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Comprehensive review

Ovarian hormones and chronic pain: A comprehensive review

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ABSTRACT

Most chronic noncancer pain (CNCP) conditions are more common in women and have been reported to worsen, particularly during the peak reproductive years. This phenomenon suggests that ovarian hormones might play a role in modulating CNCP pain. To this end, we reviewed human literature aiming to assess the potential role of ovarian hormones in modulating the following CNCP conditions: musculoskeletal pain, migraine headache, temporal mandibular disorder, and pelvic pain. We found 50 relevant clinical studies, the majority of which demonstrated a correlation between hormone changes or treatments and pain intensity, threshold, or symptoms. Taken together, the findings suggest that changes in hormonal levels may well play a role in modulating the severity of CNCP conditions. However, the lack of consistency in study design, methodology, and interpretation of menstrual cycle phases impedes comparison between the studies. Thus, while the literature is highly suggestive of the role of ovarian hormones in modulating CNCP conditions, serious confounds impede a definitive understanding for most conditions except menstrual migraine and endometriosis. It may be that these inconsistencies and the resulting lack of clarity have contributed to the failure of hormonal effects being translated into medical practice for treatment of CNCP conditions.

1. Introduction

There is a wealth of literature suggesting that there are sex differences in the perception and experience of pain, which were not detected previously, leading to the understanding that women are more sensitive to experimentally induced pain and tend to have lower pain thresholds than men [79,85,120]. In the field of chronic pain, there has been a growing recognition that many chronic noncancer pain (CNCP) conditions occur more frequently in women [14,62,109]. CNCP is a set of clinical conditions characterized by pain that persists despite removal of any stimulus and apparent healing of tissue injury, or pain that arises in the absence of any detectable damage with no relation to cancer [9,50,73,90,94]. CNCP conditions include: musculoskeletal pain (MSP) (eg, fibromyalgia, rheumatoid arthritis [RA]); migraine headache; temporomandibular disorder (TMD); and chronic pelvic pain (eg, irritable bowel syndrome [IBS], endometriosis, and interstitial cystitis). Most of these CNCP conditions display significant increases in prevalence between puberty and menopause, that is, in the reproductive years [67], suggesting that ovarian hormones may be responsible for the observed sex differences.

As a result, researchers have begun to investigate the influence of both ovarian hormone level and fluctuation on pain sensation. These studies provide evidence detailing how variations in pain perception and pain ratings are related to ovarian hormones. Based on their findings, some have concluded that sex differences in pain responses might be attributed to the fluctuation of ovarian hormones across the menstrual cycle [33,85]. In order to provide insights into what is and is not known about CNCP perception and ovarian hormones, we first provide an overview of the menstrual cycle and the associated changes in the levels of ovarian hormones. We then discuss possible mechanisms through which ovarian hormones might modulate pain. Finally, we review the existing literature regarding the influence of ovarian hormones on CNCP.

2. Ovarian hormones and the menstrual cycle

Ovarian hormones are luteinizing hormone (LH), follicle-stimulating hormone (FSH), estrogens, and progestagens. Levels

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of these hormones change over approximately 28 days, leading to the maturation of a set of oocytes, or eggs, and the ultimate release of one (the ovarian cycle). The menstrual cycle involves the concomitant changes in the uterine lining, which, if the egg is not fertilized, is shed, resulting in menses (Fig. 1). The ovarian and menstrual cycles are under the control of the hypothalamic/pituitary/ovarian axis [31]. The regular release of ovarian hormones requires the coordinated activity of: the hypothalamus, which secretes gonadotropin-releasing hormone (GnRH); the pituitary, which secretes LH and FSH; and the ovary, which secretes estrogen and progestagens. Based on the 2 observable events, ovulation and the shedding of the uterine lining, the menstrual cycle is commonly divided into 3 phases: menses, the follicular phase, and the luteal phase. The average length of the menstrual cycle is 28 days, with a range of 25-32 days [28,31,39].

Menstrual cycles are counted from the first day of the shedding of the uterine lining (menses, menstrual bleeding). After menses ends, the follicular phase starts, in which both FSH and LH are secreted, and estrogen gradually increases, peaking just before ovulation. Around mid-cycle, a peak in LH leads to the release of small amounts of progestagens. Ultimately, the follicle ruptures, resulting in ovulation and the beginning of the luteal phase. Shortly after ovulation, the corpus luteum forms and itself secretes large amounts of progestagens. Progestagens peak during the mid-luteal phase with estrogens increasing as well, though this increase is not as high as it was in the follicular phase. These increasing levels of estrogen and progestagens provide negative feedback to the pituitary, resulting in decreased secretion of LH and FSH across the luteal phase. This, in turn, decreases secretion of estrogen and progestagens, which, in the absence of fertilization, leads to the shedding of the uterine lining, menses, and a new menstrual cycle [28,31,39].

