Rheumatology International
https://doi.org/10.1007/s00296-023-05436-w

Rheumatology
INTERNATIONAL

OBSERVATIONAL RESEARCH

Familial Mediterranean fever: perspective on female fertility and disease course in pregnancy from a multicenter nationwide network

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Received: 30 July 2023 / Accepted: 14 August 2023

Abstract

The aim of this study was to analyze the pregnancy process, especially the Familial Mediterranean fever (FMF) disease course and attack types during pregnancy, and to examine the relationship between disease-related factors and female infertility in FMF patients. The study, which was planned in a multicenter national network, included 643 female patients. 435 female patients who had regular sexual intercourse were questioned in terms of infertility. Pregnancy and delivery history, FMF disease severity and course during pregnancy were evaluated. The relationship between demographic and clinical findings, disease severity, genetic analysis results and infertility was investigated. 401 patients had at least 1 pregnancy and 34 patients were diagnosed with infertility. 154 patients had an attack during pregnancy. 61.6% of them reported that attacks during pregnancy were similar to those when they were not pregnant. The most common attack symptoms were fever, fatigue and abdominal pain-peritonitis (96%, 87%, and 83%, respectively) in the pregnancy period. The disease-onset age, disease activity score, gene mutation analyses, and regular colchicine use (> 90%) were similar between the fertile and infertile groups, while the frequency of previous appendectomy and alcohol consumption rates were higher in individuals with infertility. Our results indicated no significant change in the frequency and severity of attacks during pregnancy. The low rate of infertility (7.8%) in our patients was noted. It has been suggested that the risk of FMF-related infertility may not be as high as thought in patients who are followed up regularly and received colchicine.

Keywords Infertility · Pregnancy · Amyloidosis · Serositis · Colchicine

Introduction

Familial Mediterranean fever (FMF) is the most known hereditary periodic fever syndrome, characterized by self-limited fever episodes and inflammatory serositis [1]. Disease especially influences East Mediterranean territory nevertheless patients are described worldwide. While Sephardic Jews, Armenians, Turks and Arabs are known as the communities with the highest prevalence, the disease is now recognized all over the world, albeit with a low frequency [2, 3].

The MEFV gene (MEditerranean FeVer), which is responsible for the disease with its mutation, is located on the 16th chromosome and encodes a protein called pyrin. The mutated gene can initiate antigen-independent activation of the immune system [3–6]. The frequency of MEFV mutation carriage has been reported between 1/3 and 1/10 in populations known to be at risk, and it is noteworthy that this rate is much higher than the clinical FMF frequency. Some mutations have been shown to be benign variants and not of pathogenic significance [2, 7].

The characteristic clinical manifestations of FMF can be listed as fever, serositis, arthritis and skin involvement (erysipelas-like erythema). The disease progresses with attacks that resolve within a few days. The most feared

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Published online: 02 September 2023

complication of FMF is serum amyloid A (AA) amyloidosis. As a rare clinical picture, the disease may present with AA amyloidosis before clinical symptoms appeared (Phenotype 2). Uncontrolled and frequent peritonitis attacks may cause adhesions to the peritoneum, resulting in intestinal obstructions or fallopian tube obstructions. AA amyloidosis is the most hazardous complication in untreated FMF patients. Amyloid fibers can accumulate in the liver, intestine, and cardiovascular system, especially in the kidneys [7, 8].

There is a limited number of studies on the course of pregnancy in FMF, and the majority of those have focused on the pregnancy outcomes. It is noteworthy that there is a gap in the types of attacks during pregnancy, while analysis of pregnancy outcomes and attack frequency in the pregnancy period have appeared in the literature. It has been reported that during pregnancy, the number of attacks may decrease and even the disease may progress with remission. The rate of preterm birth is between 14 and 24%, and the rate of miscarriage is between 3 and 6.5%, which are similar to the healthy population [1, 9–11].

In the first study investigating the relationship between infertility and FMF, published in 1973, the rate of ovulatory dysfunction in infertile FMF cases was reported as 87%. Amyloidosis has also been considered as the main cause of ovarian dysfunction, but the mechanism of this condition has not been clearly known [12]. Pelvic adhesions due to frequent attacks have been predicted as the second possible cause of infertility. However, after 1974, it was reported that the use of colchicine in the treatment of FMF and the control of attacks decreased female infertility in FMF [13, 14].

