The Journal of Rheumatology 2021;48:608–14
doi.10.3899/jrheum.200574
First Release February 1 2021

The Journal of Rheumatology

Infertility Causes and Pregnancy Outcome in Patients With Familial Mediterranean Fever and Controls

Pavel Olegovich Sotskiy[1], Olga Leontevna Sotskaya[2], Hasmik Sureni Hayrapetyan[2], Tamara Fadei Sarkisian[2], Anna Rafaelovna Yeghiazaryan[1], Stepan Armenovich Atoyan[1], and Eldad Ben-Chetrit[2]

ABSTRACT. ***Objective.*** Recurrent attacks of peritonitis due to familial Mediterranean fever (FMF) may lead to peritoneal adhesions and fallopian tube obstruction. Colchicine, which is the treatment of choice for FMF, may disturb cell division. Secondary amyloidosis, a complication of untreated FMF, may involve the testes and ovaries. Thus, FMF and colchicine may potentially affect fertility and pregnancy in patients with FMF. The aims of the study are to evaluate the causes of infertility and pregnancy outcome in FMF patients and to compare them with 2 groups: non-FMF patients with peritoneal female genital tuberculosis (FGTB) and normal healthy controls.

Methods. This is a retrospective study in which FMF patients with reproductive disorders were recruited from the National Center of Medical Genetics and Primary Health Care in Yerevan, Armenia. The patients with FGTB and the healthy controls with reproductive problems were recruited successively from a large gynecology clinic in Yerevan. Genetic analyses for FMF were performed using ViennaLab StripAssay.

Results. The FMF group (211 patients) resembles the FGTB group (127 patients) regarding etiologies of infertility. However, *in vitro* fertilization (IVF) success rate and pregnancy outcome were comparable between the FMF patients and the control group (162 patients). Infertility in patients with FMF was clearly associated with a more severe disease and a lack of adequate colchicine treatment.

Conclusions. Colchicine medication and controlled FMF disease do not adversely affect the reproductive system and pregnancy outcome. However, a lack of an appropriate colchicine treatment may cause infertility and poor pregnancy outcome.

Key Indexing Terms: colchicine, familial Mediterranean fever, pregnancy, infertility

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterized by recurrent attacks of fever and serositis such as peritonitis, pleuritis, synovitis, and pericarditis[1]. Multiple episodes of peritonitis may lead to peritoneal adhesions, which may cause intestinal obstruction and fallopian tube obstruction[2]. One of the main complications of untreated FMF is serum amyloid A amyloidosis. In this condition, amyloid fibers are deposited in kidneys, liver, and intestines, and later may involve the cardiovascular system as well[3,4]. The gene associated with FMF (*MEFV*) was isolated in 1997 by 2 independent groups[5,6]. It is located on the short arm of chromosome 16. The treatment of choice for FMF is colchicine, which is able to control FMF attacks and prevents the development of amyloidosis. However, *in vitro* studies showed that a high dose of colchicine may affect cell division[7]. Thus, the potential complications of FMF (serosal fibrosis and amyloidosis) and colchicine treatment may affect the reproductive system either by obstruction of the salpinx, causing mechanical infertility, or by defective sperm and oocyte proliferation, leading to difficulties in obtaining pregnancy and normal deliveries[8,9,10,11].

In 1970, Mamou investigated the reproductive system in 20 women with FMF and reported that ovarian insufficiency was the cause of infertility in most cases[9]. Ismajovich, *et al* found ovulatory disturbances in 13 out of 45 patients with FMF and primary sterility[10]. Ehrenfeld, *et al* investigated the fertility and obstetric history of 36 women with FMF[11]. Thirteen (36%) women had infertility, 6 (46%) of whom had ovulatory dysfunction and 4 (31%) of whom had peritoneal adhesions.

It should be emphasized that most of the above studies described patients who had FMF before the colchicine era, and therefore their fertility and pregnancy outcome were poor. Following the introduction of colchicine for FMF patients, their fertility, pregnancy course, and outcome improved significantly[12]. In our recent literature review, we looked for large studies dealing with the reproductive system in FMF. We found a few publications, some of which summarized previous findings while others studied a small number of patients, sometimes without controls[13,14,15,16]. Therefore, we decided to study the reproductive

[1]*P.O. Sotskiy MD, PhD, A.R. Yeghiazaryan, MD, S.A. Atoyan, MD, PhD, Center of Medical Genetics and Primary Health Care, Yerevan, Armenia;* [2]*O.L. Sotskaya, MD, PhD, H.S. Hayrapetyan, MD, PhD, T.F. Sarkisian, MD, PhD, Center of Medical Genetics and Primary Health Care, and Yerevan State Medical University after Mkhitar Heratsi, Yerevan, 0025, Armenia;* [3]*E. Ben-Chetrit, MD, Rheumatology Unit, Hadassah - Hebrew University Medical Center, Jerusalem, Israel.*

The authors declare no conflicts of interest.

