Original Article

Sex hormone (FSH, Estrogen and Testosterone) changes in follicular and luteal phases and sexual dysfunction in women with Multiple Sclerosis

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Abstract

Introduction:
Multiple sclerosis is the most common cause of progressive disability in young adults who may be sexually active. MS patients experience high levels of sexual dysfunction and abnormalities in the hypothalamus-pituitary-gonadal (HPG) axis. The present study was conducted to evaluate sexual dysfunction and the relationship between serum levels of the sex hormones under scrutiny during the sexual cycle and the sexual response in women with MS.

Materials and Methods:
A total of 30 female patients with relapsing-remitting MS (RRMS) at an age range of 20 to 40 (mean age=31.46) divided into 3 groups based on their expanded disability status scale (EDSS<1.5, EDSS=1.5-3 and EDSS>3) and 30 healthy female controls (mean age=32.09) entered the study. The female sexual function index (FSFI) was used to determine the subjects' sexual dysfunction. Serum follicle stimulating hormone (FSH), estradiol and testosterone were measured in the follicular and luteal phases of the women's menstrual cycle.

Results:
Based on the findings of the study, hormonal abnormalities in MS patients consisted of decreased testosterone levels in the follicular and luteal phases, decreased estradiol and FSH levels in the luteal phase and significantly increased estradiol levels in the follicular phase of the menstrual cycle. FSFI scores including the range of sexual desire, arousal, orgasm, lubrication and sexual satisfaction were significantly decreased in the case group compared to the control group.

Conclusion:
The results showed that MS can affect serum sex hormone levels in follicular and luteal phases. A positive correlation was observed between serum levels of the examined hormones and certain domains of FSFI. Serum levels of sex hormones can therefore affect sexual function in MS patients.

Keywords: Multiple Sclerosis, Sex Hormones, FSFI, Follicular Phase, Luteal Phase

Introduction

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease affecting the central nervous system (1). Important neuroimmunoendocrine interactions have been determined in the course of the disease (2). MS is more common in women than in men, the highest prevalence rate of which has been observed between the ages of 20 and 40

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years. Affecting young adults and debilitating them during the reproductive ages, are two main characteristics of MS, and indicate the particular importance of this disease and the need for further research in various fields of MS. One of the problems of women with MS is dysfunction in hypothalamus-pituitary-gonad (HPG) axis caused by demyelination of nerve fibers and the effect of the immune system on this axis which can lead to menstrual disorders and consequently, infertility (3 and 4). However, demyelination of nerve cells, especially in the spinal cord, affects the nerve pathways controlling the sexual reflexes and orgasm, all of which reinforce the hypothesis of reproductive dysfunction in the course of this disease (2). Sexual function is a complex process influenced by various factors, such as nervous, vascular, and endocrine systems, as well as social and psychological factors, including family and sexual partner, and individual factors, such as self-concept and self-esteem. Sexual dysfunction in these patients may result from a combination of physiological, psychological, and biological conditions mainly caused by lesions in the neural pathways involved in the physiologic function. In addition, side effects of medications and physical symptoms, such as fatigue, muscle weakness, menstrual changes, pain, and concern about urinary and fecal incontinence are effective in its incidence (5 and 6). Bowel and bladder dysfunctions are associated with changes in vaginal lubrication and orgasm (7). Since the occurrence of sexual problems in patients with MS obviously affects all aspects of their lives, more attention should be focused on this aspect of the disease when evaluating the patients (8). So far, many studies have been conducted on sex hormones and sexual dysfunction in patients with MS, but none of them have scrutinized hormonal changes, sexual dysfunction, and its prevalence rate based on the Expanded Disability Status Scale (EDSS). Therefore, the present study aimed to evaluate the levels of sex hormones (FSH, estradiol, and testosterone) in follicular and luteal phases during the menstrual cycle in women with MS and also examine the sexual dysfunction according to EDSS and investigate the relationship between hormones and sexual dysfunction.