To our knowledge, the number of studies on the pregnancy process and infertility in FMF are limited in the literature, and no study has been found relating with FMF attack symptoms in pregnancy. Moreover, the gap in the association between infertility and FMF clinical characteristics draws attention. Therefore, we aimed to analyze the attack types and disease course in pregnancy and to examine the relationship between disease-related factors and female infertility in FMF.

Materials and methods

Wide-ranging retrospective research was designed with a national network developed by the Turkish League against Rheumatism League against Rheumatism. Ankara Numune Education and Research Hospital ethics committee approval was obtained (Approval date/no:22.11.2017/E-17-1626). Written informed consent was collected from all patients. The study was carried out in accordance with the Helsinki principles.

Patients who had continued to regular visits in the same specialist for at least 6 months were included. The clinical information of the patients was recorded in electronic case report forms (http://www.trasd-network.org) during the routine specialist doctor examination in the outpatient [15]. Male patients, females without sexual partners, patients received cancer diagnosis, chemotherapy and radiotherapy were excluded from the study. A total of 643 female FMF patients were added by 31 researchers from 22 centers. Adult patients (≥ 18 years) who were evaluated with Tel Hashomer criteria, as revised by Livneh et al. [16], and diagnosed with FMF were included. Required criteria for the diagnosis of FMF are: ≥ 1 major criteria or ≥ 2 minor criteria or 1 minor criteria plus ≥ 5 supporting criteria or 1 minor criteria plus ≥ 4 of the first 5 supporting criteria.

435 female patients who had regular sexual intercourse were questioned in terms of infertility. Infertile was named in patients who could not achieve clinical pregnancy after 12 months of regular and unprotected sexual intercourse [17].

During routine visits with physicians, patients were examined in detail and their sociodemographic data including age, education, alcohol consumption and smoking were questioned. Disease history and clinical characteristics: family history, appendectomy history, disease-onset age, attack symptoms (fever, peritonitis, pleuritis, muscle and joint involvement, skin signs, …), renal involvement and amyloidosis, attack frequency, overlapping autoimmune syndromes, and medications were noted. Colchicine resistance was described as ≥ 2 attacks in the last 6 months despite the colchicine use for 12 months [18].

The scoring developed by Pras et al. was used to calculate FMF disease activity [19]. This score includes six titles as age of onset, colchicine dosage, attack frequency, arthritis, amyloidosis, and erysipelas-like erythema, and the total score varies from 2 to 19 points. Disease severity is grouped into three levels (severe disease: ≥ 10 points, moderate disease: 6–10 points, and mild disease ≤ 5 points).

Patients' global assessments are estimated with a visual analog scale (PG-VAS). They were asked to answer their general health status over the last week by taking a 10 cm line as a guide.

Complete blood count, C-reactive protein (CRP), fibrinogen levels, and proteinuria results were examined.

Genetic mutation analysis results of 268 patients who had a complete gene analysis were documented. Mutations were analyzed with routine FMF strip assay, Polymerase Chain Reaction (PCR) amplification, and automatic deoxyribonucleic acid (DNA) sequence. Peripheral complete blood samples are used for DNA isolation. The same mutation in 2 alleles is specified as homozygous, the mutation in 1 allele is specified as heterozygous and different mutations in 2 alleles are specified as compound heterozygous.

The pregnancy process and outcome of the patients were questioned. Drugs used during pregnancy, disease activity, frequency of attacks and attack types were recorded in this period.

In addition to demographic characteristics and clinical and laboratory findings of FMF, genetic analysis results were also compared in patients with and without spontaneous pregnancy.

As it is a retrospective analysis, G*power 3.1.9.4 software was used for post hoc power analysis (for differences between two independent means) Power of the study was 0.79 with an α level of 0.05. Statistical analyses were completed using the SPSS (Statistical Package for Social Sciences) for Windows 23 package program. Normality was evaluated with The Shapiro–Wilk test. Mean (standard deviation), median (minimum–maximum), numbers, and percentages were performed for general descriptive statistics. For two group comparisons the Mann–Whitney *U* test, the Students' *t* test, the Chi-square test, and the Fisher test were completed. Statistical significance was set at $p < 0.05$.

