The Relationship Between Hormonal Contraceptives, Level of Anxiety and Emotional Awareness: Pilot Project

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Summary

An important part of the side effects of combined oral contraceptives (COC) usage is its psychological impact, which includes mood changes, anxiousness and depression. The psychological impacts are expected to be caused by physiological fluctuations of sex hormone levels during the menstrual cycle; this cycling is, however, suppressed in COC users. In our study, we assessed the differences in emotional awareness and anxiousness between women long term users of anti-androgenic COC (AA) and women with no COC use in their medical history (C). We also searched for intraindividual differences by comparing the results of both groups for the follicular and luteal phase of their cycle. A total of 45 women aged 18 to 22 participated in this study. The respondents were given our battery of questionnaires at the beginning of their follicular phase – this battery included two State-Trait Anxiety Inventory questionnaires (STAI-I, STAI-II), as well as a Levels of Emotional Awareness Scale (LEAS) test. The respondents were given only STAI-I in their luteal phase. We also analyzed the hormonal profile of our respondents. Our results show a significant difference in the LEAS analysis, implying the possibility of altered emotional awareness in AA group. STAI-I and STAI-II analysis did not yield any significant results, showing that anxiety levels of COC users probably do not differ from the general female population. We therefore discovered lower emotional awareness in COC using women (AA).

Key words

LEAS • STAI • Combined oral contraceptives • Anxiety • Hormonal profile

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Introduction

The cyclical changes of hormonal levels caused by the ovarian cycle are vital for the physiological functions of the female reproductive tract. This aspect of female body physiology has been extensively studied and is considered well described and documented. As lipophilic steroid derivatives, estrogen (E) and progesterone (P) can cross the blood brain barrier freely. Both E and P are crucial for the development and function of the brain, and their lack after menopause plays a central role in the cognitive changes of postmenopausal women. This level of importance of both E and P is due to the abundant expression of their respective receptors in many of the brain's regions [1]. Most notably, progesterone receptors (PR) have been detected in the amygdala, hippocampus, the frontal cortex and, naturally, in the hypothalamus [1]. Among these regions, amygdala is responsible for emotional

processing, being an integral part in the process of emotional awareness; it also has one of the highest densities of estrogen receptors (ER) in the brain [2].

If looked at individually from the behavioral standpoint, E and P exhibit opposite effects on reaction to reward, disgust and reaction to negative stimuli [3,4]. However, their individual roles are exchanged in each situation as P increases reactivity to negative stimuli and disgust and decreases the reaction to reward; E exhibits the exactly opposite effects [3].

While taking combined oral contraceptives (COC), the concentration of all of the sex hormones is lower than it would be through most of the physiological menstrual cycle [5]. An important aspect of COC prescription is the level of androgenic activity of its gestagenic component, which can vary significantly. This adds another dimension to an already intricate endocrine-neurological interference of hormonal contraceptives.

Broadening the already complex hormonal interplay, cortisol should not be omitted. The effect of cortisol on emotional processing is time dependent, as cortisol exhibits rapid (non-genomic) and long-term (genomic) effect as well. As of the rapid effect, cortisol promotes the state of hypervigilance, enhancing the connectivity between amygdala and prefrontal cortex and increasing activity in the amygdala, increasing processing of fear and anxiety, heightening the emotional interference, reducing the focus and selected attention on the presented task with emotional distraction present. The long-term effect, on the other hand, decrease the emotional interference, promoting the top-down regulation, from the prefrontal cortex [6]. Cortisol levels are heavily context dependent although the HPA axis reactivity to psychological and physiological stressors in naturally cycling women varies across the menstrual cycle, increasing throughout the luteal phase [7]. The COC use blunts the luteal cortisol response, however elevated circulating cortisol levels has been recorded as well, suggesting a possible dysregulation in HPA axis. Elevated trait anxiety has not been shown to impact cortisol levels, yet the psychological stress response seems to be amplified [8].

