REPRODUCTIVE HORMONES IN PATHOPHYSIOLOGY OF FIBROMYALGIA SYNDROME

Ms. Suman Tanwar*, Dr. Suman Jain†, Dr. Uma Kumar‡, Dr. Rima Dada§, Dr. Renu Bhatia¶

Abstract

Fibromyalgia syndrome (FMS) is a chronic, non-inflammatory pain syndrome characterized by diffuse myalgia and tenderness. Fibromyalgia is typically associated with sleep disturbance, fatigue, anxiety, depression, and morning stiffness and often occurs concomitantly with other conditions such as irritable bowel syndrome and headaches. This is a disorder of unknown etiopathogenesis and affects women around 9-10 times more often than men. The higher frequency of fibromyalgia particularly in women strongly suggests that sex hormones may have a role in the expression of this disease. Further there are a number of reports about varying levels of sex hormones in patients with fibromyalgia. This review addresses the status of sex hormones observed at different menstrual phases in fibromyalgia patients and their comparison with healthy subjects.

Keywords: Chronic Pain, Luteinizing Hormone, Follicle Stimulating Hormone, Estrogen, Progesterone.

Introduction

Fibromyalgia syndrome is characterized by widespread chronic pain affecting the musculoskeletal system, with well-defined tender points apparent on examination (Figure 1 & Table 1).

Fibromyalgia is a poorly understood condition that is characterized by widespread musculoskeletal pain and presents with other symptoms such as fatigue, cognitive dysfunction, sleep disturbances, anxiety, depression, gastrointestinal discomfort and stiffness. American College of Rheumatology (ACR) has proposed diagnostic criteria for FMS which includes implementation of the widespread pain index (WPI) and symptom severity scale (SSS) to supplement the previous gold standard of a tender point count with widespread pain for at least 3 months in at least 3 of the 4 quadrants of the body.

Epidemiology of Fibromyalgia

Fibromyalgia syndrome is the second most common rheumatologic disorder, after osteoarthritis, with 2 to 4% of the populations of industrialized countries affected. FMS affects an estimated 11 million persons in the United States, 80-90% of whom are women. FMS patients are typically sedentary and overweight and physical inactivity being a common contributory factor towards increased risk for related metabolic co-morbidities in this population. Female gender,

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Table 1. Tender points with their number and location (ACR, 1990 criteria)

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<tr>
<th>1</th>
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<th>16</th>
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<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>occipital</td>
<td>Supraspinatus muscle</td>
<td>Upper quadrant of Gluteal muscle</td>
<td>Greater trochanter</td>
<td>Low cervical</td>
<td>Trapezius</td>
<td>2nd rib lateral to costochondral junction</td>
<td>Lateral epicondyle</td>
<td>Knee</td>
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There are 18 "tender points" which are important for the diagnosis of fibromyalgia. There is bilateral symmetry of the tender points. Tenderness on palpation of at least 11 of these sites in a patient with at least a three-month history of diffuse musculoskeletal pain is recommended as a diagnostic standard for fibromyalgia.

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Volume 6, No.3, Jul - Sep, 2016
old age, low educational, low socio-economic status and single status have been associated with FMS. Psychological distress is a major risk factor for long term complaints and comorbidity with anxiety and depression is high. The patients display generalized hyper vigilance, characterized by a greater sensitivity to external stimuli for various modalities. Pain catastrophizing and low pain-self efficacy are common psychological factors that prevent healthy adjustment to FMS and contribute to disability, pain, depression and poor well-being of the patient.

Relationship of gynecologic pathologies and FMS

Several studies have examined the relationship of gynecologic pathologies and FMS (Table 2). Some researchers have also reported fluctuations in pain levels with the phases of menstrual cycle. Hysterectomies and early menopause also occur more commonly in FMS patients than in rheumatoid arthritis controls. Interestingly, there are reports of increased frequency of hysterectomies in patients developing bladder pain syndrome (Interstitial cystitis) an entity, very commonly associated with the incidence of FMS. Further, women with FMS who were hysterectomized showed worse symptom severity than those who were not. Also 90% of the FMS patients with hysterectomies reported undergoing the surgical procedure before the onset of FMS and there was poor general health of the patients. The sex differences in the prevalence of chronic pain conditions have generated multiple views about the role of sex hormones in pain onset and maintenance. Though substantial evidence links gonadal hormones and pain, the exact relationship between the two is not fully understood.