Results

A total of 643 female patients were included in the study. 435 patients, who had regular sexual intercourse were questioned in terms of infertility. It was learned that 401 patients had one or more pregnancies and 34 patients were diagnosed with infertility. The sociodemographic characteristics of the patients are analyzed in Table 1. The distinctive feature was the difference in alcohol consumption rates (14.7% in the infertile group and 4.2% in the others).

When the pregnancy process of 401 pregnant women was questioned, it was seen that there were 585 pregnancies in total. Of the total pregnancies, there were 437 (74.7%) live births, 41 (7%) preterm delivery, 106 (18.1%) abortions, and 32 (5.8%) stillbirths. The number of children born with fetal anomaly was 10 (1.7%). 154 patients had an attack during pregnancy. 95 (61.6%) of these patients reported that the attacks they had during pregnancy were similar to those when they were not pregnant while 54 (35.1%) patients said that the attacks were more severe than the pre-pregnancy period. It was observed that 62 (40.2%) of the patients continued to use colchicine during pregnancy. The types of attacks experienced by the patients during this period and the medications are summarized in Table 2.

34 patients with infertility and 401 patients with at least 1 pregnancy; were compared in terms of disease-onset age, FMF attack characteristics, and presence of overlap autoimmune syndrome. While the age of disease onset, renal involvement, protracted febrile myalgia and coexistence with overlapping autoimmune disease were similar between the two groups, it was notable that the frequency of previous appendectomy was higher in individuals with infertility. In addition, protracted arthritis was not seen in the patients with infertility (Table 3).

Table 1 Sociodemographic characteristics of the female patients with FMF

	Infertile females ($n=34$)	Fertile females ($n=401$)	*p*
Age (mean, ±)	42.5 ± 10.3	45.47 ± 10.71	0.068
Education (*n*, %)			0.050
Illiterate	2 (5.9%)	20 (4.9%)	
Primary education	13 (38.2%)	244 (60.8%)	
Secondary education	14 (41.7%)	102 (25.4%)	
University	5 (14.7%)	35 (8.7%)	
Employment status (*n*, %)			0.258
Employed	11 (32.4%)	84 (20.9%)	
Unemployed	23 (67.6%)	317 (79.1%)	
Smoking (*n*, %)			0.470
Yes	10 (29.4%)	82 (20.4%)	
Ex-smoker	3 (8.8%)	39 (9.7%)	
No	21 (61.7%)	280 (69.8%)	
Smoking, pack-year			0.202
Mean, ±	14.82 ± 10.97	11.41 ± 9.94	
Median (min–max)	14 (1.25–40)	10 (0.40–60)	
Alcohol (*n*, %)			0.002
Yes	5 (14.7%)	17 (4.2%)	
Ex-alcohol	1 (2.9%)	1 (0.2%)	
No	28 (82.3%)	383 (95.1%)	
Consanguineous marriage of parents (*n*, %)	6 (17.6%)	62 (15.5%)	0.736

FMF familial Mediterranean fever

Table 2 Characteristics of FMF attacks and treatments in pregnancy period

	Patients with at least one attack during pregnancy ($n=154$)
FMF attacks during pregnancy	
Abdominal pain/peritonitis (*n*, %)	128 (83.1%)
Fever (*n*, %)	134 (87.1%)
Fatigue (*n*, %)	148 (96.1%)
Chest pain/pleuritis (*n*, %)	69 (44.8%)
Diarrhea (*n*, %)	79 (51.2%)
Headache (*n*, %)	102 (66.2%)
Constipation (*n*, %)	72 (46.1%)
Vomiting (*n*, %)	68 (44.2%)
Myalgia/arthralgia (*n*, %)	114 (74.1%)
Acute Arthritis (*n*, %)	55 (35.7%)
Heel pain (*n*, %)	79 (51.3%)
Erysipelas-like erythema (*n*, %)	31 (20.1%)
Protracted arthritis (*n*, %)	8 (5.1%)
Protracted febrile myalgia (*n*, %)	7 (4.5%)
Attack frequency in pregnancy	
< 1 attack per month (*n*, %)	55 (35.7%)
1–2 attacks per month (*n*, %)	59 (38.3%)
> 2 attacks per month (*n*, %)	40 (25.9%)
Attack treatment in pregnancy	
Colchicine (*n*, %)	62 (40.2%)
Attack-controlled colchicine dose higher than 2 g (*n*, %)	8 (5.1%)
Colchicine resistance (*n*, %)	7 (4.5%)
Steroids (*n*, %)	2 (1.2%)
NSAID (*n*, %)	5 (3.2%)

FMF familial Mediterranean fever, *NSAID* nonsteroidal anti-inflammatory drugs

The disease activity, the patient's global VAS assessment, the frequency of attacks, the medications, and the colchicine resistance were compared in the fertility and non-fertile groups. The frequency of attacks, regular colchicine use and the colchicine resistance were found to be similar in the two groups. Only severe disease rate was higher in the fertile group (Table 4).