Data regarding COC effect on mood varies, with some studies showing positive and other negative effects [9,10]. It is important to state, that the women without mood or affective side effects would be more likely to continue with the COC use, creating a “survival effect” [9,10].

Emotional awareness is a cognitive ability which allows us to differentiate and regulate emotions experienced as a part of allostasis [11]. Very low emotional awareness may manifest in terms of alexithymia, where patients cannot name and describe their emotions, while simultaneously attributing them to somatic experience. Structural basis of this ability lies in the corticolimbic connection, namely prefrontal cortex, insula, anterior cingulate complex, hippocampus, amygdala and hypothalamus [12]. Through hypothalamus, the hypothalamic-pituitary-adrenal axis (HPA axis) and autonomic system are included as well. Finally, just like other cognitive abilities, emotional awareness follows a developmental model, patterned after Piaget's cognitive developmental model, which is utilized in the performance test used in this study called Levels of Emotional Awareness Scale (LEAS) [12].

Another psychometric method utilized in this study is State-Trait Anxiety Inventory (STAI) questionnaire. STAI is a commonly used measure of trait and state anxiety developed in the early 1960s, and proves to be a useful diagnostic method for anxiety, as well as for the differentiation between anxiety and depressive disorders. STAI retained its clinical relevance thanks to multiple updates it received over the course of years [13].

The aim of this study was to measure and quantify the levels of emotional awareness, anxiousness as a long-term trait and anxiety in long-term COC users and compare it to naturally cycling women using psychometric methods. We chose methods which do not require a high level of psychological education, as they may present an easily available tool for ambulatory physicians considering prescribing COC.

Methods

Ethical approval and subjects

The study was approved by the Ethical committee of the Faculty of Medicine, Masaryk University Brno, Czech Republic. It was conducted in accordance with the principles stated in the Declaration of Helsinki. All respondents were informed about the aim and purposes of the study and they signed an informed consent that was archived.

This study included 45 women aged 18 to 22. The participants were divided into 2 groups: anti-androgenic COC group (AA, 22 women; age: 20.9 years old) and control group (C, 23 women; age: 20.8 years old). All COC users were using monophasic combined hormonal contraception (ethinylestradiol 0.03 mg,

dienogest/chlormadinone acetate 2 mg) for at least one year. None of the women in the C group had a medical history of COC usage. Both groups denied any use of psychotropic medication and/or drugs and stated no mental health diagnosis in the entry questionnaire. During the respondent recruitment, the women were kindly asked to use a reliable menstrual calendar app in their smartphones to allow us to precisely plan their visits to our laboratory. All respondents had two appointments with our team, during which they were given the questionnaires as a part of a complex evaluation of their health parameters. Both appointments were scheduled during the same menstrual cycle – the first appointment at the beginning of the follicular phase (2-4 days after the start of the cycle) and the second appointment during the luteal phase (usually 21st day of the cycle).

Psychometric tests

LEAS uses model situations, in which the person states how she/he would feel, while also stating how they think another person would feel in the same situation. In this research, participants were presented with a shortened version of LEAS containing 10 model situations (LEAS B). They were supposed to consider and write down their emotions in each of the situations (evaluated in category: LEAS self), as well as the emotions of another person mentioned in the situation (evaluated in category: LEAS other). This act of writing down the emotions depicts conscious awareness of them. Based on the highest score achieved in both categories, a third category is evaluated as well (LEAS together). Depending on the number and differentiation of emotions written, the person receives a score for herself, the other person, and for the situation as a whole [12]. Lower results in this test are associated with depression and psychosomatic diseases, post-traumatic stress disorder or addiction to various substances [13]. Higher results are on the other hand associated with anxiety and generalized anxiety disorder [12,13]. This method provides a more complex depiction of emotional recognition and processing, where not only the simple emotions, but complex blends of emotion, including the ability to differentiate the emotion that the other person would feel, are evaluated. LEAS B questionnaires were evaluated by 2 independent analysts. 10 random tests were then evaluated by 2 people independently to calculate the inner test reliability as Pearson correlation in all three categories.