Address correspondence to Dr. E. Ben-Chetrit, MD, Professor of Medicine (Rheumatology), Rheumatology Unit, Hadassah-Hebrew University Medical Center, POB: 12000, Jerusalem, Israel. Email: eldad@hadassah.org.il.

Accepted September 9, 2020.

system and pregnancy outcomes in our female patients with FMF in Armenia. We compared them with 2 additional groups: non-FMF patients with peritoneal female genital tuberculosis (FGTB) and healthy controls with reproductive disorders but without FMF, FGTB, or any systemic inflammation or malignancy. The patients with FGTB were chosen due to their peritoneal involvement, which may resemble FMF peritonitis. The healthy individuals served as controls for both groups (FMF and FGTB).

MATERIALS AND METHODS

FMF patients' group (group 1). This group was chosen from the large dataset of the National Center of Medical Genetics and Primary Health Care in Yerevan, Armenia. During the years 1998–2018, there were 32,000 individuals screened for *MEFV* mutations. Of this group, we chose successively women in their reproductive years (18–49 yrs) who had a confirmed diagnosis of FMF based upon clinical and genetic criteria, and who were investigated for reproductive problems.

The most frequent complaints about reproductive function were as follows: irregular and painful menstruation, primary and secondary infertility, early and late miscarriage, complications of pregnancy, *in vitro* fertilization (IVF) failures, problems in ovulation, or recurrent inflammation of the uterus and appendages. Patients who had premature delivery, ovarian apoplexy, or ectopic pregnancy were also included in the study.

Regarding FMF, a severity score was calculated for each patient according to the Tel Hashomer criteria, which includes age of disease onset; attack frequency; presence of arthropathy, erysipeloid rash, or proteinuria; and kidney complications or poor response to colchicine treatment[17]. There were 3 grades of disease severity: mild (2–5), moderate (6–9), and severe (> 10).

FGTB group (group 2). Since FMF is a prototype of a noninfectious peritoneal inflammation, we thought that patients of the same age and origin who have peritoneal genital tuberculosis with concomitant reproductive problems could form an adequate group for comparison. Two authors (POS and OLS) run a large clinical center for patients with FGTB peritonitis and fertility problems. Age-matched FGTB patients were recruited successively from this clinic during the years 2010–2018.

Healthy controls (group 3). Women with reproductive problems, but without any concomitant systemic disease (especially excluding FMF or FGTB), served as a control group. They were recruited successively from a population of women who visited the same gynecology clinic between the years 2010–2018.

All the patients recruited for the study (3 groups) were interviewed and checked by OLS and POS. For the patients with FMF, a large chart containing demographic, clinical, laboratory, and genetic data was filled (Supplementary Table 1, available from the authors on request). In addition, a full gynecological evaluation was carried out for all the patients analyzed in the study (Supplementary Data 1, available from the authors on request). Informed consent was obtained from all participants. Ethics board approval was obtained from the ethics committee of the Center of Medical Genetics and Primary Health Care (ethics approval number 2/13, 11.02.2018).

Molecular genetic methods for FMF diagnosis. All patients with FMF were followed at the National Center of Medical Genetics and Primary Health Care in Yerevan. Diagnosis of FMF was confirmed using the Tel Hashomer criteria[18] and by molecular genetic analyses. We employed the ViennaLab Diagnostics StripAssay, which covered the 12 most common *MEFV* mutations among Armenians: E148Q, P369S, F479L, M680I (G/C), M680I (G/A), I692del, M694V, M694I, K695R, V726A, A744S, and R761H.

Statistical methods. Statistical analysis was performed using a complex data processing package (SPSS 21.0, IBM Corp.). Mean SD and standard error were used to describe numerical data. For qualitative data, rates and proportions were applied. For comparison of continuous variables, a 2-sided *t*-test for independent groups was used. For comparison of quantitative outcomes between groups, we used Pearson chi-square test. It was also used to analyze intergroup differences on quantitative features. In case of quantitative limitations, a 2-sided Fisher exact test was used. In all cases, results were considered statistically significant at $P \leq 0.05$.

