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Brief communication

The progesterone level, leukocyte count and disgust sensitivity across the menstrual cycle

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HIGHLIGHTS

- The hypothesis on protective role of disgust in mid-luteal phase was tested.
- The measurements were performed at the menstrual (M) & the mid-luteal (L) phase.
- Disgust sensitivity, WBC, and progesterone were higher in the L phase.
- At the L phase, disgust sensitivity correlated with progesterone but not with WBC.
- The rise in disgust sensitivity was independent of increases in progesterone and WBC.

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ABSTRACT

According to the compensatory prophylaxis hypothesis, women in the luteal phase, characterized by a high progesterone level, which suppresses various mechanisms of immune response, should exhibit higher disgust sensitivity, compared to the follicular phase. In this study we test the hypothesis on the compensatory role of disgust sensitivity at the luteal phase of the menstrual cycle, when immune functions are expected to change due to a rise in progesterone level.

Disgust sensitivity, progesterone level (P) and white blood cell count (WBC), a general marker of immunocompetence, were measured in 30 healthy women of reproductive age. Disgust sensitivity was evaluated with: 1) Disgust Scale Revised (DS-R) containing three subscales: Core Disgust, Animal Reminder and Contamination Disgust, 2) Pathogen Disgust and Moral Disgust domains of the Three-Domain Disgust Scale. Measurements were conducted twice - in menstruation (the lowest P) and in the mid-luteal phase (the highest P). The results were analyzed longitudinally and using cross-sectional comparisons.

Progesterone level, WBC count, and the level of disgust sensitivity in Animal Domain were higher in the mid-luteal phase comparing to menstruation. The level of disgust sensitivity (DS-R score, Animal, Contamination, Pathogen Disgust) correlated only with P (not WBC) and only in the mid-luteal phase (not in menstruation) in between-subjects comparisons.

On the base of these results, we hypothesize that the level of disgust sensitivity in the whole menstrual cycle of a woman is "adjusted" to the luteal phase with the highest P level i.e. when immunosuppression is the greatest.

1. Introduction

The emotion of disgust is considered as an adaptive mechanism which may serve as a first line of defense against infections by triggering behavioral avoidance of pathogens [1]. Since such prophylactic behavior involves some cost, the aversive reaction should be adjusted to the level of an individual's immunocompetence, and is expected to rise when immunological functions are lower and the risk of pathogen infection is higher.

Progesterone is a known immunosuppressant in humans [2,3]. Fessler [4] suggested that since both pregnancy and the luteal phase of the menstrual cycle are characterized by a rise of progesterone level, and thus possibly immunosuppression, one should observe higher disgust sensitivity in women in these periods of time, in order to compensate for changes in the immune effectiveness. This hypothesis was described as the compensatory prophylaxis hypothesis [5], and this effect seems to be confirmed in gestation [5,6]. Studies using a self-reported questionnaire - the Disgust Sensitivity scale [7] - showed that pregnant women exhibit the highest disgust sensitivity in the first trimester of gestation [5,6]. In comparison to the second and third

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trimesters, the first trimester is characterized by a heightened vulnerability to infection due to a suppression of immune functions, allowing semi-allogenic blastocyst to implant [5]. On the other hand, the results of the studies investigating changes in a disgust sensitivity across the menstrual cycle are less univocal. Fessler & Navarrete [8] failed to show differences in disgust sensitivity between women in the follicular phase and women in the luteal phase [8]. However, studies employing images, presenting disgusting stimuli in a visual way [1], showed a higher disgust sensitivity in women in the luteal phase in comparison to women in the follicular phase (Fleischman & Fessler, 2009, in: [9]), as well as a positive correlation between salivary progesterone level and disgust sensitivity [10].

Those studies ([8], Fleischman & Fessler, in: [9]), investigating the hypothesized adaptive fluctuations of disgust sensitivity within the menstrual cycle, were based on a cross-sectional design, estimating immunosuppression on the basis of self-reported phase of the menstrual cycle, which may not be accurate. Also the study showing the correlation between a woman's disgust sensitivity and progesterone level [10] suffers from the lack of inclusion of immunological parameters in the analyzes, which would allow to better understand the relationship between disgust sensitivity and immune functions. To date, the relationship between the level of disgust sensitivity and immunocompetence has been examined only using indirect measures of immune system efficacy, such as frequency and recency of infection or childhood health data [11,12].