Materials and Methods

This applied quasi-experimental study was conducted on a control group (healthy people) and patients (female patients with relapsing-remitting MS). The patients were selected from women with MS aged from 20 to 40 years who were members of Shiraz Multiple Sclerosis Society. Since the highest prevalence rate of MS was observed in the age group of 20-40 years, this age range was selected (9). Women are sexually active in this age range and have menstrual cycle and fertility potential (10). The relapsing-remitting MS is the most common type of this disease that has affected approximately 85% of MS patients (1) and most of the patients referred to Shiraz Multiple Sclerosis Society were also diagnosed with this type of disease and thus, they were more easily accessible. Having the age of 20 to 40 years, being married, having relapsing-remitting MS, no relapses in the last three months, having used no corticosteroids of any kind in the last three months, having menstrual cycle, no pregnancy and lactation, having no gynecological diseases, and completing the consent form were considered as inclusion criteria. Refusing a blood test on the specified date and giving incomplete responses to the questionnaires were considered as exclusion criteria.

In addition to female MS patients, 30 healthy women aged from 20 to 40 years who matched the patient group in terms of education level, marital status, and employment status (being employed or a housewife) were selected as the control group.

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In order to assess the extent of physical disability in the patients, EDSS, which is one of the most important standards for assessing the extent or severity of the physical disability in patients with MS, was used. The final EDSS scores of the patients were determined by a neurologist and based on the results of all examinations collected in a special form. The EDSS scores of the patients were between 0 and 5.5 (mean = 5.2) and the patients were divided into three groups of 10 people based on their EDSS scores (EDSS <1.5, EDSS =1.5-3, EDSS >3).

To determine the phase of the menstrual cycle in both control and patient groups, the first day of the last menstrual period and the interval between the onset of each menstrual cycle in the previous months were asked of the individuals. Based on this information, the sampling date for each individual was determined. Days 4-8 of the menstrual cycle were considered for follicular phase, and days 20-24 were considered for luteal phase. Fasting blood samples were drawn in the morning in the Medical Laboratory of Shiraz Jahad Daneshgahi. Hormone levels were measured using ELISA.

In this study, the Female Sexual Function Index (FSFI) was used to assess participants' sexual function. This questionnaire measures women's sexual function in six independent domains, including sexual desire, sexual arousal, lubrication, orgasm, sexual satisfaction, and pain. A maximum of six scores can be given to each domain. The minimum and maximum scores are 2 and 36 in this questionnaire. The Persian version of the FSFI is a valid and reliable instrument for assessing women's sexual function.

The above-mentioned questionnaire has been used in many studies and has shown a high degree of internal consistency and reliability. In the study conducted by Mohammadi et al., the internal consistency was calculated using Cronbach's alpha coefficient for each of the six domains and the whole scale for the patient and control groups and all subjects, and an alpha of 0.7 and higher was considered acceptable (11). In the present study, a Cronbach's alpha of 0.77 was obtained.

Statistical analysis was performed between different groups using SPSS version 21. To determine if there is a significant difference between the groups, one-way ANOVA and Tukey's test were applied and to examine the relationship between the hormones and different domains of FSFI, the Pearson's correlation coefficient was used. P values less than 0.05 ($P<0.05$) were considered statistically significant. EXCEL was used to draw the graphs.

Results

In this study, serum follicle stimulating hormone (FSH), estradiol and testosterone were measured in the follicular and luteal phases of both control and patient groups (Table 1).

The results of one-way ANOVA indicated that FSH level in the luteal phase was significantly lower in the groups with EDSS=1.5-3 and EDSS>3 than in the control group. The level of FSH was also significantly lower in the group with EDSS>3 than in the group with EDSS<1.5. In other words, as the disability in the patients increases, the level of this hormone significantly decreases in the luteal phase. However, no significant difference was observed between groups regarding FSH in the follicular phase. The results of one-way ANOVA indicated that the level of estradiol was significantly lower in the luteal phase in all patient groups than in the control group, but no significant difference was observed between groups. In addition, the results showed that the level of estradiol in the follicular phase was significantly higher in the group with EDSS>3 than other groups. Serum levels of testosterone also showed a significant decrease in patients in comparison with the control group in both phases. However, the severity of the disease had no effect on the serum levels of this hormone. The analysis

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of FSFI showed that the mean total score of the control group was 28.32±2.05 and the mean total score of the patients group was 21.43 ±2.3. As for disease severity, the mean total scores of the patients were 23.37 for EDSS<1.5, 20.57 for EDSS=1.5-3, and 20.43 for EDSS>3. A significant difference was observed between the patient and control groups for domains of sexual desire, sexual arousal, lubrication, orgasm, and satisfaction (P≤0.001) and in all these domains, a significant decrease was observed in the patient group in comparison with the control group.