RESULTS

The studied groups. Supplementary Figure 1 (available from the authors on request) depicts the flowchart for recruiting the patients with FMF and reproductive problems. It is shown that out of 32,000 individuals screened in the National Center of Medical Genetics and Primary Health Care in Yerevan between the years 1998–2018, there were 5679 women in their reproduction period that carried *MEFV* mutations (1 or 2). Of this group, 1102 women were excluded, since they were healthy carriers of a single mutation (heterozygotes) without any clinical manifestation. From the remaining 4577 patients with definite FMF (clinically and genetically), 211 patients were found with reproductive disorders.

During the years 2010–2018, there were 127 patients with FGTB and reproductive disorders recruited for the study. Concomitantly, 162 women with reproductive problems but without FMF, FGTB, or any other systemic disease were recruited as controls.

Demographic feature comparison of FMF, FGTB, and control groups. During the study period, the age of the patients in group 1 ranged between 18 and 45 years (average 21.3 ± 6.4 yrs), while the range was between 20 and 46 years (average of 28.4 ± 7.0 yrs) in group 2. The age in the control group was the highest, with an average of 31.4 ± 7.0 years ($P < 0.001$). Most of the patients in groups 2 and 3 were over the age of 20 years.

Two hundred and fifty-three out of the 500 patients studied were classified in a low socioeconomic status (SES). Of those, 94 (74%) patients were from the FGTB group and 112 (53%) were from the FMF group, while only 47 (29%) belonged to the control group. Patients with low SES were defined by their lack of high school education, and a lack of either a permanent job or private property. Patients in the middle SES were characterized by living in urban areas and having a higher education, stable income, and access to qualified medical services.

Infertility. According to the World Health Organization (www.who.int) recommendations, *infertility* is defined as the absence of clinical pregnancy following 12 or more months of regular sexual intercourse without protection. Table 1 shows that 139 (65.9%) out of 211 FMF patients had infertility, of whom 116 (83.5%) had primary infertility. In the FGTB group, infertility was diagnosed in 69 (54.3%) patients, of whom 58 (84.1%) had primary infertility. The control group included 115 (71.0%) infertile patients consisting of 47 (40.9%) patients with primary infertility. The most prevalent cause of infertility was tuboperitoneal. It was diagnosed in 128 infertile patients (92.1%) from the FMF group, in 67 (97.1%) from the FGTB group, and in only 40 (34.8%) in the control group ($P = 0.001$; Table 1). In 80 (49.4%) patients from the control group, infertility was caused by adhesive processes due to inflammation of the uterus and its

Table 1. Association between infertility types with FMF and tuberculosis in comparison with the control group.

	FMF, n = 139		FGTB, n = 69		Controls, n = 115			
Types of Infertility	N	%	N	%	N	%	Chi-square	*P*
Tuboperitoneal	128	92.1	67	**97.1**	40	34.8	106.1	0.001
Tubes are passable	77	55.4	16	23.2	105	**91.3**	35.1	0.001
Tubes are obstructed	21	15.1	51	**73.9**	10	8.7	23.7	0.001
Disovulation	77	55.4	10	14.5	68	**59.1**	43.8	0.001
Endometrial hyperplasia/ polyposis	13	9.4	5	7.2	22	**19.1**	15.7	0.001
Endometritis	10	7.2	19	27.5	31	**27.0**	27.2	0.001
Asherman syndrome	4	2.9	11	**16.0**	8	7.0	23.7	0.001
Absolute	2	1.4	12	**17.4**	4	3.5	25.2	0.001
Combined	8	5.8	1	0.1	23	**20.0**	15.0	0.001
Primary	116	83.5	58	**84.1**	47	40.9	74.6	0.001
Secondary	23	16.5	11	15.9	68	**59.1**	74.6	0.001

Values significantly higher or lower in comparison with other groups are in bold. FGTB: female genital tuberculosis; FMF: familial Mediterranean fever.

appendages, endometriosis, and operative interventions (cystectomy and salpingectomy).

