

The variation in chronic widespread pain and other symptoms in fibromyalgia patients. The effects of menses and menopause

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Abstract

Objectives

We determined the relationship between the menstrual cycle and fibromyalgia (FM) symptoms in premenopausal women. In addition, we compared the clinical features of FM patients diagnosed pre-and postmenopausally.

Methods

We included 80 premenopausal, and 72 postmenopausal patients with FM. All patients were questioned about the severity of their pain and symptoms of FM by using a visual analog scale (VAS). In addition, the patients were asked questions about symptoms of somatization, depression and anxiety. Postmenopausal subjects were asked about the change in their FM symptoms with the onset of menopause; and premenopausal subjects were asked whether their FM symptoms changed during the menses. In addition, 40 premenopausal patients were requested to fill in a diary about their FM symptoms using VAS throughout one menstrual cycle.

Results

Postmenopausal patients had more severe pain on VAS ($p = 0.048$). Of all the postmenopausal females, 25% said that their FM symptoms started with the onset of menopause and 26.4% said that the severity of their previous symptoms increased after menopause. Of all the premenopausal females, 45% admitted to higher pain severity and 57.5% to a higher fatigue severity during the menses. The patients who defined an increase in their symptoms during the menses were the ones with higher sleep disturbance scores, more somatization symptoms and more tender points (p values < 0.05). The results of the diaries revealed that the mean pain and fatigue scores in the menstrual and luteal phases were higher than the scores in the follicular and premenstrual phases (p values < 0.05).

Conclusions

The menstrual cycle and the onset of menopause affect pain and the severity of other FM-related symptoms in approximately one half of the subjects.

Key words

Fibromyalgia, chronic widespread pain, menstrual cycle, menopause, menses.

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Introduction

Females tend to exaggerate many clinical diseases associated with pain (1). Fibromyalgia (FM) is mostly seen in females and the female/male ratio is about 10/1. In any healthy population, females complain of recent pain and pain in a greater number of body regions more than males (2,3). Experimental studies generally showed that pain hypersensitivity is more frequent in females (1,4). Several authors suggested that psychological factors might explain the higher frequency of pain sensitivity in females (5). However, one of the most important factors which explains the difference in the perception of pain between males and females is the role played by gonadal sex hormones (6). Exacerbation of certain medical conditions at specific phases of the menstrual cycle is a well-recognized phenomenon (7). Hormonal changes are observed throughout the menstrual period and this makes changes in a large range in both the peripheral and the central nervous system (6). In addition, different studies reported differences in the perception of pain of various periods of the menstrual cycle (8,9). However, all those studies report quite different, contradictory results (10).

In our study, we evaluated the effects of menopausal status and the menstrual cycle on the symptoms in order to determine the role of hormonal factors in women with FM.

Patients and methods

Eighty regularly menstruating premenopausal and 72 postmenopausal females diagnosed with FM at the Rheumatology Department of Trakya Medical Faculty were included in the study. All the patients were diagnosed with FM according to ACR 1990 criteria (11). The patients were questioned about their menstrual cycles. Patients using oral contraceptives or hormonal replacement therapy, those having irregular menses, and those who had another systemic disease other than FM that could explain the chronic widespread pain (CWP) were not included in the study. All the premenopausal subjects had normal menstrual cycles

(26-31 days). Verbal consent was obtained from prospective participants and all the patients agreed to complete the questionnaires. All the patients were questioned about the severity of their CWP, fatigue (0-100), paresthesia, sleep disturbance (0-10) by using a visual analog scale (VAS), the duration of CWP (years) and morning stiffness (min.). In addition, the patients were asked questions about the history of any psychiatric treatment. All the patients underwent physical examination and their tender points were determined.

The functional items of the FM impact questionnaire (FIQ) were asked to all the patients. Sarmer *et al.* (12) performed the Turkish validation and reliability of the FIQ score. The reliability and validity of FIQ in Italian and in Spanish has been confirmed in recent studies (13,14). In order to detect a somatization disorder, the somatic symptom checklist consisting of 6 items was asked (15). This scale includes: trouble in breathing, frequent vomiting, loss of voice for more than 30 minutes, being unable to remember what you had done for hours or days (without any intake of alcohol or drugs), difficulty in swallowing, and frequent pain in the fingers or toes. There is an additional item for females – frequent trouble with menstrual cramps. This checklist was originally validated as a screening test for somatization disorders. These symptoms are included in the American Psychiatric Association criteria for somatization disorders (16). In order to avoid spurious associations with persistent CWP, only non-pain somatic symptoms were examined (i.e. frequent trouble with menstrual cramps and frequent pain in the fingers and toes were excluded). Therefore, the total score was between 0 and 5.