Table 1: Serum levels of examined hormones in the follicular and luteal phases in women with MS and healthy control subjects

Hormone		Luteal phase				Follicular phase			
	Group	Mean	Standard deviation	F-value	P-value	Mean	Standard deviation	F-value	P-value
Follicle stimulating	Control	5.8	2.6	9.2	0.001	4.8	1.3	1.5	0.2
	EDSS<1.5	5.05	1.6			3.5*	1.7		
	EDSS=1.5-3	3.5*	1.3			5.1*	1.4		
	EDSS>3	2.07*	0.6			4.7*	2.2		
Estradiol	Control	132.7	52.08	8.9	0.001	27.4	12.09	21.1	0.001
	EDSS<1.5	57.7*	59.09			41.6	16.3		
	EDSS=1.5-3	57.4*	30.03			67.8	34.6		
	EDSS>3	37.6*	28.2			*†‡149.8	63.7		
Testosterone	Control	0.78	0.1	6.8	0.001	0.65	0.2	5.2	0.004
	EDSS<1.5	0.44*	0.3			0.37*	0.1		
	EDSS=1.5-3	0.45*	0.2			0.44	0.1		
	EDSS>3	0.36*	0.1			0.39*	0.1		

* Significant difference in comparison with the control group (P<0.01)
† Significant difference in comparison with the group with EDSS <1.5 (P<0.01)
‡ Significant difference in comparison with the group with EDSS=1.5-3 (P<0.01)

However, no significant difference was observed between the patient and control groups in the domain of pain (P=0.1). The severity of disability in patients had no effect on satisfaction and speed of reaching orgasm. However, an increase in the severity of disability in patients showed a greater decrease in lubrication.

According to the results obtained from the Pearson's correlation coefficient, there is a positive relationship between FSH and the sexual desire (Diagram 1), in that as FSH increases in the luteal phase, the level of sexual desire significantly increases in these patients (r =0.682 and P = 0.030).

Diagram 1: Point diagram and the assessment of the type and degree of correlation between FSH in the luteal phase in MS patients with EDSS<1.5 and the degree of sexual desire in the FSFI