The second cause of infertility in patients from the FMF group was disovulation, found in 77 patients (55.4%). In many cases it was concomitant with tuboperitoneal infertility. Disovulation rate in the FMF group was comparable with that of the control group (59.1%). However, the prevalence of endometrial hyperplasia was significantly lower in the FMF group: 9.4% compared with 19.1% in the control group ($P = 0.001$).

Permanent infertility was much more common in the FGTB group. It was documented in 12 (17.4%) women, most of whom underwent internal organ resection. Disovulation and uterine hyperplasia were moderately expressed in this group (14.5% and 7.2%, respectively), and were caused by peritoneal tuberculosis. Spontaneous recovery of infertility was observed in higher rate among the normal control (54%) compared with the FGTB (15.9%) and FMF groups (33.1%, $P < 0.0001$; data not shown).

Thrombophilia was found in 31 patients (14.7%) in group 1, in 5 patients (3.9%) in group 2, and in 73 patients (45.1%) in the control group (Table 2). Thrombophilia was defined as a hypercoagulation state supported by laboratory investigation, including global coagulation tests, identification of thrombophilia markers (thrombin–antithrombin fragments and serum D-dimer), and platelet aggregation. We have also looked for factor-V Leiden deficiency, mutation in the prothrombin gene *C20210A*, and mutations in the *MTHFR* gene.

Ovarian and peritoneal amyloidosis and premature ovarian insufficiency were found in the FMF group only. Kidney, liver, and intestinal amyloidosis were detected in 7 (3.3%) patients with FMF. There was no difference in the prevalence of concomitant endocrine diseases among all the groups, including Hashimoto thyroiditis, thyroid nodules, pituitary microadenomas, or hyperprolactinemia.

IVF outcome. The highest rate of successful pregnancy ratio to the absolute number of embryo transfers was seen in the FMF group (26/44, 59.1%) and the lowest was seen in the FGTB group (13/34, 38.2%). This may reflect the relatively lower rate of damaged endometrium (7.1%) in the FMF group compared with 50% in the FGTB group and 23.5% in the control group (data not shown).

For quality assessment of IVF, we used the "take-home baby rate" index, defined as the ratio of the actual number of babies born with survival over 27 days and the number of transfer embryo procedures. The take-home baby index in the FMF group was 36.4%, and it resembled that of the control group (37.5%). The lowest take-home baby rate was in the FGTB group (23.5%). Moreover, the frequency of spontaneous miscarriages in the first trimester was the highest in the FGTB group compared with the FMF and control groups (25% vs 16.7% and 17.6%, respectively; data not shown).

Analysis of pregnancy outcomes and obstetric complications. The main pregnancy outcome analysis included abortions, early termination of pregnancies, and congenital malformations. In the FMF group, 251 pregnancies were documented, of which 149 (59.4%) ended up with a normal outcome (Table 3). Forty pregnancies terminated as early spontaneous miscarriages (15.9%), 4 pregnancies ended as late miscarriages (1.6%), and 4 newborns (1.6%) had congenital malformations. Ectopic pregnancy was observed in 17 patients (6.8%). In the control group, out of 312 pregnancies, 190 (60.9%) ended successfully with live born babies, 51 pregnancies ended with early spontaneous miscarriages (16.3%), and 10 (3.2%) as late miscarriages. Eight (2.6%) newborns had congenital developmental abnormalities.

In the FGTB group, of 133 pregnancies, 79 (59.4%) pregnancies terminated with delivery (Table 3). Fourteen (10.5%) pregnancies ended in early spontaneous miscarriages, 11 (8.3%) ended as late miscarriages. Among late complications of pregnancy, antenatal mortality of fetuses was seen less often than in the control group: 2.3% and 3.5%, respectively. However, fetal hypoxia was significantly higher in the FGTB group (Table 3).

Delivery types among patients with complicated pregnancies. Table 4 shows the types of delivery in complicated pregnancies among the 3 groups. In the FMF group, there were 76 deliveries out of the 102 (74.5%) complicated pregnancies that were on time using natural methods. Thirteen (12.7%) deliveries required cesarean section. In the FGTB group, 36 out of 54 (66.7%)

Table 2. Genital and extragenital diseases in the cohorts examined.

