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Effect of familial Mediterranean fever on sexual and reproductive health in women

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Background/aim: The aim of this study was to investigate the relationship between familial Mediterranean fever and female sexual dysfunction and premenstrual syndrome.

Materials and methods: This study included 36 patients with familial Mediterranean fever and 33 healthy volunteers. Familial Mediterranean fever was diagnosed according to the Tel Hashomer criteria and familial Mediterranean fever mutations were identified in all of the patients. The patients and healthy volunteers were compared in terms of anxiety, depression, sexual dysfunction, and premenstrual syndrome, and a model was created that describes the relationships among these variables.

Results: We found statistically significant differences between the groups in terms of anxiety, premenstrual syndrome, and Golombok Rust Inventory of Sexual Satisfaction frequency and vaginismus subscale scores. There was no difference in depression scores between the groups.

Conclusion: Familial Mediterranean fever is a rheumatic disease that predisposes patients to sexual dysfunction and premenstrual syndrome, which emerges as direct and indirect psychological factors.

Key words: Familial Mediterranean fever, premenstrual syndrome, sexual dysfunction

1. Introduction

Familial Mediterranean fever (FMF) is an inherited autoinflammatory disease. The prevalence of FMF in Middle Eastern populations and other ethnic groups living around the Mediterranean basin, such as Jews, Armenians, Turks, and Arabs, is 1/200–1/1000 (1,2). The clinical manifestations include recurrent, self-limiting episodes of fever and painful polyserositis, particularly peritonitis, pleuritis, and arthritis; nausea and vomiting; common weakness; and chest and joint pain (3,4).

In the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5), female sexual dysfunction (FSD) includes sexual interest/arousal disorder, orgasmic disorder, genito-pelvic pain/penetration disorder, substance/medication-induced sexual dysfunction, and other specified and unspecified sexual dysfunctions (5). It is a highly prevalent problem that is often underestimated in the general population (6).

Another common clinical presentation in women with FMF is premenstrual symptoms (7), which is defined as a set of affective, cognitive, and physical symptoms during the premenstrual phase of the menstrual cycle (8). The most common premenstrual symptoms are low mood, tension, bouts of anger or irritability, mood swings, headache, abdominal distention, and appetite and sleep disturbances (9). Its prevalence has been reported as 3%–8% (10,11).

Studies have shown that chronic rheumatic diseases negatively affect female sexual function and premenstrual symptoms (12,13). The drugs used in the treatment of chronic rheumatic diseases, the pathogenesis of the rheumatic disease, and disease-caused psychosocial factors can trigger new cases of premenstrual symptoms and FSD or aggravate existing cases (14,15). Female sexual function has not been studied sufficiently in patients with FMF, and there are few studies regarding the relationship between FMF and premenstrual syndrome. As such, the aim of this study was to investigate the effects of FMF and depression/anxiety associated with FMF on female sexual function and premenstrual symptoms.

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2. Materials and methods

This study was organized jointly by the Rheumatology Department, outpatient clinics, and Psychiatry Department of Ankara Atatürk Training and Research Hospital, a tertiary care hospital. The protocol was approved by the ethics committee of Yıldırım Beyazıt University (Ankara Atatürk Training and Research Hospital is affiliated with Yıldırım Beyazıt University, Faculty of Medicine) and conducted in accordance with the Declaration of Helsinki and the Guideline for Good Clinical Practice. Written informed consent was obtained from the participants.

2.1. Participants and procedure

FMF was diagnosed according to the Tel Hashomer criteria (16) in 36 female patients admitted to the Ankara Atatürk Training and Research Hospital Rheumatology Outpatient Department. Mediterranean fever mutations were identified in all of the patients (Table 1). Other research inclusion criteria were as follows: 18–50 years of age, married or sexually active. The exclusion criteria of the research were the presence of abdominal pain attack, comorbid medical conditions, diagnosis of psychiatric disorder in the previous 6 months, and regular use of drugs or substances other than colchicine or contraception medication. Thirty-three healthy volunteers matched for age and education level (education levels were determined according to the last schools from which they graduated) were recruited using the same criteria.