The other psychometric test used in our research was the STAI questionnaire. We used the Form X of STAI (STAI X), which, although containing only 20 items, is suitable even for the differentiation of trait and state anxiety and not only for the estimation of general anxiety level. Its original form had 40 items, 20 of them related to trait anxiety (STAI II) and 20 to state anxiety (STAI I). Higher scores in STAI are associated with higher levels of anxiety.

During the follicular phase, LEAS, STAI II and STAI I (STAI I F) were conducted. During the luteal phase, STAI I (STAI I L) was conducted again.

Hormonal profile assessment

The respondents had their blood drawn during both of their scheduled sessions in our laboratory. The samples were handled according to common laboratory practice, centrifuged and the resulting aliquots were stored in a freezer in -80 °C. The levels of estradiol (E2), progesterone (P) and cortisol (GC) were analyzed using the ELISA method. Physiological ranges of hormones are provided by laboratory guidelines. This analysis was conducted in cooperation with the Department of Pharmacology & Department of Laboratory Methods of the Faculty of Medicine of Masaryk University and with the Department of Laboratory Methods of Masaryk Memorial Cancer Institute.

Statistical analysis

For our statistical analysis, we used the program Statistica 14.1. (StatSoft). Given the Gaussian distribution, we used the average and standard deviation as descriptive statistics. However, because of non-homogeneity of variance between groups, we used nonparametric statistic tests for comparison. First, we used the Mann-Whitney test to find differences in studied parameters between AA and C groups. Paired Wilcoxon test was used for comparison between luteal and follicular phases. Paired samples *t*-tests were used for the comparison between STAI for the assessment of the role of anxiety in the immediate psychological state (STAI I) and for the evaluation of long-term anxiousness as a personality trait (STAI II), as well as the LEAS questionnaire.

Results

The results of the psychometric tests used in this research are displayed in Table 1. Our analysis has yielded a statistically significant difference in the LEAS score between the group AA and the group C, showing lower scores of emotional awareness in the group of women using COC with anti-androgenic effect. More

specifically, the statistically different results occurred in the "Others" and "Together" categories.

Statistically significant differences in anxiety and anxiousness between the groups were not found within STAI II; neither was there a difference in STAI I between follicular and luteal phase within or between the groups. The results of STAI I and STAI II were analyzed according to the percentile tables [14]. STAI I F and STAI I L in AA were in 45 percentile. In C, STAI I F was in 35 percentile, and STAI I L was in 25 percentile. STAI II in AA was in 55 percentile and STAI II in C was in 30 percentile.

The results of the hormonal analysis between AA and C groups are shown in Table 2. In the follicular phase both groups were within the reference interval, without any statistically significant difference among them. As for the luteal phase, the mean AA group E2 was below the reference interval. The mean E2 levels in C group were within the reference interval, significantly higher than in the group AA. The results of E2 levels between the follicular phase and the luteal phase in groups are represented in the Figure 1. We found significant difference in E2 between the follicular phase and the luteal phase in both groups.

In the follicular phase the AA group had the mean P slightly out of the reference interval, while the mean C group concentration of P was on the lower limit of reference interval. In the luteal phase the mean C group level of P was within the reference interval while the AA group P level remained lower than the physiological range. The results of P levels between the follicular phase and the luteal phase in groups are shown in the Figure 2. We did not find significant difference in P between the follicular phase and the luteal phase in AA. In C the concentration of P was significantly higher in the luteal phase.

In the follicular phase, the mean C group GC level was on the lower end of the reference interval, while the mean AA group level was on the upper limit of the reference range. In the luteal phase, this difference became even more prominent, with the mean C group GC level being physiological and the AA group GC level being higher than the reference interval upper limit. The results of GC levels between the follicular phase and the luteal phase in groups are represented in the Figure 3. We did not find significant difference in GC between the follicular phase and the luteal phase in both groups.

Table 1. STAI and LEAS Results.