Mutational analyses of the MEFV gene were performed in a total of 268 patients. It was seen that 43 (16.1%) patients were homozygous. The rates of patients carrying homozygous/heterozygous mutations were similar in the two groups. The carriage rate of the M649V allele was 76.9% in the infertile group and 43.6% in the fertile group. Allele frequency is shown in Table 5.

Discussion

In the present study, the pregnancy process, attack frequency and attack types in pregnant women with FMF were examined and factors associated with female infertility in FMF patients were analyzed. Our results indicated that 401 of the patients have at least one pregnancy and 38.4% of them had attacks during pregnancy. 61.2% of the attacks during pregnancy were similar to those in the non-pregnancy period. Abdominal pain, fever and fatigue were the most common types of attacks. 34 of the patients were diagnosed with female infertility. It was noted that the rate of alcohol consumption was higher in the patients diagnosed with infertility. Disease-onset age, disease activity score, regular colchicine use, renal involvement, presence of overlap autoimmune disease, and genotypic characteristics (homozygous/heterozygous) were similar between fertile and infertile groups. It is noteworthy that the history of abdominal surgery due to appendectomy is more common in infertile patients.

It has been observed that the number of studies investigating the effects of FMF on pregnancy is limited. The number of attacks may decrease in patients, and remission may be observed during pregnancy; however, pregnancies may continue with severe and frequent attacks [9]. In two different studies, the rate of patients who had an FMF attack during pregnancy was 51.5% and 28.2% [10, 11]. In our study, the rate of patients who had an attack during pregnancy was 38%. In more than half of the patients (61.2%), the attacks' severity was similar to the pre-pregnancy period. The rate of frequent attacks (> 2 attacks/per month) was 25.9% in the pregnancy period. On the other hand, including non-pregnant periods of female patients, this rate was 26% (113/434 patients). The fact that our patients indicated no significant change in the frequency and severity of attacks during pregnancy is consistent with the literature.

It has been discussed that recurrent peritonitis and fever attacks may increase the risk of preterm birth. On the other hand, FMF attacks imitate pregnancy complications that require delivery, thus there is a possibility of some preterm deliveries to be induced ones actually. Therefore, it is not possible to say clearly that FMF increases the risk of preterm births [10]. The preterm birth rate reported in the literature is between 14 and 24%, the abortion rate is between 3 and 6.5%, and the fetal anomaly rate is around 4%. No increased risk was found in patients with FMF compared with the control group [1, 10, 11]. In our study, similar to the literature, the rate of preterm birth was 7% and the rate of fetal anomaly was 1.7%; however, the miscarriage rate was 18.1%, which seems to be higher than the other studies. Although earlier reports mentioned an

Table 3 Clinical features of FMF attack and presence of overlapped immune disease in patients with and without fertility

	Infertile females ($n=34$)	Fertile females ($n=401$)	p
Disease-onset age (mean, ±) Median (min–max)	19.79 ± 11.18	22.14 ± 11.84	0.285
Symptom onset age (n, %)			
≤ 20	22 (64.7%)	204 (50.9%)	0.121
> 20	12 (35.3%)	197 (49.1%)	
Family history of FMF (n, %)	15 (44.1%)	247 (61.6%)	0.046
Appendectomy history (n, %)	15 (44.1%)	91 (22.1%)	0.005
Persistent proteinuria (n, %)	1	16 (4.0%)	0.944
Amyloidosis (n, %)	0	8 (1.9%)	1.000
Chronic renal failure (n, %)	0	5 (1.2%)	1.000
Dialysis (n, %)	0	2 (0.5%)	1.000
Phenotype II (n, %)	0	5 (1.2%)	1.000
Joint involvement			
Acute arthritis	19 (55.9%)	147 (36.6%)	0.026
Protracted arthritis	0	46 (11.5%)	
Protracted febrile myalgia	2 (5.9%)	16 (4.0%)	0.425
During attack			
Leukocytosis (n, %)	5 (14.7%)	47 (11.7%)	0.606
Elevated CRP (n, %)	13 (32.2%)	129 (38.2%)	0.469
Elevated fibrinogen (n, %)	5 (14.7%)	52 (13.0%)	0.946
Overlapping autoimmune disease (n, %)			
Axial spondyloarthritis	2 (5.9%)	43 (10.7%)	
Rheumatoid arthritis	0	13 (3.2%)	
Systemic lupus erythematosus	1 (2.9%)	6 (1.5%)	
Sjogren syndrome	0	2 (0.5%)	
Vasculitis	0	1 (0.2%)	
Behçet's disease	0	2 (0.5%)	
Juvenile idiopathic arthritis	0	1 (0.2%)	
Hidradenitis suppurativa	0	1 (0.2%)	
Uveitis	0	1 (0.2%)	
Total	3 (8.9%)	70 (17.4%)	0.196