Severity of depression and anxiety, which are considered to have an impact on sexual function, and premenstrual symptoms were determined by a scale. The severity of premenstrual symptoms and sexual dysfunction were evaluated by the same method. All scales were self-report questionnaires and were introduced to the participants before being filled out. The scales were applied in an appropriate environment considering the privacy of the participants and participants were given up to 30 min to complete them. The theory about the relationship between these measured variables and FMF was statistically tested.

2.2. Data collection instruments

2.2.1. Beck Depression Inventory (BDI)

This scale was developed by Beck in 1961 to determine risk of depression and to assess the level and severity of changes in depressive symptoms. A Turkish validity and reliability study of the BDI was conducted in 1988 by Hisli. The scale contains 21 items, and each item is assigned a score of 0–3 based on four self-assessment options (17,18).

2.2.2. Beck Anxiety Inventory (BAI)

This scale, developed by Beck and colleagues, is a self-rating scale used to determine the severity of anxiety symptoms. This scale consists of 21 items and it is scored on a Likert-type scale of 0–3. A Turkish validity and reliability study of the BAI was conducted in 1998 by Ulusoy et al. (19).

2.2.3. Premenstrual Assessment Form (PAF)

This 95-item self-report scale is used to measure emotional, behavioral, and physical changes that might occur during the premenstrual period. The PAF was developed by Halbreich et al. (20), and a Turkish validity and reliability study was conducted by Dereboy et al. (21). The PAF was used to assess the severity of premenstrual symptoms.

Table 1. *MEFV* gene mutations in FMF patients.

Mutations	N	%
M694V (homozygous)	10	27.8
M694V (heterozygous)	5	13.9
E148Q (homozygous)	8	22.2
E148Q (heterozygous)	2	5.6
M680I (heterozygous)	2	5.6
M694I (heterozygous)	2	5.6
M694V/V726A (compound heterozygous)	2	5.6
M694V/M680I (compound heterozygous)	1	2.8
M680I/R761H (compound heterozygous)	1	2.8
R202Q (heterozygous)	1	2.8
E148Q/P369S (compound heterozygous)	1	2.8
M694V/E148Q (compound heterozygous)	1	2.8

2.2.4. Golombok Rust Inventory of Sexual Satisfaction (GRISS) (women's form)

This scale, developed by Rust and Golombok, provides information regarding seven areas (frequency, communication, satisfaction, avoidance, touch, vaginismus, and anorgasmia) of sexual function (22). A Turkish validity and reliability study of the scale was conducted by Tuğrul et al. (23).

2.3. Statistics

The statistical significance threshold was considered to be $P < 0.05$. The distribution of variables was assessed by the Shapiro–Wilks test and the Mann–Whitney U test was used for comparisons. A model was created describing the effects of FMF on anxiety, depression, PMS, and sexual function. The significance of the model was examined by path analysis. The effect size was calculated by considering group means, assuming alpha of 0.05 and power of 0.80.

In the path analysis, we examined how sexual function, anxiety, depression, and PMS are associated with FMF. Path analysis can be used to describe the effects of exogenous variables (group and depression) on endogenous (vaginismus, frequency, anxiety, PMS) variables directly, indirectly, and by the sum of these variables. Path analysis enables an easy understanding of these effects by visualization in a path diagram. Exogenous variables in the model are those that are not explained by any variable. Endogenous variables in the model are those that are explained by exogenous variables or other endogenous variables (anxiety was both endogenous and exogenous in our study) (24,25). Path analysis can predict that the equations system determines all causal links in a variables system, solves complex relationships between variables, and clearly reveals the strength of the relationship (26). Suhr stated that if a path coefficient value is smaller than 0.10, there is the presence of a weak effect; if a path coefficient value is between 0.10 and 0.50, there is the presence of a moderate effect; and if a path coefficient value is greater than 0.50, there is the presence of a strong effect (27).