	STAI I F	**STAI I L**	**STAI II**	**LEAS**		
				Self	**Others**	**Together**
AA	39±7.2	39±11	47±10.8	31±4.6	30±4.2	35±4.8
C	37±6.8	35±6.8	43±10.8	32±3.8	33±3.5	39±3.8
p-level	NS	NS	NS	NS	p<0.05	p<0.05

Parameters are expressed as mean ± standard deviation. State-Trait Anxiety Inventory (STAI), STAI measures of state anxiety (STAI I), STAI measures of trait anxiety (STAI II), the follicular phase of cycle (F), the luteal phase of cycle (L), Levels of Emotional Awareness Scale (LEAS), women long term users of anti-androgenic contraception (AA), women with no contraception use in their medical history (C), non-significant difference (NS).

Table 2. Hormonal profile.

		E2 [pmol/l]	**P [nmol/l]**	**GC [nmol/l]**
Follicular phase	*Reference interval*	40-606	0.5-4.4	76-536
	AA	95.8±75.5	0.41±0.16	458.1±159.6
	C	136.5±41.9	0.55±0.2	222.5±95.4
	p-level	p<0.05	p<0.05	p<0.01
Luteal phase	*Reference interval*	121-718	14.1-89.1	76-536
	AA	19.8	0.4	565.2
	C	509.4	21.9	180.0
	p-level	p<0.01	p<0.01	p<0.01

Parameters are expressed as mean ± standard deviation. Estradiol (E2), progesterone (P), cortisol (GC), women long term users of anti-androgenic contraception (AA), women with no contraception use in their medical history (C), non-significant difference (NS).

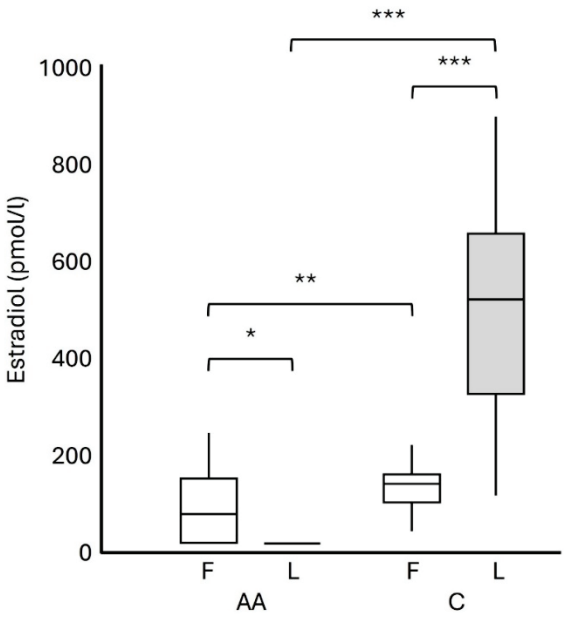

Fig. 1. Estradiol levels in the follicular phase and the luteal phase in AA and C groups. Boxplot: median-middle line; box range – lower and upper quartile; line-range of non-outliers. Follicular phase (F); Luteal phase (L); women long term users of anti-androgenic contraception (AA), women with no contraception use in their medical history (C); F vs. L: Wilcoxon paired test; AA vs. C: Mann-Whitney test; Statistical significance: * p<0.05; ** p<0.01, *** p<0.001.