The Duke anxiety-depression scale (Duke-AD) has been validated as a screening instrument for anxiety and depression (17) and it is a subscale of DUKE which contains 7 items. The Duke-AD scale was translated into Turkish by two authors. The back translation of the questionnaire to English was performed by an independent translator. The initial and final English

version were concordant with one another. However, the formal validated form of the translated version is not present.

Eighty patients (who later) had regular menstrual cycles were questioned about the variation in their CWP throughout their menses. Forty of these premenopausal patients were asked to keep diaries about their FM symptoms. These patients also kept diaries about their severity of CWP, fatigue, unrestorative sleep by using VAS (0-10) and sleep duration (hour) and morning stiffness (minute) during the menstrual cycle. The menstrual cycle has 4 phases including the menstrual (1-7 days), follicular (8-14 days), luteal (15-21 days) and premenstrual phases (22-28 days). The postmenopausal patients were asked whether there was a change in the character of their CWP after the menopause.

Chi-square, unpaired and paired t-tests were used for statistical analysis.

Results

The demographic and clinical features of regularly-menstruating premenopausal and postmenopausal patients are seen in Table I. Smoking was more frequent among the premenopausal patients; and a higher proportion of postmenopausal subjects were divorced and had a history of previous psychiatric treatment (Table I). In addition, the severity of CWP on VAS was higher and the duration of CWP was longer in postmenopausal women than in premenopausal patients (p values respectively, 0.048 and 0.024) (Table I).

Eighteen (25%) of 72 postmenopausal females admitted that their symptoms of CWP and FM started after menopause, and 19 (26.4%) stated that their premenopausal symptoms increased after the menopause. Thirty-five patients noticed no change in their FM symptoms after the menopause.

Thirty-eight of the 80 (47.5%) premenopausal patients who were questioned claimed that the severity of their CWP was variable throughout the menses. During the menses, the intensity of CWP increased in 36 patients (45%), the intensity of pain decreased in 2 patients (2.5%). In addition, 46 patients

Table I. Comparison of the demographic and clinical features of postmenopausal and regularly-menstruating patients.

	Premenopausal women	Postmenopausal women	p
n	80	72	
Age	36.6 ± 8.3 (15-49)	54.4 ± 7.7 (42-74)	
Smoking, n (%)	30 (37.5)	12 (16.7)	0.004
Married, n (%)	69 (86.3)	65 (90.3)	NS
Divorced, n (%)	2 (2.5)	6 (8.3)	0.017
Previous psychiatric therapy, n (%)	30 (38.5)	39 (54.1)	0.048
Previous NSAID therapy, n (%)	56 (70)	48 (66.7)	NS
Alcohol, n (%)	4 (5)	0	NS
University degree, n (%)	17 (21.3)	7 (9.7)	
Education duration < 8 years	35 (43.8)	42 (58.3)	NS
Duration of pain (years)	4.28 ± 4.7	6.5 ± 7.1	0.024
Severity of CWP (0-100)	50.3 ± 19.6	56.5 ± 18.8	0.048
Sleep disturbance (0-10)	5.78 ± 2.92	6.16 ± 2.7	NS
Unrestorative sleep (0-10)	7.245 ± 2.2	7.04 ± 2.48	NS
Paresthesia (0-10)	5.3 ± 2.68	5.14 ± 2.36	NS
Fatigue severity (0-100)	55.6 ± 25.4	49.7 ± 26.83	NS
Morning stiffness (min.)	27.0 ± 1.29	27.61 ± 1.14	NS
FIQ physical function score (0-3)	1.14 ± 0.68	1.16 ± 0.64	NS
Duke anxiety depression score (0-14)	6.74 ± 2.71	6.81 ± 2.21	NS
Total somatization symptom (0-5)	2.61 ± 1.6	2.1 ± 1.65	NS

NS: not significant.