3. Results

There were no statistically significant differences between the groups in terms of age and educational level (age: $M_{FMF} = 38.5$, $SD_{FMF} = 6.9$, $M_{Controls} = 36.3$, $SD_{Controls} = 6.1$, $t(68) = 1.405$, $P = 0.165$; education: χ^2 (2) = 0.648, $P = 0.723$). All of the FMF patients in this study had been using colchicine. The mean duration of colchicine use was 5.9 ± 7.1 years. Thirteen of the patients with FMF (36.1%) were using colchicine at 1 mg/day and 23 of the patients with FMF (63.9%) were using colchicine at 1.5 mg/day. We did not find a significant difference between patients with FMF using colchicine at 1 mg/day and patients with FMF using colchicine at 1.5 mg/day in terms of BAI, BDI, PAF, and GRISS total and subscale scores. We found statistical differences between groups in terms of BAI total score, PAF total score, GRISS total score, and frequency and vaginismus scores (subscales of GRISS). There were no differences between groups in terms of BDI total score or GRISS communication, satisfaction, touch, avoidance, and anorgasmia subscale scores. Comparisons between the total scale and subscale scores of the groups are shown in Table 2. We used the 19th item of the BDI as an indirect indicator of disease severity. When the 19th item was compared between groups, there was no statistical difference ($Mdn_{FMF} = 0$, $Mdn_{Controls} = 0$, $U = 490$, $P = 0.090$).

A model was established that included statistically significant variables between the two groups. The variables included groups (FMF and healthy control groups), GRISS frequency and vaginismus subscales, BDI, BAI, and PAF. The Figure shows the described model. According to the model, the group variable was found to have an effect on the GRISS frequency and vaginismus subscale variables, independent of anxiety and depression levels. In addition, it had no direct effect on premenstrual syndrome, but it was observed to have an effect on total PAF score (increased level of anxiety). The group variable had no effect on depression, but depression scores had a significant effect on total PAF score. The values of the fitness of the model are CMIN = 9.129; DF = 9; CMIN/DF = 1.014; P = 0.425; GFI = 0.956; IFI = 0.999; CFI = 0.999; and RMSEA = 0.015.

4. Discussion

Our path model showed a perfect fit. One of the most important results obtained from our study is that FMF moderately increased the GRISS frequency and vaginismus subscale scores. Previous studies have shown that psychological factors caused by rheumatic disease can cause sexual dysfunction (12). Similarly, other studies have suggested that rheumatic diseases can directly (28) or indirectly (29,30) cause physical effects on sexual function (31). Although it has been reported that autonomic neuropathy caused by amyloidosis may lead to impotence in men (32), there is not enough information about the direct effects of FMF on female sexual function in the literature. According to our model, anxiety and depression levels cannot explain the sexual dysfunction. Therefore, another psychological factor is probably responsible. It can be said that this psychological factor is anxiety sensitivity. FMF is a disease characterized by episodes of abdominal pain, which can adversely affect functionality (33,34). Patients might avoid situations that cause this pain (35), and patients with FMF may exhibit avoidance or precautionary behaviors, believing that they can reduce or stop pain in this way. Some studies have suggested that exercise and emotional factors might increase episodes of pain in patients with FMF (36). In addition, although

Table 2. Comparison between groups in terms of anxiety, depression, sexual dysfunction, and premenstrual syndrome.

	Groups	n	Median	IQR		Z	P	d
				25th	75th			
BAI	P_{FMF}	36	19	10.5	29.0	−4.418	<0.001	1.46
	HC	33	7	1.5	13			
BDI	P_{FMF}	36	13.5	7.25	20.0	−1.732	0.083	0.37
	HC	33	10	5	14.5			
PAF	P_{FMF}	36	208.5	161.7	262.7	−2.883	0.004	0.43
	HC	33	154	127	201.5			
GRISS	P_{FMF}	36	40.5	34.0	50.75	−2.019	0.043	0.73
	HC	33	36	22.5	47			
Frequency	P_{FMF}	36	6	2	12	−2.786	0.005	0.78
	HC	33	4	1	5			
Communication	P_{FMF}	36	5.5	3	7	−1.126	0.260	0
	HC	33	4	3	6			
Satisfaction	P_{FMF}	36	5	3	7	−0.924	0.355	0.33
	HC	33	4	2	7			
Avoidance	P_{FMF}	36	4.8	2	7	−0.459	0.646	0
	HC	33	4	2	7.5			
Vaginismus	P_{FMF}	36	6.7	4	9	−2.124	0.034	0.50
	HC	33	5	4	7			
Anorgasmia	P_{FMF}	36	6	4	7.7	−0.966	0.334	0.33
	HC	33	5	2.5	7.5			
Touch	P_{FMF}	36	4.5	3	7	−1.420	0.156	0.33
	HC	33	4	2	6.5			

