

ORIGINAL ARTICLE

Role of Hypothalamic–Pituitary–Gonadal Axis Hormones in Patients with Fibromyalgia Syndrome

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ABSTRACT

Fibromyalgia syndrome (FMS) is characterized by widespread chronic pain affecting the musculoskeletal system, with defined tender points, sleep disturbance, anxiety, depression and fatigue. FMS is more prevalent in women than in men. The skewed sex distribution in the prevalence has prompted questions of if and how sex hormones may be involved in the pathophysiology of FMS. Neuroendocrine abnormalities have been observed in FMS, including dysregulation of hypothalamic–pituitary–gonadal axis. We investigated abnormalities of the hypothalamic–pituitary–gonadal axis in patients with fibromyalgia syndrome (in the mid-luteal phase of their menstrual cycle). A total of 117 subjects participated - 64 healthy volunteers, 53 patients with fibromyalgia syndrome. We examined concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH) and estrogen. There were no significant differences in luteinizing hormone (LH), follicle stimulating hormone (FSH) as well as estrogen levels in fibromyalgia patients compared to healthy controls. Therefore, larger clinical studies and follow-up surveys are needed to further investigate the levels of these hormones in relation to HPG axis.

Keywords: Fibromyalgia syndrome, luteinizing hormone, follicle stimulating hormone, estrogen, hypothalamic–pituitary–gonadal axis.

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INTRODUCTION

Fibromyalgia is a common syndrome of unclear etiology that is characterized by chronic widespread pain and specific painful tender point sites [1]. Other complaints, such as chronic fatigue, stiffness, sleep disturbance, and psychological distress, are frequent as well. A range of other symptoms co-occurs with FMS, including chronic fatigue and non-restorative sleep [2, 1, 3]. Although FMS is not fatal, patients report severe disability [4, 5, 6, 7]. A community-based study reported the prevalence rates of 4.9% for women and 1.3% for men [8]. The difference expands when treatment-seeking patients are considered, with the ratio of approximately 10:1, females to males [9].

Given the greater prevalence of FMS in women, the role of sex hormones is a natural consideration. Little is currently known about the association between sex hormones and FMS. This indicates that alterations in reproductive gonadal hormone levels may be involved in the pathophysiology of fibromyalgia syndrome. Although most patients who suffer with FMS are women, only a few investigations have paid attention to the changes of sex hormones in FMS [10, 11, 12]. Riedel et al investigated female patients with FMS and healthy subjects who were all in their follicular phase [10]. They observed that patients with FMS have significantly lower oestrogen levels despite raised follicle stimulating hormone (FSH) levels. Korszun et al., [13] found no abnormalities in the hypothalamic pituitary gonadal (HPG) hormone axis.

There are conflicting reports regarding the aberrations in HPG hormone axis in FMS patients therefore, the present study aimed to investigate the levels of key reproductive hormones (luteinizing hormone, follicle stimulating hormone, estrogen) which are integral part of hypothalamic–pituitary–gonadal axis.

MATERIALS AND METHODS

The research was conducted in the Pain research and TMS Lab, Department of Physiology, All India Institute of Medical Sciences, New Delhi. The subjects recruitment was done from year 2013-2016.

Ethical clearance- The Institute Ethics Committee of the All India Institute of Medical Sciences, New Delhi, approved (Ref No: IESC/T-251/15.06.2013) all procedures and the research was also registered on Clinical Trial Registry India (Ref No: CTRI/2013/12/004228). A written informed consent was obtained from each subject before inclusion in the study.

Study participants- A total of 117 subjects participated in this study—64 healthy volunteers and 53 patients with FMS, recruited from Rheumatology clinic of All India Institute of Medical Sciences, New Delhi. All subjects were normal menstrual cycle and patients fulfilled the American College of Rheumatology (ACR) criteria for FMS. All subjects were provided with written informed consent at the start of the study.

Exclusion criteria for patients with FMS and healthy controls were (i) recent or past history of psychiatric disorders—for example, major depressive disorder, alcohol dependence, substance abuse, schizophrenic or paranoid disorder, personality disorder, and somatoform disorder; (ii) immune-compromised subjects; (iii) subjects with neurological, inflammatory, endocrine or clinically significant chronic disease, such as diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, and organic brain disorders; (iv) abnormal liver function tests, such as serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and c-glutamyl transpeptidase; and (v) pregnant women.