Because menses, itself, is observable, the menstrual cycle is often used as a proxy for the ovarian cycle, with assumptions being made about levels of hormones secreted at the different phases. However, it is well established that there are both inter- and intra-subject variations in the length of the total cycle as well as actual amounts of estrogens and progestagens secreted [11].

3. Ovarian hormones and mechanisms of pain modulation

Although the mechanisms and exact dynamics by which ovarian hormones modulate pain remain unclear, ovarian hormones (especially estrogens) are known to play a role at key points along the pain pathway, including: 1) primary afferent nerve fibres where they might modulate signal transduction and the transmission of nociception [3,12,17,33,81,105]; 2) the spinal cord (substantial gelatinosa), where the density of estrogen receptors changes with changes in estrogen levels over the menstrual cycle [6,7]; and 3) the brain where estrogen receptors are prevalent in regions (periaqueductal grey, thalamus, amygdala, and central grey) that modulate pain perception [81,97,99,104] (Fig. 2). Additionally, ovarian hormones may affect pain perception by modulating numerous neurotransmitters including: serotonin, dopamine, β-endorphins, and γ-amino-butyric acid (GABA) [54,66,91]. In fact, the interaction between estrogen and GABA has been shown to be one of the most important neurotransmitter interactions for pain modulation, with estrogens modulating GABA synthesis, release, and production, as well as upregulation of GABA receptors, and modulation of their binding affinity [3,54,91,98].

4. Literature search

We searched Medline, PubMed, and Google Scholar, as well as the references of papers that reviewed the relationship between the menstrual cycle, ovarian hormones, and pain. References of papers were searched in order to identify potentially relevant studies that might not have been retrieved by traditional subject searching. Results were limited to those in English. In order to capture as many studies as possible, the search was unlimited by any time interval. Search terms were *chronic pain*, *chronic non-cancer pain*, *migraine headache*, *temporomandibular joint disorder*, *irritable bowel syndrome*, *fibromyalgia*, *rheumatoid arthritis*, and *chronic pelvic pain*, each in turn crossed separately with *ovarian hormones/steroids*, *estrogen/progesterone*, *hormonal replacement therapy*, *oral contraceptives*, *menopause*, and *menstrual cycle*.

Focusing on CNCP conditions and their relation to hormonal changes, the search produced 385 papers (dates ranging from 1983-2012). We excluded any that were not clinical, leaving a total of 50 studies: 8 for MSP, 9 for migraine headache, 5 for TMD, and 28 for chronic pelvic pain (6 IBS and 22 randomized controlled trials [RCTs] testing the efficacy of hormone therapy in alleviating chronic pelvic pain due to endometriosis). For all these studies, patients were diagnosed with a CNCP condition and pain was assessed by at least one self-report measure. All studies recorded changes in pain severity either by: 1) querying current pain intensity (visual analogue scale, verbal rating scale, and/or McGill Pain Questionnaire); 2) inducing pressure pain to measure pain pressure threshold (PPT) by pressure dolorimetry; 3) using physiological changes such as grip strength, finger joint size, and rectal sensitivity, or stool softening. Most studies used the menstrual cycle as a proxy for the absolute levels of estrogens and progestagens. They counted backward or forward from the first day of menstruation, assuming an average cycle length of 28 days. Some

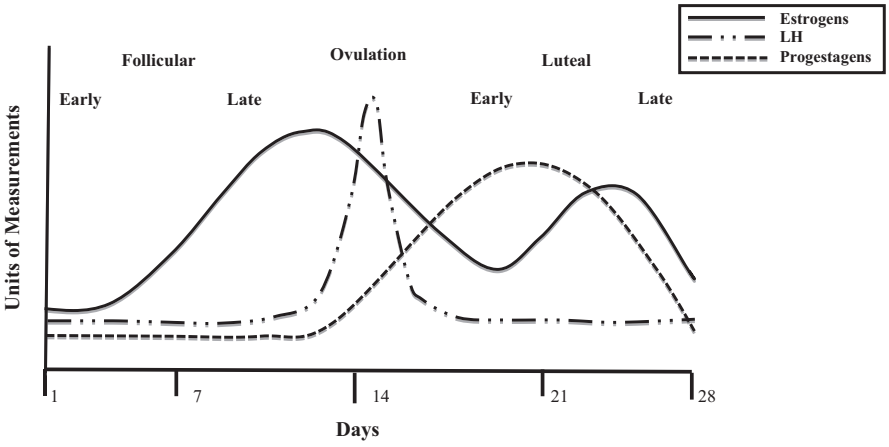

Fig. 1. Schematic of a 28-day menstrual cycle. LH, luteinizing hormone.

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