P_{FMF}: Patients with familial Mediterranean fever, HC: healthy controls, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, PAF: Premenstrual Assessment Form, GRISS: Golombok Rust Inventory of Sexual Satisfaction (women's form), IQR: interquartile range, d: Cohen's d.

the probability of incidence decreases after colchicine treatment (37), pelvic adhesions due to recurrent episodes of abdominal serositis and exploratory laparoscopy (38) can cause pain during sexual activity, or patients might worry that FMF attacks might be triggered during sexual activity. Therefore, patients might avoid sexual activity to prevent pain attacks. This hypothesis may be a distinct research topic.

The second important result of the model is that FMF has no direct effect on PMS, but it indirectly increased the total PAF score by increasing anxiety levels. The effects of FMF on anxiety levels and the effects of anxiety on PMS are strong. It has been shown that estrogens can inhibit interleukin 6 production and inhibition of this interleukin may indirectly ameliorate the inflammatory process (39). Thus, menstruation can trigger pain attacks in patients with FMF (40). As such, the expectation of a pain attack during menstruation might cause increased levels of anxiety (41). Pain, including abdominal pain, is known to elicit anxiety (42). Similar to our study, other studies have shown strong positive correlations between anxiety and PMS (43,44).

The reasons for the small sample size of this study are that the research was planned as a single-center study, the