All FMS patients and healthy controls had normal menstrual cycles and were not taking contraceptive pill. It was ensured that subjects were free of any infection, inflammation or allergic reactions for at least 2 weeks before blood sampling and free of drugs known to affect immune or endocrine functions and of hormonal preparations. All healthy volunteers were free from any kind of pain (Visual Analog Scale < 3) and none was a regular drinker or with history of psychotropic drug intake.

Sample collection and storage

Blood samples were collected in the morning (9.00–11.00 am) after an all night fast and plasma was separated immediately by centrifugation; the serum samples obtained were stored at -80°C until required for hormonal assaying.

Estimation of Hormones

All hormones were assayed by the “Electro Chemi-Luminescence Immunoassay (ECLIA)” (ELECSYS, Roche Diagnostics; Mannheim, Germany) method. Briefly, as described by the manufacturer, the protocol is as follows: 20 μL /50 ml of sample for LH, a biotinylated monoclonal LH-specific/FSH/estrogen specific antibody, and a monoclonal LH-specific/FSH/estrogen specific antibody labelled with a ruthenium complex reacted to form a sandwich complex. After addition of streptavidin-coated microparticles, the antigen-antibody complex binds to the micro particle solid phase via interaction of biotin and streptavidin. The reaction mixture was aspirated into the measuring cell where the micro-particles were magnetically captured onto the surface of the electrode and unbound substances were then removed with washing buffer. Voltage application to the electrode induced chemi-luminescent emission from ruthenium which was measured by a photomultiplier. Results were determined via a built in calibration curve provided by the manufacturer.

Statistical analyses

Statistical analysis was done with the help of GraphPad Prism software version 5.0. Statistical significance was tested using unpaired t-test/ Mann Whitney test. Normality was assessed by D’Agostino and Pearson omnibus/ Shapiro-Wilk normality tests. All statistical tests were two sided; $p < 0.05$ was considered to be significant. Results are expressed as the mean (SD).

RESULTS

All patients with FMS and healthy controls were reproductive pre-menopausal women; and mean ages were 36.8 ± 7.52 and 38.6 ± 6.74 respectively for both groups.

The general body characteristics FMS patients and healthy controls are summarized in Table 1. All of the patients had debilitating clinically evaluated and medically unexplained chronic pain that does not resolve with bed rest and severe enough to significantly reduce daily activity for at least 3 months.

The two groups were comparable in their demographic background and vital signs at the time of first laboratory visit. There wasn't significant differentiation between ages, height and body weight of two groups ($p > 0.05$).

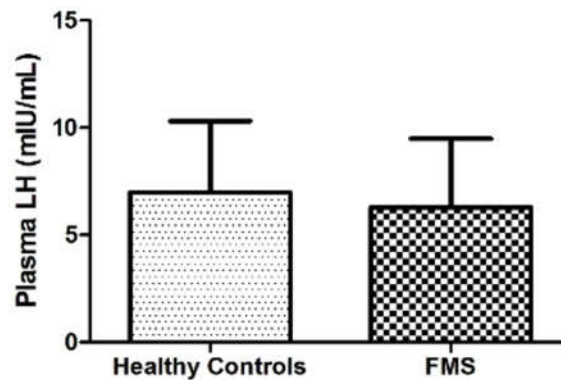
The levels of HPG axis hormones for regularly menstruating women with FMS were fairly comparable with those for regularly menstruating pain-free healthy controls.

There were no significant differences between the levels of LH, FSH and estrogen in FMS patients as compared to healthy controls in mid-luteal phase ($p > 0.05$) (Figure 1). Comparison of LH, FSH and estrogen is presented in Table 2.