FMF familial Mediterranean fever, *CRP* C-reactive protein

increased risk of miscarriage and preterm birth, current publications support positive pregnancy outcomes [1, 10, 11, 20–24]. Severe abdominal attacks and fever are also held responsible for the possible miscarriage risk mechanism in patients with FMF. In our analysis, the number of attacks and the rate of severe attacks were not high. The miscarriage rate, which is higher than the literature, is remarkable, nevertheless it is not possible to assess a causal relationship between miscarriages and disease severity according to this retrospective analysis results.

Although FMF is a periodical fever syndrome, the attacks of the disease are not periodical, in a variety of severity and frequency. Attacks are characterized by fever and serositis with a common manifestation of abdominal pain and/or chest pain and/or joint pain and swelling. Erythematous rash attacks should be kept in mind in the diagnostic stage. The most common attacks are described as fever and peritonitis at a rate of nearly 90% [2]. When the literature is examined, it is noteworthy that there is a gap in the types of attacks during pregnancy, while analysis of pregnancy outcomes and frequency of attacks and remission during pregnancy were reported. Attack types during pregnancy were analyzed in our patients. The most common symptoms were fever, fatigue and abdominal pain-peritonitis (96%, 87%, and 83%, respectively). In addition, the rate of erysipelas-like erythema was 20.1%, protracted arthritis was 5.1%, and protracted febrile myalgia was 4.5%. In our previous study conducted with 979 patients with FMF, when the symptoms of attacks are examined, it is seen that the first three symptoms are again listed as fatigue, abdominal pain and fever. In the same study, the rate of erysipelas-like erythema was 18.7%, protracted arthritis 6.2%, and protracted febrile myalgia 4.3% [15]. Tufan et al. declared that the rate of joint attack was around 50%, but of the protracted arthritis was

Table 4 Disease activity and drugs administered to FMF patients

	Infertile females ($n=34$)	Fertile females ($n=401$)	p
Patients' global VAS (mean, ±)	6.97 ± 2.03	6.91 ± 2.26	0.864
Attack frequency			0.098
< 1–2 per month (n, %)	14 (41.2%)	181 (45.1%)	
1–2 per month (n, %)	10 (29.4%)	117 (29.2%)	
> 2 per month (n, %)	10 (29.4%)	103 (25.7%)	
Disease severity			0.016
Mild (n, %)	10 (29.5%)	204 (50.9%)	
Moderate (n, %)	24 (70.5%)	183 (45.6%)	
Severe (n, %)	0	14 (3.5%)	
Disease severity (mean, ±)	6.29 ± 1.91	5.73 ± 2.51	0.116
Colchicine resistance (n, %)	3 (8.8%)	46 (11.5%)	0.404
Drugs (n, %)			
Colchicine (regular)	33 (97.1%)	367 (91.5%)	0.254
Canakinumab	1 (2.9%)	3 (0.7%)	
Anakinra	0	1 (0.2%)	
Etanercept	1 (2.9%)	4 (1.0%)	
Infliximab	0	1 (0.2%)	
Adalimumab	0	1 (0.2%)	
Golimumab	0	2 (0.5%)	
Corticosteroids	0	5 (1.2%)	

FMF familial Mediterranean fever, *VAS* Visual Analog Scale

less than 5% [7]. Protracted febrile myalgia is an important finding that leads to intense pain and sensitivity lasting up to 6 weeks and impairs the quality of life in patients with FMF. It has been reported that this condition occurs between the rates of 1–3% in various series, affecting female gender more frequently [25]. The frequency of erysipelas-like erythema is not uncommon and has been reported between 7 and 40% [3]. Considering the attack types during pregnancy, it can be concluded that peritonitis and fever are the most common symptoms, and that the rates of erysipelas-like erythema, protracted arthritis and febrile myalgia are similar to the general FMF population.