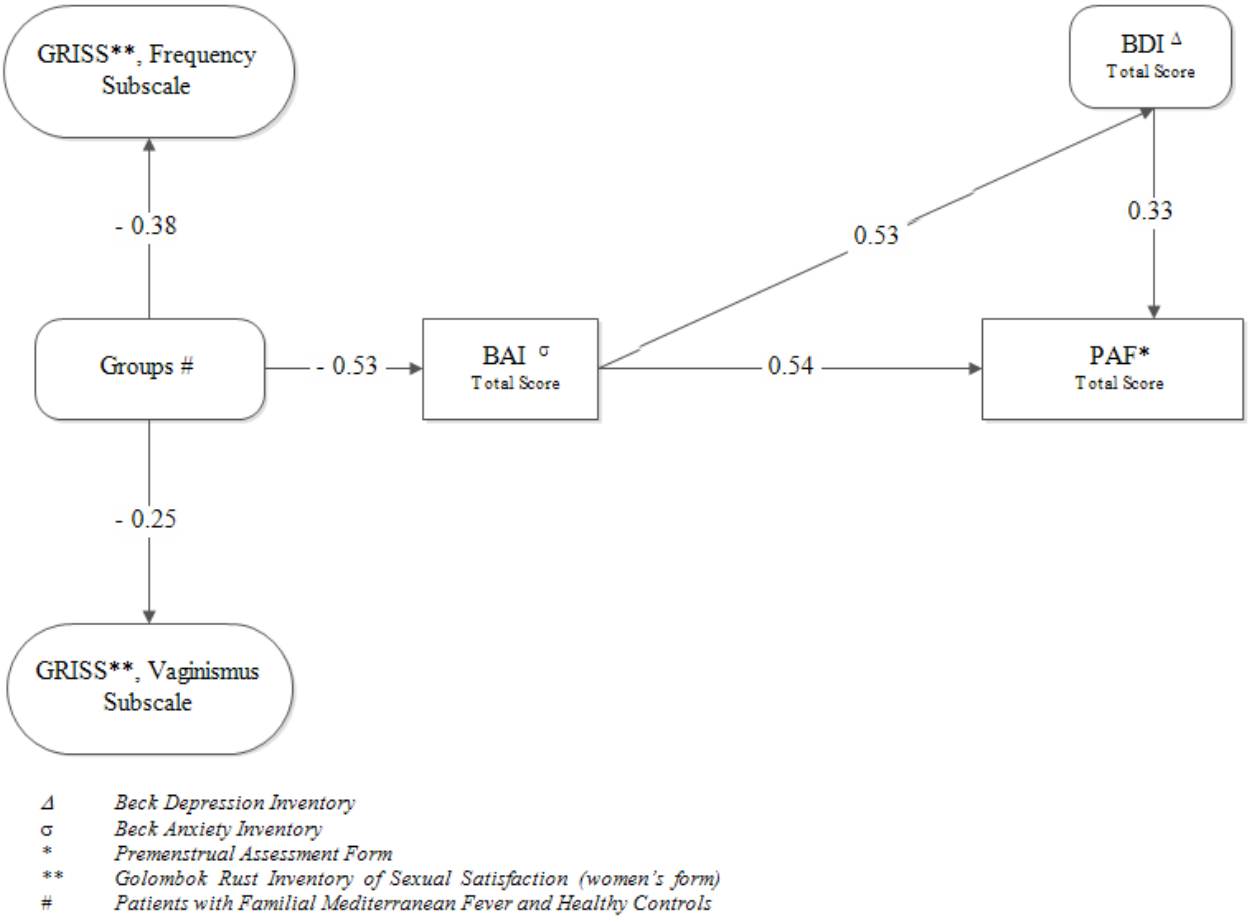

Figure. Schematic representation of the effects of FMF on sexual and reproductive health in women.

inclusion criteria were strict, and both FMF patients and healthy controls were reluctant to participate due to the questions regarding sexual function. However, despite the small sample size, for many variables, the effect size was moderate or high (especially anxiety), and the difference between groups was supported by path analysis. One of the limitations of the study is that all of the FMF patients were using colchicine, which might have caused sample bias. However, colchicine (used in the treatment of FMF) is generally well tolerated and there is no evidence of sexual side effects (45), and no evidence was found in the literature, using several screening databases (PubMed, Science Direct, EBSCO), that colchicine has negative effects on sexual function or PMS. Another limitation of our study is the lack of a tool that directly measures the severity of FMF (such as frequency of episodes of abdominal pain). However, we tried to overcome this problem by using the 19th item of the BDI. It measures the perspective of the participants of their own health status in the last week. We found that there was no significant difference in perceived health between the two groups and concluded that clinical measurements were performed under ideal circumstances.

Improving the quality of life in patients with FMF is as important as improving the symptoms associated with FMF. With drugs such as colchicine, the symptoms of FMF can be largely controlled, and long-term complications associated with FMF have been greatly reduced. However, psychiatric complications that adversely affect the quality of sexual and reproductive life are still observed in FMF patients. Therefore, it is extremely important that FMF patients be evaluated for psychiatric comorbidities such as sexual dysfunction and PMS.