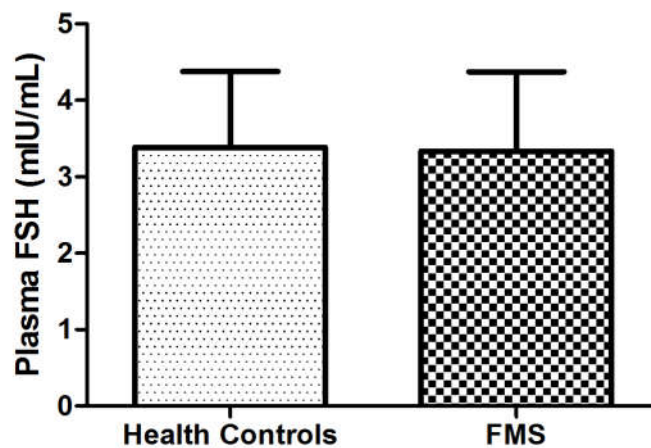
	Groups		P value
	Controls (n=64)	FMS (n=53)	
Age (years)	36.8±7.52	38.6±6.74	0.13
Height (cm)	156.9±5.53	158.4±4.66	0.12
Body weight (kg)	60.7±7.62	62.5±6.46	0.29

	Groups		P value
	Controls (n=64)	FMS (n=53)	
LH (mIU/mL)	6.97±3.34	6.28±3.2	0.26
FSH (mIU/mL)	3.38±1.03	3.33±1.02	0.78
Estrogen (pg/mL)	190.0±58.84	166.8±70.19	0.07

(A)



(B)



(C)

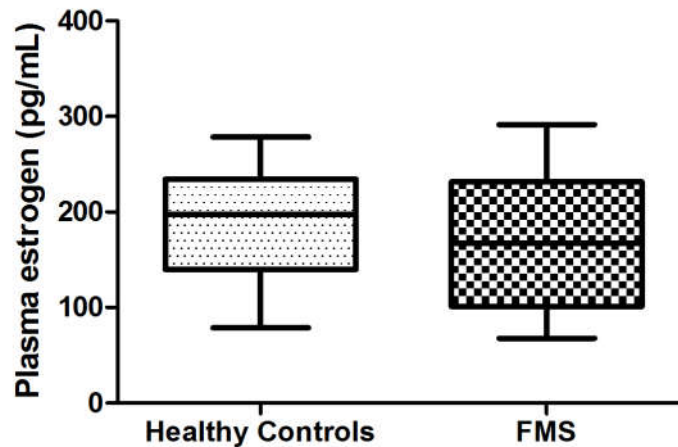


Figure 1. Comparison of concentrations of hormones of the HPG axis (A) LH (B) FSH and (C) Estrogen. Data is expressed as (Mean \pm SD/ Median (Min-Max)).

DISCUSSION

The primary purpose of this study was to investigate the hormonal profile in mid- luteal phase of menstrual cycles of women with FMS, relative to age matched healthy controls. The mid- luteal phase of menstrual cycles in this study appeared to show normal patterns for both groups.

In our study, reproductive HPG axis hormone levels demonstrated no significant differences in women with FMS from controls during luteal phase suggesting that abnormal HPA axis may not be a cause for a wide variety of symptoms. These findings are in agreement with those of Korszun *et al*, who reported data from nine patients with FM and eight with chronic fatigue syndrome [13]. They showed no significant differentiations of reproductive axis function in both of patients groups in estrogen and progesterone levels, as well as LH pulsatility during the follicular phase.

Our results are also consistent with one of the studies [14] in which researchers investigated abnormalities of the hypothalamic- pituitary-gonadal axis and cortisol concentrations in young women with primary fibromyalgia and effect of depression, fatigue, and sleep disturbance on hormonal profiles of the patients. These authors estimated Follicle stimulating hormone, luteinising hormone, oestradiol, progesterone, prolactin, and cortisol concentrations in 63 women with FM were compared with those in 38 matched healthy controls. They did not find abnormality in HPG axis.

However, different results were obtained by Studd and Panay [15], who reported data from 28 premenopausal women with Chronic Fatigue Syndrome (CFS). Of these, 25% showed low plasma estradiol concentrations. Those authors reported that CFS may represent a hypoestrogenic state and recommended the use of hormone replacement therapy for women with CFS. In addition, they claimed that 80% of patients improved after treatment with estradiol patches and cyclical progesta-gens. A similar suggestion as to the effect of HRT has been made for women with fibromyalgia by Waxman and Zatskis [16]. The authors reported estrogen deficit as a prominent promoting factor in the majority of patients with fibromyalgia and recommended estrogen therapy for treatment of fibromyalgia. Further clinical and experimental studies are required to determine the role of sex hormones in the pathogenesis of this condition.