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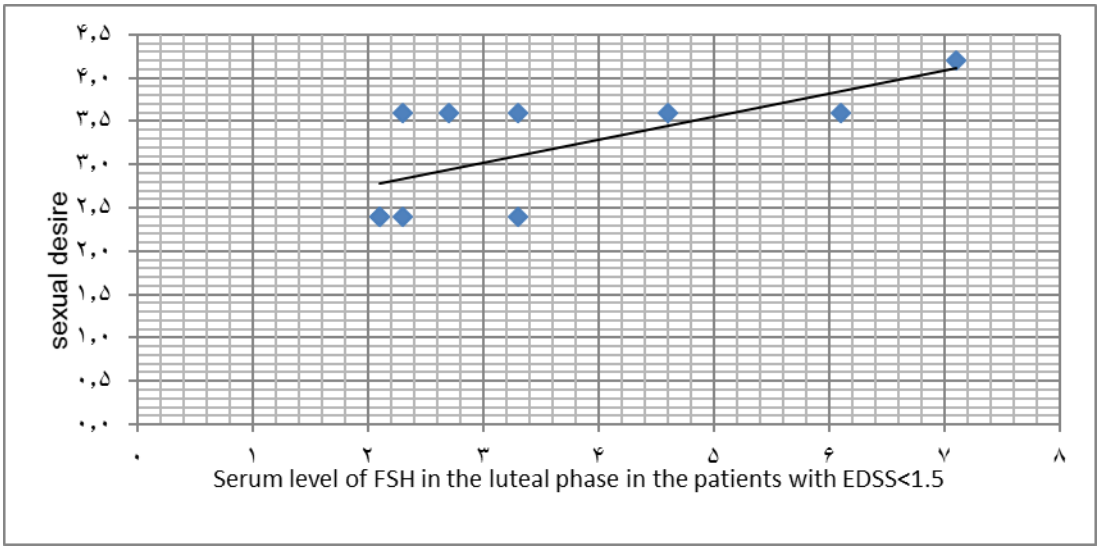
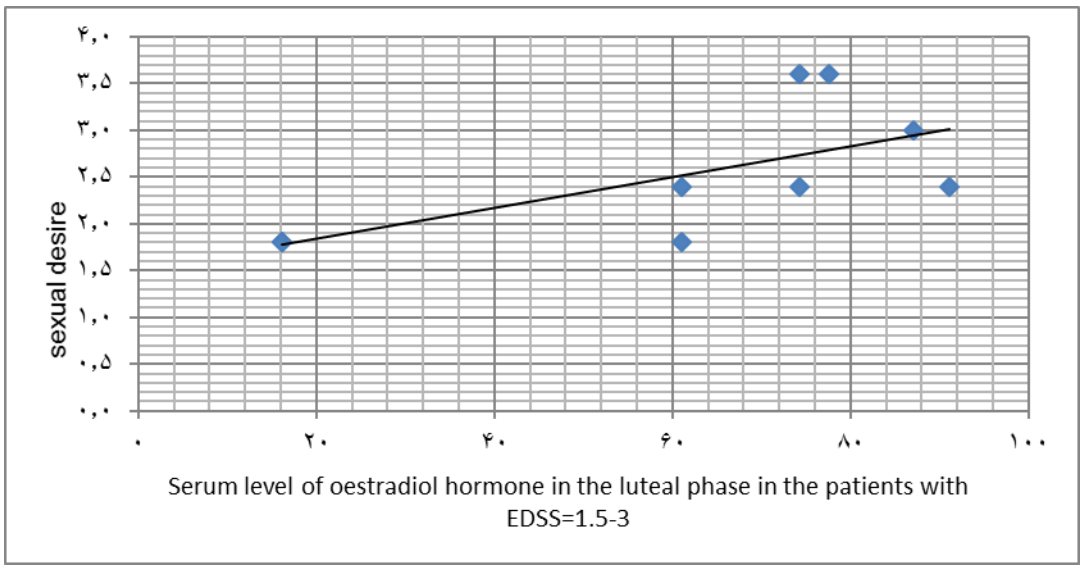


Based on the Pearson's correlation coefficient, a positive correlation was observed between the serum levels of estradiol in the luteal phase and the level of sexual desire in the patients with EDSS=1.5-3 (Diagram 2), in that as the serum estradiol increases in the luteal phase in the patients, the level of sexual desire significantly increases (r =0.691 and P=0.027).

Diagram 2: Point diagram and the assessment of the type and degree of correlation between estradiol in the luteal phase in MS patients with EDSS=1.5-3 and the area of sexual desire in the FSFI



A positive correlation was also observed between the serum levels of testosterone and lubrication as well as the speed of reaching orgasm in the patients, in that as the serum levels of testosterone increased, the amount of lubrication and the speed of reaching orgasm in the patients significantly increased (lubrication p=0.030 and r =0.682) and (orgasm p=0.036 and r =0.666).

Discussion

The present study confirms the hypothesis that MS and different intensities of this disease probably affect the serum levels of sex hormones (FSH, estrogen, and testosterone) in the follicular and luteal phases of menstrual cycle of patients. This disease also affects the sexual function of female patients and thus their reproductive ability.