References

1. Kollainis I, Ritis K, Moutsopoulos H. Familial Mediterranean fever associated pyrin mutations in Greece. Ann Rheum Dis 2003; 62: 479-481.
2. La Regina M, Nucera G, Diaco M, Procopio A, Gasbarrini G, Notarnicola C, Kone-Paut I, Touitou I, Manna R. Familial Mediterranean fever is no longer a rare disease in Italy. Eur J Hum Genet 2003; 11: 50-56.
3. Makay B, Emiroğlu N, Ünsal E. Depression and anxiety in children and adolescents with familial Mediterranean fever. Clin Rheumatol 2010; 29: 375-379.
4. Mijatovic V, Hompes PG, Wouters MG. Familial Mediterranean fever and its implications for fertility and pregnancy. Eur J Obstet Gyn R B 2003; 108: 171-176.
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). Arlington, VA, USA: APA; 2013.
6. Raina R, Pahlajani G, Khan S, Gupta S, Agarwal A, Zippe CD. Female sexual dysfunction: classification, pathophysiology, and management. Fertil Steril 2007; 88: 1273-1284.
7. Dotters-Katz S, Kuller J, Price T. The impact of familial Mediterranean fever on women's health. Obstet Gynecol Surv 2012; 67: 357-364.
8. Rapkin A. A review of treatment of premenstrual syndrome & premenstrual dysphoric disorder. Psychoneuroendocrinology 2003; 28: 39-53.
9. Frank E, Severino S. Premenstrual dysphoric disorder: facts and meanings. J Pract Psychiatry Behav Health 1995; 1: 20-28.
10. Wittchen HU, Becker E, Lieb R, Krause P. Prevalence, incidence and stability of premenstrual dysphoric disorder in the community. Psychol Med 2002; 32: 119-132.
11. Campbell E, Peterkin D, O'Grady K, Sanson-Fisher R. Premenstrual symptoms in general practice patients. Prevalence and treatment. J Reprod Med 1997; 42: 637-646.
12. Ugurlu GK, Erten S, Ugurlu M, Caykoylu A, Altunoğlu A. Sexual dysfunction in female patients with primary Sjögren's syndrome and effects of depression: cross-sectional study. Sex Disabil 2014; 32: 197-204.
13. de Moura Cal SFL, Alonso LC, de Almeida AG, Santiago MB, Miranda-Scippa Â. Association between premenstrual dysphoric disorder and systemic lupus erythematosus: exacerbation of major depression symptoms? Open Journal of Rheumatology and Autoimmune Diseases 2013; 3: 209-215.
14. Lara LADS, Silva ACJDS, Romão APMS, Junqueira FRR. Abordagem das disfunções sexuais femininas. Rev Bras Ginecol Obstet 2008; 30: 312-321 (in Portuguese).
15. Perdriger A, Solano C, Gossec L. Why should rheumatologists evaluate the impact of rheumatoid arthritis on sexuality? Joint Bone Spine 2010; 77: 493-495.
16. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, Migdal A, Padeh S, Pras M. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997; 40: 1879-1885.
17. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561-571.
18. Hisli N. Beck Depresyon Envanterinin üniversite öğrencileri için geçerliği, güvenirliği. Psikoloji Dergisi 1989; 7: 3-13 (in Turkish).
19. Ulusoy M, Sahin N, Erkmen H. Turkish version of the Beck Anxiety Inventory: psychometric properties. J Cogn Psychother 1998; 12: 163-172.
20. Halbreich U, Endicott J, Schacht S, Nee J. The diversity of premenstrual changes as reflected in the Premenstrual Assessment Form. Acta Psychiatr Scand 1982; 65: 46-65.
21. Dereboy C, Dereboy I, Yigitol F, Coskun A. Psychometric data for the Premenstrual Assessment Form: a cluster analytic study. Turk Psikiyatri Derg 1994; 5: 83-90.
22. Rust J, Golombok S. The Golombok-Rust inventory of sexual satisfaction (GRISS). Br J Clin Psychol 1985; 24: 63-64.
23. Tuğrul C, Öztan N, Kabakçı E. Golombok-Rust cinsel doyum ölçeği'nin standardizasyon çalışması. Türk Psikiyatri Derg 1993; 4: 83-89 (in Turkish).
24. Oktay E, Akıncı MM, Karaaslan A. Research on the interaction of statistics with the courses in business administration curriculum with using path analysis. Atatürk University Journal of Graduate School of Social Sciences 2012; 16: 513-527 (in Turkish with English abstract).
25. Şimşek Ö. Yapısal Eşitlik Uygulamalarına Giriş. Ankara, Turkey: Ekinoks Yayınları; 2007.
26. Lleras C. Path analysis. In: Kempf-Leonard K, editor. Encyclopedia of Social Measurement. Vol. 3. Amsterdam, the Netherlands: Elsevier; 2005. pp. 25-30.
27. Suhr D. Step your way through path analysis. In: Western Users of SAS Software Conference Proceedings; San Francisco, CA, USA; 2008.
28. Marchesoni D, Mozzanega B, De Sandre P, Romagnolo C, Gambari PF, Maggino T. Gynaecological aspects of primary Sjogren's syndrome. Eur J Obstet Gynecol Reprod Biol 1995; 63: 49-53.
29. Abdel-Nasser AM, Ali EI. Determinants of sexual disability and dissatisfaction in female patients with rheumatoid arthritis. Clin Rheumatol 2006; 25: 822-830.
30. van Berlo WT, van de Wiel HB, Taal E, Rasker JJ, Weijmar Schultz WC, van Rijswijk MH. Sexual functioning of people with rheumatoid arthritis: a multicenter study. Clin Rheumatol 2007; 26: 30-38.
31. Parıldar H, Sakallıoğlu O. Secondary amenorrhea as the presenting symptom of familial Mediterranean fever. Türkiye Aile Hekimliği Dergisi 2014; 18: 113-114 (in Turkish with English abstract).
32. Shohat M, Halpern GJ. Familial Mediterranean fever - a review. Genet Med 2011; 13: 487-498.