(57.5%) reported an increase in the intensity of fatigue, 27 (33.8%) in morning stiffness, 34 (42.5%) in unrefreshing sleep and 22 (27.5%) in sleep disturbance during the menstrual period. When the features of subjects who admitted to an increase in the severity of their pain during the menses were compared to those who had no increase, the former group had a higher sleep disturbance score (p=0.04), a higher number of somatization symptoms (p=0.01), and more tender points (p=0.03). The comparison of the general features of the two groups is seen in Table II. Of all the patients who reported an increased intensity of pain during the menses, 11 had it on the first two days of the menses, 8 had it on the 2 days before the menses, 6 had it on the all of the days of the menses, 11 had it both on the 2 days before and also on the first 2 days of the menses.

Eighteen of the 40 patients (45%) who were asked to fill in diaries completed their diaries. On the initial interrogation, 10 of them defined a change in

pain during the menses. There was no difference when the baseline features (like age, symptom scores) of patients who completed and did not complete their diaries were compared (all p values >0.05). The mean values of the symptom scores during the menses according to diary results are seen in Table III. It was observed that the CWP and fatigue scores during the menses and luteal phases was significantly higher than those in the follicular and premenstrual phases (all p values < 0.05) (Table III). The score for morning tiredness was higher in the menses than in the premenstrual phase (p = 0.017).

Discussion

In our study, the severity of pain in postmenopausal FM patients was higher. In addition, the FM symptoms in 25% of postmenopausal FM patients had started with the onset of menopause and in 26.4% the severity of already present FM symptoms increased. Although the finding of a lower pain threshold in ovariectomized rats sup-

Table II. The comparison of the general features of patients who reported and who did not report an increase in the intensity of widespread pain during the menses.

	Subjects with no increase in pain during the menses	Subjects with an increase in pain during menses	p
n	42	36	
Age (yrs)	37.4 ± 8.6	35.8 ± 7.9	NS
Smoking, n (%)	17 (40.5)	13 (36.1)	NS
Previous psychiatric therapy, n (%)	14 (33.3)	15 (41.7)	NS
Duration of CWP, yrs	5.2 ± 5.8	3.3 ± 2.8	NS
Severity of CWP (0-100)	49.5 ± 20.7	50.4 ± 17.6	NS
Sleep disturbance (0-10)	5.01 ± 2.8	6.3 ± 2.9	0.04
Unrestorative sleep (0-10)	6.8 ± 2.4	7.8 ± 2.1	NS
Paresthesia (0-10)	5.2 ± 2.8	5.3 ± 2.6	NS
Severity of fatigue (0-100)	51.3 ± 26.1	59.2 ± 4.3	NS
Morning stiffness (minute)	25 ± 12	29.2 ± 13.6	NS
FIQ functional score (0-3)	1.07 ± 0.74	1.25 ± 0.6	NS
Duke anxiety-depression score (0-14)	6.36 ± 2.7	7.4 ± 2.8	NS
Total somatization symptom (0-5)	2.2 ± 1.4	3.3 ± 1.6	0.01
The number of tender points	12.3 ± 2.1	13.5 ± 2.4	0.03

NS: not significant.

Table III. The distribution of FM-related symptoms in the menstrual cycle phases.

	Menstrual phase	Follicular phase	Luteal phase	Premenstrual phase
Widespread pain (0-10)	5.32 ± 1.92 ^{a,b}	3.94 ± 1.98	4.95 ± 1.85 ^{c,d}	4.22 ± 1.92
Fatigue (0-10)	4.51 ± 2.14 ^e	3.62 ± 2.12	4.42 ± 1.85 ^f	3.72 ± 2.39
Unrestorative sleep (0-10)	4.09 ± 2.37 ^g	3.26 ± 2.15	4.01 ± 2.28	3.46 ± 2.5
Morning stiffness (min.)	25.41 ± 42.6	18.8 ± 32.9	19.24 ± 32.9	18.8 ± 31.2
Sleep duration (hrs)	7.53 ± 1.14	7.41 ± 1.06	7.05 ± 0.93	7.46 ± 1.04

^a p = 0.005 menstrual phase different from follicular phase.^b p < 0.001, menstrual phase different from premenstrual phase.^c p = 0.005, luteal phase different from follicular phase.^d p = 0.024, luteal phase different from premenstrual phase.^e p = 0.014, menstrual phase different from premenstrual phase.^f p = 0.019, luteal phase different from follicular phase.^g p = 0.017, menstrual phase different from premenstrual phase.

ports our results, there are studies with contradictory results to ours (18, 19). A recently reported population-based study stated that CWP was not related to age at menopause (20). However, in half of our patients, FM symptoms either appeared or increased in intensity with the onset of menopause.