The non-existence of clinical pregnancy despite at least 12 months of regular sexual intercourse without contraception is described as infertility [8]. The rate of infertility among general population has been reported to be 9–18%; however, among the women aged between 15 and 49 years as 12.2% [26]. The first study evaluating the association between infertility and FMF was conducted in 1970 and reported the etiology of infertility as ovarian insufficiency in a majority of 20 female patients with FMF [8]. In similar years, infertility rates were found as 28–36% in patients with FMF [12, 27]. Infertility was reported as more common in women with FMF than in the normal population, and it has been noted that the majority of the infertile patients do not receive colchicine treatment [25]. Although the relationship between FMF and female infertility is not clear, the cause of infertility is often observed as pelvic adhesions and ovulatory disorders. While the most important influencing factor for pelvic adhesions is peritonitis attacks, the possible mechanism in ovulatory disorders is considered to be the ovarian amyloid deposition [13]. It was identified that since 1974, the prevention of attacks by the use of colchicine in FMF decreased the rates of infertility and improved the pregnancy outcomes in patients with FMF [8, 14]. Our findings revealed a quite low rate of infertility (7.8%), on the other hand the literature is scarce regarding this knowledge. Our findings might be related to some outstanding properties of the sample group of which being followed up regularly by the same specialist for at least 6 months in the rheumatology outpatient clinic, with a colchicine usage rate of higher than 90%.

Our study comparing the sociodemographic characteristics, clinical and laboratory findings between fertile and infertile females presented about three times higher rate of alcohol consumption in the infertile group (14.7%) than the fertile (4.2%). However, the relationship between alcohol and female infertility is not clear yet. Alcohol consumption during the reproductive period was considered to be associated with high estrogen and low progesterone levels, and these hormonal disorders may disrupt fertility. However, the studies evaluating the effect of alcohol consumption on female fertility are contradictory, of which the majority reporting no correlation [28].

Table 5 Allele frequency in MEFV gene mutations of female FMF patients with and without fertility

	Infertile females ($n=17$)	Fertile females ($n=251$)	p
Homozygote mutations (n, %)	6 (35.2%)	37 (14.7%)	0.062
Heterozygote mutations (n, %)	8 (47.1%)	147 (58.6%)	
Compound heterozygote mutations (n, %)	3 (17.6%)	67 (26.7%)	
Homozygote mutations (n)			
M694V/M694V	6	21	
M680I/M680I	0	5	
R202Q/R202Q	0	5	
E148Q/E148Q	0	2	
V726A/V726A	0	1	
Other/other (c932C > T; c2080A > G; rs11466018)	0	3	
Heterozygote mutations (n)			
M694V/Wt	6	64	
M680I/Wt	0	15	
E148Q/Wt	0	23	
R202Q/Wt	0	15	
V726A/Wt	1	12	
Other[a]/Wt	1	18	
Compound heterozygote mutations (n)			
M694V/M680I	0	11	
M694V/V726A	0	13	
M694V/E148Q	2	8	
M694V/Other[b]	0	2	
M694V/R202Q	1	15	
M680I/E148Q	0	2	
R202Q/E148Q	0	3	
R202Q/V726A	0	1	
R202Q/Other[b]	0	5	
V726A/Other[b]	0	2	
V726A/E148Q	0	1	
V726A/M680I	0	1	
E148Q/Other[b]	0	2	
Other/other[b]	0	1	

FMF familial Mediterranean fever, *MEFV* MEditerranean FeVer

[a]P369S, R761H, A744S, F479L, K695R, C2177T > C, C1437 > G, R408Q, M694I

[b]K695R, F479L, A744S, R761H, P369S, c.605G

Analyzing the clinical properties of FMF in our patients pointed out that disease-onset age, persistent proteinuria, protracted febrile myalgia, amyloidosis, renal involvement and presence of overlap autoimmune syndrome were found to be similar in the infertile and fertile groups. On the other hand, it was notable that the frequency of previous abdominal surgery due to appendectomy was higher in patients with infertility. Pelvic adhesions have been predicted as one of the causes in female infertility [13]. Our results suggest that previous abdominal surgeries may also increase the risk of infertility by causing pelvic-abdominal adhesions.