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Tomassini et al. 2005 studied 35 MS women and 18 healthy women as the control group, and reported a reduction in the serum FSH in the patients in comparison with the control group in both follicular and luteal phases, but the difference was not significant (12). In another study conducted on patients with MS, amenorrhea was reported to accompany a reduction in the FSH due to hypothalamus damage (13). However, in a study conducted by Zakrzewska-Pniewska et al. on 46 women with a definite diagnosis of MS to examine the hormonal disorders and their relationship with the course of MS, it was found that 56% of patients had hormonal disorders, particularly increased levels of estradiol. There was a correlation between hormonal disorders and MRI changes, but no correlation was found with the changes in the hypothalamus and disease parameters, such as EDSS, relapse rates, and duration of disease, (14) which corresponds to the findings of the present study. This study showed that the testosterone level in follicular and luteal phases in women with MS was lower than in the healthy individuals, but the degree of disability had no effect on testosterone level. Similar results were found in a study that reported serum testosterone level was significantly lower in women with MS in both phases of the menstrual cycle (follicular and luteal) than in healthy people and there was a correlation between the concentration of testosterone, tissue damage and clinical disability. In addition, female patients with lower testosterone levels had more brain lesions in MRI compared with female patients with normal testosterone levels (12). In a recent study conducted by Foroughi et al. 2012, testosterone levels decreased in follicular and luteal phases in women with MS in comparison with the control group (15). Since estradiol (E2) is produced from testosterone in granulose cells during steroidogenesis in the ovary, a reduction in testosterone can lead to a reduction in estradiol in the luteal phase (12). In addition, testosterone can affect estrogen receptors either directly or through changing into estrogen by aromatase (16). In the present study, decreased testosterone in the luteal phase may have led to a decrease in estradiol. Androgens potentially affect women's sexual function, particularly their sexual desire. Androgen deficiency is among factors causing sexual dysfunction, especially decreased sexual desire (17 and 18). The effects of reduced testosterone levels on the sexual function of the patients with MS are beyond the sexual desire and testosterone therapy improves sexual desire, arousal, orgasm, and sexual satisfaction in women with sexual problems (19). A combination of estradiol and testosterone can restore menopausal women's sexual desire, but its mechanism is unknown (20). In the present study, there was a significant decreased sexual desire in the patients compared with the control group and the disease severity also had an effect on the decreased level of sexual desire which can be caused by a decrease in serum testosterone levels and the existence of a positive correlation between that and sexual desire.

In this study, interesting results were obtained regarding the relationship between hormonal disorders and sexual dysfunction. Among these, a positive correlation was observed between serum FSH levels and sexual desire, arousal, and satisfaction. A positive correlation was observed between serum estradiol levels and sexual desire. Estradiol plays an important role in women's sexual function, particularly reproductive tissue survival. The effects of estradiol deficiency on sexual function are complex (21). Estradiol paves the way for increased blood flow to vagina by vasodilation and leads to congestion in the genital organ and vaginal moisture. The deficiency of this hormone can cause thinning of the vaginal epithelium, loss of elasticity, a reduction in vaginal lubrication, and consequently vaginal dryness,

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dyspareunia, and decreased sexual desire (22). According to Hays, the sexual desire decreases in patients with vasomotor symptoms and insomnia due to painful intercourse or genital atrophy and the use of estrogen supplements in these patients can increase sexual desire, although its role has not been well known in enhancing sexual desire and arousal (23, 24). In the present study, no positive correlation was found between estradiol levels in the luteal phase in patients with EDSS =1.5-3 and sexual desire. In other words, as estradiol levels increased, sexual desire also enhanced which is consistent with previous studies.

For more severe cases, a positive correlation was observed between testosterone levels and the amount of lubrication and the time of reaching orgasm, in that increased serum levels of this hormone in patients with EDSS=1.5-3 were associated with an increase in the amount of lubrication. A positive correlation was also observed between increased serum testosterone and the speed of reaching orgasm in patients with EDSS>3. The results showed that testosterone can affect the amount of lubrication and the speed of reaching orgasm, especially at more severe conditions of the disease. Davis et al. also reported that the use of testosterone and its derivatives for a short time can enhance sexual desire and reaching orgasm which itself can confirm the existence of a positive correlation between testosterone levels and reaching orgasm (25). However, in a study by Lombardi et al. 2010, no significant correlation was observed between serum levels of sex hormones and different domains of FSFI (26). This contradiction may be due to the difference in the assessment of patients. As mentioned, patients in the present study were divided into different groups based on the severity of the disease which can increase the accuracy of the study results.

According to the present study, MS can affect serum levels of sex hormones in the follicular and luteal phases and lead to hormonal imbalances. Serum levels of sex hormones also affect various aspects of patients' sexual function and their fertility and those patients suffering from more severe disabilities will have more hormonal disorders and sexual dysfunction.

There is little research on the relationship between sex hormones and sexual dysfunction and further studies with larger sample size and on different forms of MS (primary progressive, secondary progressive, and relapsing progressive forms) are needed.

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