In our study, an important proportion of our premenopausal patients reported an increase in the intensity of pain and fatigue during the menses. This result shows that symptoms in FM patients are affected to a great degree by the menstrual period. Other studies on FM

stated that the symptoms increased in intensity in the perimenstrual period, in pregnancy and in the postpartum period in most of the cases (21, 22). However, experimental data and results of meta-analyses in humans suggest that the most important factor in the response to and perception of pain is sex difference, independent of the hormonal status, and that the effects of the menstrual cycle and hormones are to a lesser degree (1, 4, 6, 9). In addition, it might be assumed that the effects of gonadal hormones are only partial because, apart from sex difference, psy-

chological factors like cognitive and affective status, anxiety and pain coping have important effects on pain perception and sensitivity to pain (6). Consequently, we might say that the hormonal changes in the menstrual cycle affect the pain threshold and the response to pain; however, the formation of pain is a complex event affected by many factors, and the hormonal effect might be prominent in only a certain subgroup of patients. Therefore, the detection of subgroups whose symptoms are mostly affected by changes in the hormonal and menstrual cycle gains importance (6). Our FM patients with a higher intensity of pain during their menses were those who had more prominent sleep disturbance, those who had higher somatization scores and those who had more tender points. Making such a distinction between subgroups and their features might be important in deciding about hormonal treatment modalities. One study on FM patients found that the number of tender points was greater in the follicular phase when compared to the luteal phase. However, this difference was not observed among patients who used oral contraceptives (23). As a result, it seems likely that hormonal treatment modalities would be effective in the therapy of certain subgroups of chronic pain-related conditions.

When we considered the results of the diaries, the severity of pain and fatigue in the menstrual and luteal phases was seen to be significantly higher than in the other phases. Although different studies reported an increase in the perception of pain in the premenstrual phase, during ovulation and in the period following menstruation (8, 23-25), some studies did not observe any change in the perception of pain throughout the menstrual cycle (10). One meta-analysis of these studies showed that painful stimulation caused a higher pain threshold and tolerance in the follicular phase when compared to the luteal phase. However, it reported that the effect of the menstrual cycle was small to moderate (9). Most clinical studies in patients with chronic pain-related disorders stated that the effects of the cycle on pain symptoms

are most prominent in the luteal and menstrual phases similar to our study (7). Studies on the FM patients have put forward that there is an increase in symptoms in the perimenstrual symptoms (22).

There are three main limitations of our study. The first is the drawback of comparing premenopausal and postmenopausal patients. We tried to minimize this by excluding postmenopausal patients who had any disease that might cause CWP. However, undiagnosed degenerative musculoskeletal diseases might have contributed to the higher pain intensity in this group. The second drawback was that an important proportion of patients asked to keep diaries was lost to follow-up. This effect was minimized by the similarity of the initial features of the patients who kept and did not keep diaries. The third limitation of our study was that controls were not included; it might have been helpful to compare physical and psychological changes during the menses and menopause between FM patients and normal women, in order to understand if these parameters were influenced by FM. Nevertheless, instead of taking real controls, we considered the results of previous studies about the effects of the menses on pain and fatigue in normal women.

Consequently, our postmenopausal FM patients felt more pain when compared to our premenopausal FM patients and, in one fourth of those patients, FM started after the menopause. Almost one half of our premenopausal FM patients reported an increase in pain and in other symptoms – especially fatigue – during their menses. When the results of the diaries were considered, the severity of pain and fatigue increased in the menstrual period, as described by the patients, and also in the luteal phase. Our results suggest that physicians should take into account the ef-

fects of the menopause and the menstrual cycle on the perception of pain in female subjects. However, it is known that pain in FM has a chronobiology which varies from season to season and even within a 24-hour period. In addition to the hormonal effect of oestrogen and progesterone on pain, the circadian rhythms of the hormones of the hypothalamic-pituitary axis, or season fluctuations in levels of serotonin might also be important.

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