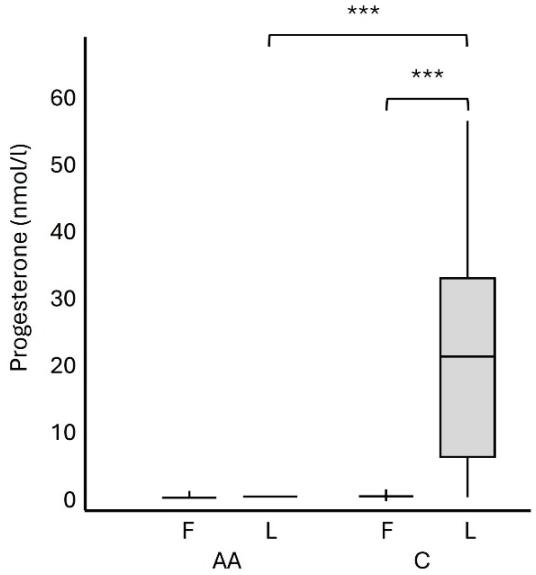

Fig. 2. Progesterone levels in the follicular phase and the luteal phase in AA and C groups. Boxplot: median-middle line; box range – lower and upper quartile; line-range of non-outliers. Follicular phase (F); Luteal phase (L); women long term users of anti-androgenic contraception (AA), women with no contraception use in their medical history (C); F vs. L: Wilcoxon paired test; AA vs. C: Mann-Whitney test; Statistical significance: * p<0.05; ** p<0.01, *** p<0.001.

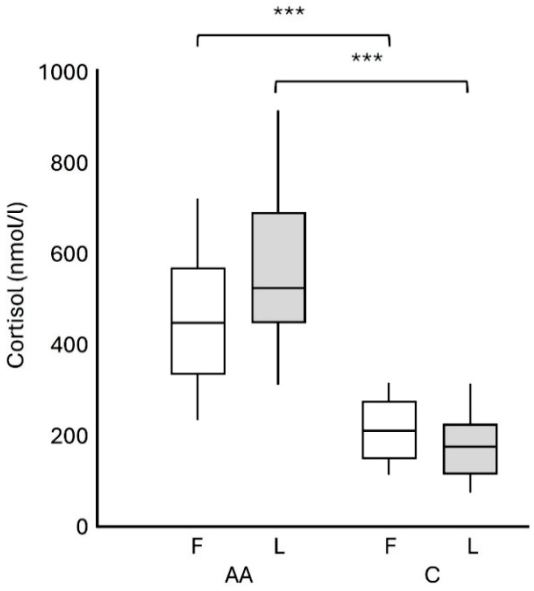

Fig. 3. Cortisol levels in the follicular phase and the luteal phase in AA and C groups. Boxplot: median-middle line; box range – lower and upper quartile; line-range of non-outliers. Follicular phase (F); Luteal phase (L); women long term users of anti-androgenic contraception (AA), women with no contraception use in their medical history (C); F vs. L: Wilcoxon paired test; AA vs. C: Mann-Whitney test; Statistical significance: * p<0.05; ** p<0.01, *** p<0.001.

Discussion

One of the mechanisms of COC action is negative feedback, when exogenous E and P suppress endogenous sex hormones production and induce anovulatory cycle. Our results show significantly lower E2 and P concentration in AA in comparison with C in the follicular phase. The difference between the mean groups in P and E2 levels caused by the COC, became more prominent in the luteal phase, as the corpus luteum was not formed in the AA group. The difference in E2 levels between the phases in the AA group was probably caused by earlier follicular phase progression, as the blood samples were taken 4 days after the beginning of menstruation, during which placebo pills are ingested. The similar difference in E2 concentration in COC users were found in several studies [15].

Emotional awareness combines identifying and labelling the whole spectrum of human emotions. Previous research has focused mainly on identifying emotions through facial emotion recognition test, yielding conflicting results. Radke and Dentrl and Kimming *et al*. did not find significant differences in emotion recognition, yet Hamstra *et al*. found impaired emotion recognition of negative emotions in COC using women with specific mineralocorticoid receptor haplotypes, implying the relevance of specific genomic profile [16-18]. However, these studies used facial emotion recognition tests incorporating only basic emotions. Pahnke *et al.* used more sensitive methodology and found significant differences in the recognition of complex emotions, suggesting that a more nuanced test would disclose the differences in emotion recognition [19]. Such nuance, combined with the aspect of cognitive processing through labelling is offered in LEAS.

Our results proved significant in the "others" category, where participants were not as able to attribute differentiated, complex and many times ambivalent emotions to other people in the presented scenarios. Therefore, presented results offer more complex image of emotional processing in respect to psycho – bio – social model as it reflects real – life situations in the context of the participant. Lower emotional awareness would project into more affective behavior, as it is essential for adaptive emotion regulation. The inability to accurately assess the emotions of different people hinders the quality of interpersonal exchange. In the following paragraphs, we shall explore the possible biological mechanisms by which the COC alters emotional awareness.

