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The Role of Female Hormones in Migraine: A Literature Review

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Introduction
Migraine is a prevalent and episodic headache causing throbbing and pulsating pain, especially in one side of the head. It affects more commonly people of the feminine gender (75% of the patients of migraine are women). Associated symptoms, such as nausea, photophobia and phonophobia, are more often present in women than in men. Migraine is the highest cause of disability among women between 15 and 49 years old, negatively impacting their careers, social activities and quality of life. Calcitonin gene-related peptide inhibitors have enhanced the treatment of migraine in general, but female hormones have an important role in the pathogenesis of migraine. Therefore, a better understanding of the alternance of hormones in menstrual phases of women's cycle is crucial to improve treatment.

Objectives
This summary aims to correlate the variation in serum levels of hormones – as estradiol, progesterone and prolactin – with the incidence of migraine attacks in the different phases of the menstrual cycle.

Methods
A narrative review of literature was performed based on researches in PubMed and ScienceDirect databases, using the boolean operator "and" and the describers "hormonal", "migraine" and "women". Filters were used to select articles, as publication date of the past 5 years, review and systematic review article type, and full text/open access availability. A total of 80 articles were obtained in the PubMed database, of which 15 were selected and 4 were used. In the ScienceDirect database, 155 articles were found, of which 10 were selected and 2 were used.

Results
Prolactin demonstrated to be at higher levels in migraineurs, stimulating the secretion of prostaglandin and the increase of biologically active substances that are produced in immune cells, inducing vasoconstriction and, as a consequence, causing migraine. Furthermore, prolactin acts by inhibiting ovulation and decreasing estrogen serum levels, an effect that is also related to migraine attacks. Withdrawal and rises of estradiol can provoke headache crisis. The first is more associated with migraine without aura, and the second with migraine accompanied by aura. The studies showed that estrogen levels were lower in women with migraine than in the control group between days 19 and 21 of the menstrual cycle, leading to the hypothesis that the higher and faster the decrease of estrogen during the luteal phase, the more expressive the migraine attacks, since it increases the permeability of blood vessels to pro-inflammatory mediators. Great levels of estradiol can induce neuronal excitability by stimulating or inhibiting the serotonergic, glutamatergic and GABAergic systems, which leads to the symptoms of migraine. Estrogen receptor-α (ERα), estrogen receptor-β (ERβ) and G protein-coupled estrogen receptor-1 (GPER) are expressed in cerebral regions associated with the pathophysiology of migraine, as the dorsal horn of the spinal cord, related to trigeminal transmission of painful stimulus to the brain. ERα and ERβ were also found in the cerebral cortex, influencing the cognitive perception of pain. Progesterone activates the GABAergic systems, protecting against migraine attacks and it also reduces an excessive activation of peripheral sensory nerves.

Conclusions
Migraine is a prevalent disease throughout the lifetime of women, generally starting during puberty, when the variation of hormones causes physiological disturbances that lead to headache crisis. Estrogen is the hormone most closely related to migraine attacks, due to its significant variations across the menstrual cycle, modulating the neurotransmitters systems and the processing nociceptive areas of the brain. High levels of prolactin and low levels of progesterone are also correlated with migraine attacks. Therefore, understanding the role of hormones in migraine pathophysiology is crucial for the advent of more specific and effective treatments, improving the quality of life of migraineurs.

Keywords: Estrogen; Female Hormones; Migraine; Progesterone; Prolactin; Women.