25
P max (ln)	5.42 (0.584)	5.29 (0.597)	0.25

was rather low: for Redei and Freeman (1995) 0.5 (correlation between progesterone level and daily symptom report results) and for Rapkin et al. (2011) only 0.1 (comparison between mean progesterone in PMDD women and controls). In contrast, our analyses were conducted on a group of 122 women and the corresponding estimated power of analysis was 0.8. Additionally, in our study progesterone levels were measured in daily collected saliva sample. This methodology allows for a reliable, precise progesterone assessment that cannot be achieved by taking just a few samples during a cycle (Jasienska and Jasienski, 2008).

Due to correlational character of our study we are unable to infer about the cause–effect relationship between hormone levels and mood changes. However, our results support a hypothesis proposed by Andreen et al. (2009) about the biphasic effect of $GABA_A$ receptor modulators such as allopregnanolone on mood and behavior in humans. In accordance with this hypothesis we demonstrated that low concentration of progesterone during the luteal phase was associated with negative mood effects, while no such association was found for high concentration of progesterone in this cycle phase. In particular, we found that the average saliva concentration of luteal progesterone equal to 126.5 pmol/l and midluteal progesterone equal to 160.8 pmol/l were associated with the minimal intensity of mean negative mood changes during the luteal phase. It means that women with the concentrations of luteal and midluteal progesterone equal or higher than noted above experienced on average less than 3 days with only moderately increased intensity of aggression and irritability. Since progesterone concentration in fertile women are highly correlated with the concentration of progesterone metabolites during the menstrual cycle (Wang et al., 1996) our results constitute significant evidence for the biphasic effect of progesterone metabolites on mood in healthy, non-clinical subpopulation of reproductive age women.

Although promoting effect of allopregnanolone on GABA release seems to be the most plausible candidate for physiological mechanism underlying the association between progesterone and mood changes, it should be also noted that other progesterone derivatives have the opposite effect on GABA. For instance, pregnanolone sulfatase was demonstrated to inhibit GABA release (Zheng, 2009). In addition, progesterone, allopregnanolone, pregnanolone and pregnanolone sulfatase may influence mood by affecting levels of other brain neurotransmitters. For instance, allopregnanolone and pregnanolone sulfatase were demonstrated to influence dopamine release, and allopregnanolone and progesterone to inhibit serotonine release (Zheng, 2009). Furthermore, estradiol is important modulator of the progesterone effect on mood and was found to potentiate the negative effect of low progestine dose on mood in postmenopausal women (Björn et al., 2003). Thus future study should also investigate alternative physiological mechanisms explaining the association between mood and reproductive hormone levels.

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References

Adamopoulos, D.A., Loraine, J.A., Lunn, S.F., Coppen, A.J., Daly, R.J., 1972. Endocrine profiles in premenstrual tension. Clinical Endocrinology 1 (3), 283–292.

American College of Obstetricians and Gynecologists (ACOG), 2000. Premenstrual syndrome. ACOG practice bulletin no. 15 or International Journal of Gynecology & Obstetrics 95, 183–191.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th edition. American Psychiatric Association, Washington, DC, p. 715.

Andreen, L., Nyberg, S., Turkmen, S., Wingen, G., Fernández, G., Bäckström, T., 2009. Sex steroid induced negative mood may be explained by the paradoxical effect mediated by $GABA_A$ modulators. Psychoneuroendocrinology 34 (8), 1121–1132.

Bäckström, T., Andreen, L., Birzniece, V., Björn, I., Johansson, I.-M., Nordenstam-Haghjo, M., Nyberg, S., Sundström-Poromaa, I., Wahlström, G., Wang, M., 2003. The role of hormones and hormonal treatments in premenstrual syndrome. CNS Drugs 17 (5), 325–342.

Bäckström, T., Carstensen, H., 1974. Estrogen and progesterone in plasma in relation to premenstrual tension. Journal of Steroid Biochemistry 5 (3), 257–260.

Bäckström, T., Wide, L., Sodergaord, R., Carstensen, H., 1976. FSH, LH, TeBG-capacity, estrogen and progesterone in women with premenstrual tension during the luteal phase. Journal of Steroid Biochemistry 7 (6-7), 473–476.

Björn, I., Sundström-Poromaa, I., Bixo, M., Nyberg, S., Bäckström, G., Bäckström, T., 2003. Increase of estrogen dose deteriorates mood during progestin phase in sequential hormonal therapy. Journal of Clinical Endocrinology and Metabolism 88 (5), 2026–2030.

Campagne, D.M., Campagne, G., 2007. The premenstrual syndrome revisited. European Journal of Obstetrics, Gynecology, and Reproductive Biology 130 (1), 4–17.

Campbell, E.M., Peterkin, D., O'grady, K., Sanson-Fisher, R., 1997. Premenstrual symptoms in general practice patients: prevalence and treatment. Journal of Reproductive Medicine 42 (10), 637–646.

Dennerstein, L., Spencer-Gardner, C., Brown, J.B., Smith, M.A., Burrows, G.D., 1984. Premenstrual tension-hormonal profiles. Journal of Psychosomatic Obstetrics and Gynaecology 3 (1), 37–51.

Dennerstein, L., Spencer-Gardner, C., Gotts, G., Brown, J.B., Smith, M.A., Burrows, G.D., 1985. Progesterone and the premenstrual syndrome: a double blind crossover trial. British Medical Journal 290 (6482), 1617–1621.

Eriksson, E., Sundblad, Ch., Lisjö, P., Modigh, K., Björn, A., 1992. Serum levels of androgens are higher in women with premenstrual irritability and dysphoria than in controls. Psychoneuroendocrinology 17 (2-3), 195–204.