The immunosuppressive impact of progesterone affects both innate and adaptive immune response, including, among the others, macrophage function [13], T cell proliferation [14], NK cell activity [15] and/or Th1 cytokine secretion inhibition [16,17]. Those changes in the T helper lymphocytes balance (Th1/Th2) are considered as one of the possible mechanisms responsible for the luteal phase immunomodulation [18]. T-helper type I (Th1) and t-helper type II (Th2) lymphocytes differ in function and cytokine profile secretion. Th1 enhances cell-mediated immunity (i.e. activates macrophages, cytotoxic lymphocytes, or the complement system), playing an important role in immune defense against intracellular pathogens. Th2 stimulates antibody production and is responsible for humoral (antibody-mediated) immunity. Attenuation of cell-mediated immunity (Th1), accompanied by the humoral immunity (Th2) enhancement, is observed both during pregnancy (preventing maternal immune system from rejection of semi-allogenic fetus) and in luteal phase of the menstrual cycle (characterized by similar to pregnancy hormonal profiles) [18]. Those intricate local changes in the levels of immune factors may also affect systemic immune response to an infection, inducing a state of increased susceptibility to certain bacterial, viral or yeast pathogens. For instance, there is some evidence that gestation increases vulnerability to *Mycobacterium leprae* [19], *Toxoplasma gondii* [20], or *Listeria monocytogenes* [21] infection. What is more, influenza infection exhibits more severe symptoms, involves more complications and higher mortality rate in pregnant women [22–25]. Also, a woman's susceptibility to various infections differs as a function of the phase of the menstrual cycle. For instance, the *Chlamydia* spp. detection is the highest in the luteal phase [26]. Cyclical fluctuations in progesterone level may also be related to the recurrent *Candida albicans* vaginal infections [27]. Also, exacerbation of the symptoms of cell or antibody-mediated autoimmune diseases varies during the menstrual cycle, e.g. systemic lupus erythematosus (antibody-mediated diseases) intensifies before menstruation [28]. Thus, it seems possible, that although the immune suppression in luteal phase of the menstrual cycle is not a simple suppression of all immune functions, but rather an adaptive immunomodulation, involving shifts between different types of immune response, still those changes may "require" an increase of a woman's disgust sensitivity in order to compensate for the possible attenuation of immune functioning.

One of the general and accurate indicators of an individual's immune functions is the total number of leukocytes in blood (white blood cells – WBC) [29,30], primary immune cells, involved in the immune defense of the body, protecting the host from an invasion by microorganisms [31]. Leukocytes are divided into five classes based on their characteristics: granulocytes (mainly neutrophils), lymphocytes, eosinophils, basophils, and monocytes [32]. Each subpopulation and the total WBC count reflect the body immune potential, and are common clinical markers of general immune homeostasis, health status and the level of systemic inflammation. Both WBC count and its subpopulations can be rapidly affected in response to various stimuli, such as foreign antigen, tissue damage, or probably by sex hormone-specific stimulation (in a manner depending on the concentration), therefore WBC level, reflecting general immune status, may be also associated with hormonal changes observed in pregnancy and in the menstrual cycle. Although the previous research showed that WBC count increases gradually during pregnancy [33] (which is mainly caused by an increase of granulocytes, whereas the lymphocytes count decrease), the results of the studies on the WBC fluctuations in the menstrual cycle are inconsistent. Some researchers showed that WBC is higher in the luteal phase compared to menstruation [34], the others found that luteal phase was characterized by the lowest WBC in the menstrual cycle [35], and some researchers observed no cyclical changes in WBC count [32]. Although those changes in the total WBC count are related to both progesterone (inhibiting lymphocyte proliferation and potentially causing lymphocytopenia [36,37]) and estradiol (promoting the release of neutrophils and monocytes from the bone marrow [38]) fluctuations within the menstrual cycle, the WBC may be a good measure of a woman's general immunity, a resultant of changes in various immunological mechanisms.

The aim of this study was to test the correlation of disgust sensitivity with both progesterone level (P) and WBC count – the direct measure of immunological potential. The previous studies on changes in the level of disgust sensitivity in the menstrual cycle were cross-sectional ([8], Fleischman & Fessler 2009, in: [10]). Such study design does not allow to control the between-subjects differences resulting from different life experiences, as a long-lasting exposure to disgust elicitors may reduce disgust sensitivity toward these stimuli [11]. Therefore, this study encompasses two measurement of a woman's disgust sensitivity during one menstrual cycle: in menstruation, when the progesterone level is the lowest and in the mid-luteal phase, when the progesterone level is the highest [39]. Such study design allowed for the detailed analysis of the relationship between the level of disgust sensitivity, progesterone and WBC, as well as to test the variation of disgust within the menstrual cycle.

The hypothesis of this study predicts that a woman's disgust sensitivity increases in the mid-luteal phase compared to menstruation, and it correlates positively with progesterone level and negatively with white blood cell count.

2. Material and methods

50 women participated in the study. The exclusion criteria were: non-detected ovulation, i.e. lack of the positive result of LH test ($N = 7$), incomplete questionnaire ($N = 2$), incorrectly answered control questions on Disgust Sensitivity - Revised scale ($N = 7$), reported infection ($N = 2$), or abnormal progesterone level, i.e. above the normal range in menstruation ($N = 1$) or below the normal range in the mid-luteal phase ($N = 1$). According to the test manufacturer, for the menstrual phase the normal range of P is 0.2–1.4 ng/ml, thus the participant with P level of 15.10 ng/ml was excluded. For the luteal phase the normal range is 4–25 ng/ml, thus the participant with P level of 0.3 ng/ml was also excluded. The odd P levels in excluded participants may indicate that these women miscalculated the day of cycle or they interpreted the results of the ovulation test incorrectly.

The final sample consisted of 30 regularly cycling women, aged 19.6–36.1 years (mean: 28.9; SD: 5.4). Participants gave a blood sample (for WBC and P measurement) and completed the questionnaire measuring the level of disgust sensitivity twice: first time in menstruation