In the brain, the molecular effect of E and P is both genomic (long-term) and non-genomic (short-term). E affects the serotoninergic and P and his metabolites modulate the GABAergic system. Evidence suggests an interplay in their mechanism, as they may target structures inversely. Furthermore, synthetic sex hormones do not always suffice in all of the genomic and non-genomic mechanisms. To be more precise, long term COC use decreases the allopregnanolone (ALLO) concentration in the plasma and in the brain, while also altering the $GABA_A$ composition through a change in the γ2 subunit gene expression [20,21].

Long term use of COC influences almost all brain structures involved in emotional awareness. Based on the current literature, it seems like low doses of sex hormone derivatives in COC do not suffice in brain specific neurotrophic genomic effects of P and E. As their concentration is lower than in naturally cycling women, changes in the functional corticolimbic connectivity manifesting in diminished emotional awareness seems plausible. Furthermore, COC introduces its own specific genomic effect, such as the mentioned γ2 subunit gene expression [9,10,20].

Allopregnanolone is a potent anxiolytic agent with positive $GABA_A$ allosteric effect [22]. Its pharmacodynamics are similar to those of ethanol, barbiturates and benzodiazepines. While also peaking in luteal phase, its fluctuation is not proportionate to P plasma levels [23-25]. In respect to these fluctuations, $GABA_A$ receptor density fluctuates as well, *via* receptor up and down regulation [26]. Lower concentrations of ALLO may cause depression during pregnancy and its decrease after termination of pregnancy may lead to postpartum depression [26,27]. Suboptimal response of $GABA_A$ receptor density and $GABA_A$ hyposensitivity to ALLO fluctuation reflect anxiety, mood disruptions and irritation in women with premenstrual dysphoric disorder (PMDD). Another hypothesis postulates a paradoxical reaction to ALLO in women with PMDD, where ALLO is the direct cause of symptoms in a specific dose, proposing a U-shaped effect similar to that of P [28].

Estrogen component in COCs increases the production of corticosteroid-binding globulin (CBG), which raises total cortisol levels. This effect has been well-documented in several studies [29,30]. The elevated cortisol levels in the AA group could have also altered the emotional awareness. Remarkably, our analysis has not shown any correlation between cortisol levels and LEAS, even though cortisol plays a role in emotional

processing. It could be explained by a difference between total cortisol and free cortisol concentration. Studies show that while total cortisol may rise due to increased CBG, free cortisol may remain stable or even decrease in some cases.

Even though we can compare the effect of E and P based on measured psychometric differences between the phases of the menstrual cycle, another question would be the long-term effect of synthetic reproductive hormones as the agents of neural plasticity, especially in early adulthood, when the amygdalo-cortical projections sprout massively [31]. Human brain is nothing less than the opposite of a static system, undergoing continuous structural changes based on both internal and external conditions. This process of structural changes at the synaptic level is called neuroplasticity. Both endogenous and exogenous reproductive hormones act as mediators of such changes, including the hormones from COC [32]. Several neuroimaging studies have shown structural differences between naturally cycling and women using COC, showcasing (among other structures) reduced gray matter volume and activation in hypothalamus, yet another prominent structure in the context of emotional processing and emotional awareness [30,30,33,34]. Furthermore, COC decreases ALLO concentration in the brain, which resulted in change in social and sexual behavior in animal models, while also being suspected for affective side effects in women using COC [21]. This may be one of the many reasons why a considerate portion of COC users choose to discontinue further use of hormonal contraceptives, as they experience negative advert effects on their mood and emotions [35].

Based on the results, we can conclude that the AA group has lower emotional awareness, which could have been caused by several mechanisms. It could have been caused by both genomic and non-genomic effects of altered P and E or their synthetic counterparts included in COC. It could have been caused by a different neuroendocrine mechanism.

Conflict of Interest

There is no conflict of interest.

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