Fibromyalgia is characterized by widespread chronic pain affecting the musculoskeletal system, with defined tender points apparent on examination [1]. It is also associated with sleep disturbance and fatigue, suggesting overlap with CFS. In an another work [17], concentrations of follicle-stimulating hormone, luteinizing hormone, estradiol, progesterone and prolactin was examined in 68 patients with fibromyalgia, and 62 patients with CFS. Their study suggests that in spite of low morning cortisol concentrations, the only abnormalities in hypothalamic-pituitary-gonadal axis hormones among follicular-phase women with fibromyalgia or CFS are those of LH levels in fibromyalgia patients with a low BDI score. Similarly, another group of researchers [18], investigated abnormalities of hypothalamic-pituitary-gonadal (HPG) axis hormones in premenopausal women with CFS. They examined follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone and cortisol concentrations in 43 premenopausal women with CFS and compared matched 35 healthy controls. They

also observed no significant differences in FSH, LH, estradiol and progesterone levels in both of menstrual phases of patients versus controls.

In another study, levels of testosterone progesterone and estradiol were compared between healthy women and women with FMS during the follicular phase. They revealed elevated levels of testosterone but no differences in progesterone and estradiol [19]. Similarly, Akkus et al [12] reported no difference in the levels of estradiol, FSH, and luteal hormone at the early follicular phase between premenopausal FMS patients and healthy women. The results were replicated with the group comparison of postmenopausal women. Another research [20] indicated that retrospective report of women with FMS indicate exacerbation of symptoms during the progression of pregnancy and by oral contraceptive use. The results of a chart review [16] suggest that the majority of FMS patients become symptomatic following natural or surgical menopause. However, these findings are at variance with observations, indicating the majority of women reporting the onset of FMS symptoms at ages between 20 and 40, [21,3] suggesting that hormonal variables associated with menopause may not be a triggering factor, at least not for all women with FMS. Results of the present study are also consistent with the data obtained by one study [22] in which levels of sex hormones and pain sensitivity at different phases of a menstrual cycle were evaluated in regularly menstruating women with FMS relative to age-matched healthy women.

Differences in methodology and sample characteristics may explain the difference between the results.

Our study groups (healthy controls and FMS) did not differ in the fluctuation of luteal hormone, follicular stimulating hormone and estrogen during mid-luteal phase of menstrual cycle. The results from the present study demonstrate that the levels of sex hormones for regularly menstruating women with FMS are fairly comparable with those for regularly menstruating pain-free healthy controls, suggesting that the higher prevalence of women for FMS is not likely to be attributed solely to abnormal levels of sex hormones.

It seems too early to conclude that HPG axis hormones have no role in FMS. HPG axis hormones exert various modulatory influences on the central nervous system, not only the hypothalamus and serotonergic system but also the cholinergic system, catecholaminergic neurons, hippocampus, and others [23]. FMS is a complex disorder with multi-levels of physical and functional problems.

Some limitations of the study need to be acknowledged. Determining single basal levels of HPG axes do not reflect activity of this axis entirely. Dynamic test indicates differences in function of this axis. We did not carry out dynamic characteristics of this axis. This point is limitation of our study. Further studies are needed to evaluate the role of HPG axis hormones in FMS women taking hormonal intervention or postmenopausal FMS patients.

CONCLUSION

In this study, we were unable to describe HPG axis hormone abnormalities in luteal phase of patients with FMS. The results suggest that the predominance of females in FMS cannot be explained by the abnormal fluctuations of sex hormones. However the role of other endocrine hormones such as melatonin, growth hormone, thyroid hormone, prolactin, Adrenocorticotrophic hormone, somatomedin C, calcitonin, prostaglandin E2, and oxytocin should also be explored in order to under the disease pathology.

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COMPETING INTERESTS

The authors declare that they have no competing interest exist.

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