Gailliot, M.T., Hildebrandt, B., Eckel, L.A., Baumeister, R.F., 2010. A theory of limited metabolic energy and premenstrual syndrome symptoms: increased metabolic demands during the luteal phase divert metabolic resources from and impair self-control. Review of General Psychology 14 (3), 269–282.

Halbreich, U., Endicott, J., Goldstein, S., Nee, J., 1986. Premenstrual changes and changes in gonadal hormones. Acta Psychiatrica Scandinavica 74 (6), 576–586.

Halbreich, U., Bäckström, T., Eriksson, E., O'Brien, S., Calil, H., Ceskova, E., Dennerstein, L., Douki, S., Freeman, E., Genazzani, A., et al., 2007. Clinical diagnostic criteria for premenstrual syndrome and guidelines for their quantification for research studies. Gynecological Endocrinology 23 (3), 123–130.

Hammarback, S., Bäckström, T., 1988. Induced anovulation as treatment of premenstrual tension syndrome. A double-blind cross-over study with GnRH-agonist versus placebo. Acta Obstetricia et Gynecologica Scandinavica 67 (2), 159–166.

Hammarback, S., Damber, J.E., Bäckström, T., 1989. Relationship between symptom severity and hormone changes in women with premenstrual syndrome. Journal of Clinical Endocrinology and Metabolism 68 (1), 125–130.

Hammarback, S., Ekholm, U.B., Bäckström, T., 1991. Spontaneous anovulation causing disappearance of cyclical symptoms in women with the premenstrual syndrome. Acta Endocrinologica (Copenh) 125 (2), 132–137.

Hylan, T.R., Sundell, K., Judge, R., 1999. The impact of premenstrual symptomatology on functioning and treatment-seeking behavior: experience from the United States, United Kingdom, and France. Journal of Women's Health & Gender-Based Medicine 8 (8), 1043–1052.

Jasienska, G., Jasienski, M., 2008. Inter-population, inter-individual, inter-cycle, and intra-cycle natural variation in progesterone levels: a quantitative assessment and implications for population studies. American Journal of Human Biology 20 (1), 35–42.

Jasienska, G., Ziomkiewicz, A., Thune, I., Lipson, S.F., Ellison, P.T., 2006. Habitual physical activity and estradiol levels in women of reproductive age. European Journal of Cancer Prevention 15 (5), 439–445.

Johnson, S.R., McChesney, C., Bean, J.A., 1988. Epidemiology of premenstrual symptoms in a nonclinical sample. I. Prevalence, natural history and help-seeking behavior. Journal of Reproductive Medicine 33 (4), 340–346.

Lipson, S.F., Ellison, P.T., 1996. Comparison of salivary steroid profiles in naturally occurring conception and non-conception cycles. Human Reproduction 11 (10), 2090–2096.

Munday, M.R., Brush, M.G., Taylor, R.W., 1981. Correlations between progesterone, oestradiol and aldosterone levels in the premenstrual syndrome. Clinical Endocrinology 14 (1), 1–9.

Perez-Lopez, F.R., Chedraui, P., Perez-Roncero, Gonzalo, Lopez-Baena Maria, T., Cuadros-Lopez, J.L., 2009. Premenstrual syndrome and premenstrual dysphoric disorder: symptoms and cluster influences. Open Journal of Psychiatry 3 (1), 39–49.

Rapkin, A.J., Berman, S.M., Mandelkern, M.A., Silverman, D.H.S., Morgan, M., London, E.D., 2011. Neuroimaging evidence of cerebellar involvement in premenstrual dysphoric disorder. Biological Psychiatry 69 (4), 374–380.

Rapkin, A., Chang, L.H., Reading, A.E., 1987. Premenstrual syndrome: a double blind placebo controlled study of treatment with progesterone vaginal suppositories. Journal of Obstetrics and Gynaecology 7 (4), 217–220.

Rapkin, A.J., Morgan, M., Goldman, L., Brann, D.W., Simone, D., Mahesh, V.B., 1997. Progesterone metabolite allopregnanolone in women with premenstrual syndrome. Journal of Obstetrics and Gynaecology 90 (5), 709–714.

Redei, E., Freeman, E.W., 1995. Daily plasma estradiol and progesterone levels over the menstrual cycle and their relation to premenstrual symptoms. Psychoneuroendocrinology 20 (3), 259–267.

Reiber, C., 2008. An evolutionary model of premenstrual syndrome. Medical Hypotheses 70 (5), 1058–1065.

Rosenfeld, R., Livne, D., Nevo, O., Dayan, L., Milloul, V., Lavi, S., Jacob, G., 2008. Hormonal and volume dysregulation in women with premenstrual syndrome. Hypertension 51 (4), 1225–1230.

Wang, M., Seippel, L., Purdy, R.H., Bäckström, T., 1996. Relationship between symptom severity and steroid variation in women with premenstrual syndrome: study on serum pregnenolone, pregnenolone sulfate, 5 alpha-pregnane-3,20-dione and 3 alpha-hydroxy-5 alpha-pregnan-20-one. Journal of Clinical Endocrinology and Metabolism 81 (3), 1076–1082.

Wyatt, K., Dimmock, P., Jones, P., Obhrai, M., O'Brien, S., 2001. Efficacy of progesterone and progestogens in management of premenstrual syndrome: systematic review. British Medical Journal 323 (7316), 776.

Zheng, P., 2009. Neuroactive steroid regulation of neurotransmitter release in the CNS: action, mechanism and possible significance. Progress in Neurobiology 89 (2), 134–152.