Only one study was noticed in the literature examining the relationship between infertility and disease activity in patients with FMF. The incidence of severe disease and frequent attacks (more than 2 attacks per month) was found to be higher in infertile females, and it was suggested that the number of frequent attacks and infertility may be related [8]. Disease activity and frequency of attacks in our patients were similar between the two groups. In our study, the rate of patients describing frequent and severe attacks was lower than the other study in the literature. The regular colchicine use in our cohort is higher than 90%, and accordingly, the frequency of attacks and disease activity are lower. These

results support that the risk of infertility, associated with high disease activity and frequent abdominal attacks, may be reduced in patients in whom were compliant with the medications and regularly followed up.

Sotsiky et al. [8] evaluated infertility and genetic analysis results in FMF and found that carriers of M694V and M680I (homozygous) had a high risk of infertility. As is known, the M694V mutation is correlated with severe disease and frequent attacks, so it has been argued that increased disease severity and infertility may be associated with those carrying this mutation. Genetic analysis was also examined in our study, and homozygous/heterozygous carriage rates were similar in infertile and fertile groups. However, the carrier rate of M694V gene was higher in the infertile group than the others (76.9% and 43.6%, respectively). The relationship between female infertility and genetic mutations in FMF is a virgin theme in the literature. Although the frequency of M694V is higher in infertile patients, more comprehensive studies are needed to consider about the existence of a causal relationship.

The most important limitation of this study is the nature of other retrospective studies. Sample size and homogenization of the study group were affected because patients who were not followed up regularly for at least 6 months were not included in the study.

Conclusion

In our study, attack severity in 61.2% of the attacks during the pregnancy was similar to those in the non-pregnant period. Consistent with the general FMF population, the most common attack types were fever, fatigue, and peritonitis. The low rate of infertility (7.8%) in our patients was noted. No correlation was found between infertility and disease activity and frequency of attacks. In the infertile group, the history of surgery due to appendectomy and the high carrier rate of M694V gene were the remarkable points. Our results suggested that the risk of infertility in FMF patients receiving colchicine with a regular following up would not be as high as predicted.

Author contributions FGY, HB, HFÇ, ÜU, YK, BS, GG, OVY, MÇ, HD, YA, SH, RÇ, AYK, ŞA, MTD, HE, ZG, MT, NŞ, DA, AKC, GÇ, AND, HK, SK, MAM, MN, KN, BS, and İS made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; FGY, HB, HFÇ, ÜU, YK, BS, GG, OVY, MÇ, HD, YA, SH, RÇ, AYK, ŞA, MTD, HE, ZG, MT, NŞ, DA, AKC, GÇ, AND, HK, SK, MAM, MN, KN, BS, and İS drafted the work or revised it critically for important intellectual content; FGY, HB, HFÇ, ÜU, YK, BS, GG, OVY, MÇ, HD, YA, SH, RÇ, AYK, ŞA, MTD, HE, ZG, MT, NŞ, DA, AKC, GÇ, AND, HK, SK, MAM, MN, KN, BS, and İS approved the version to be published; FGY, HB, HFÇ, ÜU, YK, BS, GG, OVY, MÇ, HD, YA, SH, RÇ, AYK, ŞA, MTD, HE, ZG, MT, NŞ, DA, AKC, GÇ, AND, HK, SK, MAM, MN, KN, BS, and İS agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding The study was not funded.

Availability of data and material Patients did not provide consent for raw data sharing during the data collection.

Code availability Not applicable.

Declarations

Conflict of interest The authors FGY, HB, HFÇ, ÜU, YK, BS, GG, OVY, MÇ, HD, YA, SH, RÇ, AYK, ŞA, MTD, HE, ZG, MT, NŞ, DA, AKC, GÇ, AND, HK, SK, MAM, MN, KN, BS, and İS have no conflict of interests to declare.

Ethics approval All the procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments (ethic committee approval date/no:22.11.2017/E-17-1626).

Consent to participate Written informed consent was obtained from all the participants.

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