Estrogen may have pronociceptive or antinociceptive effects depending upon the type of receptor. In one of the studies, the involvement both receptors i.e. ERα and ERβ on nociceptive responses was measured in ERα and ERβ knockout (KO) C57BL/6j mice and their respective wild type (WT) littermate (male and female). It was found that ERα KO male and female mice presented a small increase in nociceptive behaviours during phase 1 of the formalin test, suggesting an antinociceptive effect of ERα. These results were confirmed by the injection of ERα-selective agonist propylpyrazoletriol (PPT) in ovariectomized mice. Interestingly, both ER agonists reduced nociceptive responses during late phase 2, suggesting an anti-inflammatory action of estrogen. Results were supported by spinal c-Fos immunohistochemistry. In conclusion, both ERα and ERβ appear to be involved in pain transmission and modulation but may be acting at distinct levels of the pain pathways. Sex steroids alter the levels of neuromodulators involved in spinal nociceptive processing. Substance P, amino acids such as gamma aminobutyric acid and glutamate has been implicated increasing in number of excitatory synapses in neurons in the cortex, cerebellum, and hippocampus.

Table 2. Gynaecological pathologies in fibromyalgia

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Subjects</th>
<th>Experimental paradigm</th>
<th>Results</th>
<th>Finding</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency and types of abdominal</td>
<td>FM (n = 80)</td>
<td>Retrospective study</td>
<td>No difference in total no. of abdominal operations between both groups</td>
<td>More hysterectomies and appendectomies in FM</td>
<td>Ter Borg EJ et al., 1999</td>
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<tr>
<td>surgery</td>
<td>RA (n = 47)</td>
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<tr>
<td>Pain perception in menstrual</td>
<td>Chronic low pain</td>
<td>Pain rating during</td>
<td>Pain rating significantly higher in menstrual /premenstrual phases than in mid-menstrual and ovulatory phases</td>
<td>Less pain sensitivity during menstrual cycle associated with high estrogen</td>
<td>Hellstrom et al., 2003</td>
</tr>
<tr>
<td>cycle</td>
<td>(n=29)</td>
<td>menstrual cycle</td>
<td></td>
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<tr>
<td>FMS Symptoms and early menopause</td>
<td>FM=115</td>
<td>VAS and FM impact</td>
<td>Frequencies of early menopause/ hysterectomy in FM significantly higher Duke anxiety and depression score was higher in patients with hysterectomy whose FM symptoms started within 14 year of post-hysterectomy</td>
<td>Early menopause and hysterectomy may be one of the factors contributing to development of FM</td>
<td>Pamuk et al., 2009</td>
</tr>
<tr>
<td>and hysterectomy</td>
<td>RA=76 (Postmenopausal)</td>
<td>questionnaire</td>
<td></td>
<td></td>
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<tr>
<td>FMS and hysterectomies</td>
<td>FM with reported</td>
<td>Quality of Well-Being Scale</td>
<td>48.3 % of the patients reported having had a hysterectomy, with 90.7 % reporting having had the surgery before their FMS diagnosis</td>
<td>Hysterectomy and a diagnosis of FM related to poorer health status and higher health care costs</td>
<td>Santoro et al., 2012</td>
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<tr>
<td></td>
<td>hysterectomy</td>
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<td></td>
<td>(n=573)</td>
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Role of sex hormones

Menstrual cycles last from 25 to 35 days, with an average of 28 days for women in their twenties and 26 days for women in their forties. In a normal ovulatory menstrual cycle there are cyclical changes in four reproductive hormones, namely luteinizing hormone (LH), follicle-stimulating hormone (FSH), estrogen and progesterone (Table 3).

Table 3. Variation in reproductive hormones in patients with fibromyalgia

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Subjects</th>
<th>Samples</th>
<th>Experimental paradigm</th>
<th>Results</th>
<th>Findings</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol, progesterone, FSH, LH</td>
<td>FM=9</td>
<td>Blood</td>
<td>Samples collected every 10 min over a 12h period</td>
<td>No significant difference</td>
<td>No indication of abnormal gonadotropin secretion</td>
<td>Korszun et al., 2000⁵²</td>
</tr>
<tr>
<td>FSH, LH, estradiol, progesterone, prolactin, Cortisol</td>
<td>FM=68 HC=46 Blood</td>
<td>Hormone assays, BDI questionnaire</td>
<td>Not significant</td>
<td>Cortisol significantly low in FM or CFS, FM patients with high BDI scores had significantly lower cortisol</td>
<td>Depression may lower cortisol and LH levels</td>
<td>Gur et al., 2004³³</td>
</tr>
<tr>
<td>Estrogen substitution treatment on Experimental/self-estimated pain</td>
<td>FM (post-menopausal) =29 Blood</td>
<td>8 weeks treatment with transdermal 17β-estradiol (50 mg/day) or placebo, QST, CPT</td>
<td>Increased serum estradiol</td>
<td>No effect on perceived pain, pain thresholds or pain tolerance</td>
<td>Stening et al., 2011⁴¹</td>
<td></td>
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<tr>
<td>Testosterone gel (transdermal)</td>
<td>FM=12</td>
<td>Blood</td>
<td>Daily dose (0.75 g of 1% w/w) for 28 days with transdermal test; Patient questionnaire, tender point counts</td>
<td>Significant increase in serum free testosterone</td>
<td>Testosterone have ability to relieve symptoms</td>
<td>White et al., 2015⁶⁸</td>
</tr>
</tbody>
</table>

Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Fibromyalgia (FM), Chronic fatigue syndrome (CFS), Healthy controls (HC), Myalgic Encephalomyelitis (ME), Beck Depression inventory questionnaire =BDI, Quantitative sensory tests (QST), Cold pressor test (CPT), Fibromyalgia Impact questionnaire (FIQ), pain visual analogical scale (VAS)

Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH)

Coordinated through the central nervous system, pulsatile release of the gonadotropin-releasing hormone (GnRH) from the hypothalamus regulates the release of the hypothalamic hormones LH and FSH that in turn regulate the secretion of estrogen. As an anchor point, cycles are counted forward from the first day of menstrual flow when the levels of all four key reproductive hormones are low. Thereafter, as FSH and estrogen levels rise, ovarian follicles develop and mature during the follicular phase. Approximately 16 h before ovulation, LH peaks; the presence of LH in urine is a reliable marker of ovulation. At ovulation an oocyte is released from the follicle and the corpus luteum then evolves from the ruptured follicle and secretes progesterone and estrogen.

About seven days after ovulation, should fertilization and implantation of the conceptus not occur, the corpus luteum degenerates and hormone production begins to decline. The post-ovulation luteal phase lasts 14-16 days. It is during the last few days of the cycle (as hormone concentrations decline) and the first days of menstruation (when hormones are low) that most negative symptoms are experienced by women.

Menstrual irregularities may be related to altered LH pulsatility and amplitude as a result of circadian rhythm disturbances and disturbed sleep as well as stress related dysfunction of the hypothalamo-pituitary-ovarian axis.³⁰
Sleep has a direct inhibitory effect on pulsatile LH secretion, contributing to a nocturnal decrease in mean LH and LH pulse frequency in adult women in the early follicular phase. Since shift workers have shorter total sleep time and a more fragmented sleep, altered menstrual function may be related to the effects of these altered sleep patterns on pulsatile LH secretion, mediated through GnRH. In turn, the menstrual irregularities and extended shiftwork are likely factors leading to fertility problems, increased risk for low birth weight or preterm births and associated stress. In one of the studies, it was reported that LH levels in patients with low depression scores were significantly higher than those of patients with high depression scores and those of controls. In patients who had sleep disturbance, LH levels were significantly higher than in controls. These findings suggest that fatigue, depression rate, and sleep disturbance may have an effect on LH levels. In this study there were no significant differences in FSH, LH, oestradiol, prolactin, and progesterone levels between patients with FM and healthy controls. Cortisol levels were significantly lower in patients than in controls.

FSH and LH secretion from the gonadotrope is controlled by the hypothalamic decapetide, GnRH. Acting primarily in the anterior pituitary, GnRH binds to its native high-affinity seven-transmembrane receptor (GnRH-R) on the cell surface of the gonadotrope, stimulating signaling cascades that confer the production of these gonadotropins. FSH and LH exert their effects on the ovaries and testes, leading to steroidogenesis and gametogenesis, highlighting their critical role in reproductive function. Released in a pulsatile manner from the hypothalamus, differential GnRH pulse frequencies and amplitudes alter the secretion patterns of FSH and LH, with increasing frequencies resulting in preferential secretion of LH, whereas decreasing frequencies result in greater FSH release. Although considerable research has been dedicated to elucidating the mechanisms by which GnRH controls the production and secretion of FSH and LH, less is known about how the gonadotrope decodes the pulsatile GnRH signal.

### Estrogen and Progesterone

Another question regarding the relationship between sex hormones and FMS is whether sex hormones interact with algesic responses to noxious stimulations, as hyperalgesia is one of the cardinal features of FMS. A large volume of research investigating the fluctuation of pain sensitivity at different hormonal stages in animals and healthy women exists. For example, tail flick latencies are reduced in ovariectomized rats following estrogen administration. In humans, however, the experimental results are far more inconsistent. For example, both increased and decreased pain sensitivity has been reported during the luteal phase. The inconsistent results may be attributable to the crude approach to define menstrual phases, such as based on the number of days since the menstrual onset without confirming the actual hormone levels.