33. Majeed HA, Al-Qudah AK, Qubain H, Shahin HM. The clinical patterns of myalgia in children with familial Mediterranean fever. Semin Arthritis Rheum 2000; 30: 138-143.

34. Sahin S, Yalcin I, Senel S, Ataseven H, Uslu A, Yildirim O, Semiz M. Assesment life quality of familial Mediterranean fever patients by short form-36 and its relationship with disease parameters. Eur Rev Med Pharmacol Sci 2013; 17: 958-963.

35. Cook AJ, Brawer PA, Vowles KE. The fear-avoidance model of chronic pain: validation and age analysis using structural equation modeling. Pain 2006; 121: 195-206.

36. Koné-Paut I, Hentgen V, Touitou I. Current data on familial Mediterranean fever. Joint Bone Spine 2011; 78: 111-114.

37. Granat M, Tur-Kaspa I, Zylber-Katz E, Schenker JG. Reduction of peritoneal adhesion formation by colchicine: a comparative study in the rat. Fertil Steril 1983; 40: 369-372.

38. Ehrenfeld M, Brzezinski A, Levy M, Eliakim M. Fertility and obstetric history in patients with familial Mediterranean fever on long-term colchicine therapy. Br J Obstet Gynaecol 1987; 94: 1186-1191.

39. Koka S, Petro TM, Reinhardt RA. Estrogen inhibits interleukin-1β-induced interleukin-6 production by human osteoblast-like cells. J Interferon Cytokine Res 1998; 18: 479-483.

40. Ben-Chetrit E, Levy M. Reproductive system in familial Mediterranean fever: an overview. Ann Rheum Dis 2003; 62: 916-919.

41. Kuczmierczyk AR, Adams HE, Calhoun KS, Naor S, Giombetti R, Cattalani M, McCann P. Pain responsivity in women with premenstrual syndrome across the menstrual cycle. Percept Mot Skills 1986; 63: 387-393.

42. Gerrits MM, van Oppen P, van Marwijk HW, Penninx BW, van der Horst HE. Pain and the onset of depressive and anxiety disorders. Pain 2014; 155: 53-59.

43. Sigmon ST, Whitcomb-Smith SR, Rohan KJ, Kendrew JJ. The role of anxiety level, coping styles, and cycle phase in menstrual distress. J Anxiety Disord 2004; 18: 177-191.

44. Nillni YI, Rohan KJ, Mahon JN, Pineles SL, Zvolensky MJ. The role of anxiety sensitivity in the experience of menstrual-related symptoms reported via daily diary. Psychiatry Res 2013; 210: 564-569.

45. Fonnesu C, Cerquaglia C, Giovinale M, Curigliano V, Verrecchia E, de Socio G, La Regina M, Gasbarrini G, Manna R. Familial Mediterranean fever: a review for clinical management. Joint Bone Spine 2009; 76: 227-233.