

Letter to the Editor

Effects of Estrogen and Progesterone Fluctuations during the Menstrual Cycle on Cognitive Functions

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DEAR EDITOR

Studies conducted in the 1960s began to describe important changes in the behavior of women which were associated with the different phases of the menstrual cycle (for review, [1]). Across the lifespan of women, there are certain times in which vulnerability for the development of mood and other psychiatric disorders increases, such as during the premenstrual or peripartum period [2,3]. Thus, the late follicular and luteal/premenstrual phases have been associated with a higher frequency of depression, increased anxiety suicides, suicide attempts, and suicidal ideation, or with criminality, mood changes and accidents [1,4,5]. As described above, these two periods are correlated with extreme hormonal changes. For example, circulating estrogen and progesterone cross the blood-brain barrier [6], and affect brain function [7], in such a way that sex hormones directly influence the activity of the hippocampus and hypothalamus, brain areas implicated in the perception of sensory information, modulation of cognition and emotion, and in particular, interpretation of socially-relevant sensory cues [8,9].

The menstrual cycle is divided into three principal phases: follicular, ovulatory and luteal. The first day of menstruation is considered as the first day of the menstrual cycle and the beginning of the follicular phase, which occurs on day 14 and continues until ovulation, in healthy women with a typical 28-day cycle [10]. The follicular phase is the one that varies most in length, but tends to become shorter near menopause. This phase is followed by the ovulatory phase, which has a duration between 16 and 32 hours, during which ovulation occurs. During this time, some women feel pain on one side of the lower abdomen (corresponding to the ovary that released the egg) that can last from a few minutes to a few hours. After ovulation, the luteal phase begins (early luteal phase), and its duration depends on whether or not the egg was fertilized. If fertilization does not occur, this phase lasts 14 days in women with a typical menstrual cycle and ends with the menstruation of the next cycle [10]. The menstrual cycle is modulated by several hormones, such as luteinizing hormone (LH), follicle stimulating hormone (FSH), and estrogen and progesterone [11]. During the menstrual cycle

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in regular and healthy women, four processes occur: 1) pituitary hormone changes, 2) development of ovarian follicles, 3) changes in estrogen and progesterone levels, and 4) changes in the thickness of the uterine lining.

During the premenstrual period, many women can show dysphoria and alterations in cognition [12]. It is now known that the greatest severity in mood symptoms begins during the late luteal phase (i.e., premenstrual) and declines within a few days after menstruation starts [13]. During the premenstrual period, around 95% of all women of reproductive age, suffer mild physiological, cognitive and emotional symptoms; however, in only about 3-8% of women are these symptoms severe [14]. Therefore, subtle changes in the levels of estrogen and progesterone have been related to these symptoms, to a lesser extent with testosterone and cortisol, as well as to premenstrual syndrome (PMS)/premenstrual dysphoric disorder (PMDD) and/or to stress, diet, lifestyle, habits, certain other medical conditions such as a history of major depression [2,12,15]. In fact, there exists a relationship between low levels of these hormones and conditions such as perimenopausal dysphoria, PMS, postpartum depression and psychosis, PMDD and dysphoria induced by oral hormonal replacement therapy [16].

A little more than 10 years ago the results on the effects of estrogen supplementation on dementia and memory in postmenopausal women (with a mean age of 69 years at the time of enrollment), known as the Women's Health Initiative Memory Study (WHIMS) were published, indicating that cognitive function in women declines after menopause. Given the results of previous preclinical and clinical studies that had strongly indicated that postmenopausal estrogen supplementation could improve performance on specific cognitive tasks and lower the risk of developing Alzheimer's related dementia [reviewed in 17]. These results led to a closer look at factors that could have accounted for the striking differences between WHIMS and previous preclinical and clinical studies. One important variable could have been the type of estrogens used in animal and clinical studies: CEE contains a mix of active estrogens, with 17 beta-estradiol (the most active of the estrogens) reportedly accounting

for only 0.7% of total estrogen content. Another important factor may be the timing at which estrogen therapy is initiated, relative to the onset of menopause.

In conclusion, the ovarian hormones estrogens and progesterone in women play an important role not only in reproduction, but in many other physiological processes such as cardiovascular health, bone integrity, and mood. These hormones are secreted into the bloodstream, mainly from the ovary, to act both on peripheral organs and on the central nervous system. Across the adult lifespan of the female, the brain is regularly exposed to fluctuations in the circulating levels of these hormones, which modulate cognitive, emotional, and sensory processing. For example, during the menstrual and early follicular phases of the menstrual cycle, there are low levels of both estrogen and progesterone, increasing rapidly before ovulation (late in the follicular phase). These hormonal changes are associated with cognitive changes and alterations in the emotional valence of specific stimuli, and, in some cases, exacerbation of certain neuropsychiatric symptoms. In animal and *in vitro* models, it has been shown that these hormones modulate the activity of various neurotransmitter systems, such as catecholaminergic, dopaminergic, serotonergic, cholinergic and GABAergic systems.

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