In an earlier study, 11 healthy, normal menstruating women were tested for pain thresholds and noxious heat at 3 points during a menstrual cycle i.e. mid-follicular, ovulatory and mid-to-late luteal phases. Women exhibited a phasic change in pain thresholds and tolerance only to the ischemia but not noxious heat. Women showed significantly greater threshold and tolerance to ischemic pain during the mid-follicular phase compared to the other two phases. Generally the hormone levels were not associated with ischemic threshold or tolerance except for progesterone with threshold only during the ovulatory phase. Unfortunately, the phasing did not include a time point when estrogen was low.

The results from one more study demonstrate that the levels of sex hormones for regularly menstruating women with FMS are fairly comparable with those for regularly menstruating pain-free women at the different phases during a menstrual cycle, suggesting that the higher prevalence of women for FMS is not likely to be attributed solely to abnormal levels of sex hormones. The results are consistent with the previous studies with single-phase assessment of sex steroids. The only exception was the level of progesterone. Women with FMS had a significantly greater elevation of progesterone at the mid-luteal phase than did pain-free women, although the elevation of progesterone at the mid-luteal phase for FMS group was within the normal limit. Furthermore, absolute levels of progesterone as well as relative changes in progesterone may be modestly related to pain thresholds in FMS women. The results are somewhat unexpected in that it was progesterone, which, compared to estrogen, has received considerably less attention in the studies of endocrine system in pain medicine.

**Effect of transdermal estrogen substitution treatment on experimental as well as self-estimated pain was observed in women suffering from FMS. It was found that hormonal replacement treatment significantly increased serum estradiol levels as expected. However, no differences in self-estimated pain were seen between treatment and placebo groups.** A number of animal studies have shown anxiolytic and antidepressant-like effects of progesterone administration. Sedative-like effects as well as increased fatigue are also documented in acute administration of progesterone in humans.

**Other hormones studied in fibromyalgia**

In addition to sex hormones, research has implicated role of other endocrine pathologies, such as those involving the hypothalamic–pituitary–adrenal (HPA) axis and thyroid in...
FM. Research on the HPA axis in FM has shown variations in cortisol levels, increased sensitivity to glucocorticoid feedback and increased cortisol release in response to a stressor. However, a number of conflicting studies have also emerged which fail to find evidence of cortisol dysregulation in FMS. Following a 3-week, multidisciplinary, FMS treatment program, improvements were noted in the function of HPA axis, specifically cortisol and corticoid receptor levels. Altogether, the literature suggests that cortisol release may be abnormal in FMS, but the nature of the pathology remains poorly understood at present.

Previous studies have suggested that the HPA axis is perturbed in FMS and hyper-reactive response to different stimuli of adrenocorticotropic hormone and growth hormone was detected, whereas in the cortisol response a decrease occurred. Crofford et al reported raised serum levels of 24 hour free cortisol, resulting in a loss of normal diurnal cortisol fluctuation, and with stimulation a brisk but lesser increase in cortisol level in FMS. In a later study by the same group, mild hypocortisolaemia was seen. Differences in methodology and sample characteristics may explain the difference between the results.

Researchers have proposed that testosterone may be effective in cases of fibromyalgia. White HD et al and Robinson TD had conducted a study to test the hypothesis that testosterone deficiency plays an important role in chronic pain. In this study 12 fibromyalgia patients were enrolled to verify that a daily dose for 28 days with transdermal testosterone gel would increase mean serum testosterone and effectively treat the pain and fatigue symptoms of fibromyalgia. The results were consistent with the hypothesized ability of testosterone to relieve the symptoms of fibromyalgia. This study needs to be explored in larger patient population to establish efficacy of testosterone in FMS patients.

A number of studies have also suggested role of melatonin, growth hormone, thyroid hormone, prolactin, Adrenocorticotropic hormone, somatomedin C, calcitonin, prostaglandin E2, and oxytocin in the pathogenesis of fibromyalgia besides reproductive hormones. Also such results lead us towards a better understanding of this chronic pain syndrome in light of aberrant hormonal profiles of the individual.

**Conclusion and Future directions**

Reproductive hormones play a significant role in pathogenesis of fibromyalgia syndrome. The symptoms of chronic pain should be correlated with the reproductive hormonal profile of the patient to further understand the role of reproductive hormones in FMS. A complete hormonal profile of patients is important to assess the mechanism and progression of the disease. Further research and reporting is therefore required to validate the present findings.

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