	FMF, n = 211		FGTB, n = 127		Controls, n = 162		*P*
	N	%	N	%	N	%	
Chronic salpingo-oophoritis	77	36.5	81	**63.8**	59	36.4	< 0.001
Uterine fibroids	6	2.8	6	4.7	19	**11.7**	≤ 0.05
Endometriosis	13	6.2	5	3.9	33	**20.4**	< 0.0001
Ovarian cyst	38	18.0	27	21.3	21	13.0	> 0.29
Urogenital infection	27	12.8	25	19.7	74	**45.7**	< 0.001
Polycystic ovary syndrome	7	3.3	3	2.4	15	**9.3**	≤ 0.05
Amyloidosis of the ovaries, peritoneum	3	**1.4**	0	0	0	0	< 0.001
Premature ovarian failure	3	**1.4**	0	0	1	0.6	< 0.001
Chronic endometritis	10	4.7	19	15.0	31	**19.1**	< 0.001
Uterine abnormality	0	0	0	0	4	**2.5**	< 0.001
Genetic factor infertility (karyotype change)	2	0.9	0	0	5	**3.1**	≤ 0.01
Hyperprolactinemia	6	2.8	12	9.4	8	4.9	> 0.05
Autoimmune thyroiditis, hypothyroidism	16	7.6	14	11.0	25	15.4	> 0.05
Fibrocystic mastopathy	9	4.3	8	6.3	10	6.2	> 0.05
Thrombophilia	31	14.7	5	3.9	73	**45.1**	< 0.0001
Renal amyloidosis, amyloidosis of other organs	7	**3.3**	0	0	0	0	< 0.0001
Chronic renal failure	3	**1.4**	0	0	0	0	≤ 0.01
Behcet disease	2	**0.9**	0	0	0	0	≤ 0.01

Values significantly higher or lower in comparison with other groups are in bold. FGTB: female genital tuberculosis; FMF: familial Mediterranean fever.

Table 3. Delivery outcomes and obstetrical complications among all investigated groups.

	FMF Pregnancy, n = 251		FGTB Pregnancy, n = 133		Control Pregnancy, n = 312	
	N	%	N	%	N	%
No complications	149	59.4	79	59.4	190	60.9
Early miscarriages	40	15.9	14	10.5	51	16.3
Late miscarriages	4	1.6	11	**8.3**	10	3.2
Late obstetrics complications: antenatal fetal death	6	2.4	3	2.3	11	3.5
Delay of fetal development	3	1.2	5	**3.8**	4	1.3
Preeclampsia	8	3.2	4	3.0	10	3.2
Fetal hypoxia	6	2.4	7	**5.3**	6	1.9
Risk of pregnancy interruption	13	**5.2**	4	3.0	10	3.2
Congenital malformations	4	1.6	0	0	8	2.6
Premature placenta abruption of normal located placenta	1	0.4	0	0	3	1.0
Pregnancy extrauterine	17	**6.8**	6	4.5	9	2.9
Chi-square			47.2			
P			0.001			

Values significantly higher or lower in comparison with other groups are in bold. FGTB: female genital tuberculosis; FMF: familial Mediterranean fever.

deliveries were on time and in natural ways. Delivery by cesarean section was performed in 4 (7.4%). In the control group, 74 out of 122 (60.7%) deliveries were on time and in the natural way. A cesarean section was performed in 16 cases (13.1%).

Perinatal outcome. Height-weight indices at birth were significantly lower in the FGTB group, compared with the FMF and control groups. The body weight of neonates was 1890 ± 790 g in the FGTB group, 2800 ± 500 g in the FMF group, and 2770 ± 580 g in the control group ($P \leq 0.05$). The average height was 42 ± 7 cm in the second group compared with 48 ± 2.5 cm and 49 ± 3 cm in the first and third groups, respectively ($P \leq 0.001$; data not shown).

Analysis of the FMF subgroups. Of the 211 patients with FMF, 139 had infertility. Infertile FMF patients had a significantly higher rate of attacks, earlier onset of FMF, and higher frequency of fever compared with fertile patients (Table 5). When the genotypes of fertile and infertile FMF patients were compared, it was found that the rate of infertile patients among the homozygotes was slightly higher than that of the compound heterozygotes but significantly higher than the rate of heterozygotes

Table 4. Delivery types of complicated pregnancies in the 3 groups.

No. Complicated Pregnancies	FMF, n = 102		FGTB, n = 54		Controls, n = 122	
	N	%	N	%	N	%
Delivery on time, natural birth	76	74.5	36	66.7	74	60.7
Cesarean section	13	12.7	4	7.4	16	13.1
Premature delivery (36–38 w), natural birth	9	8.8	4	7.4	7	5.7
Premature delivery (36–38 w), cesarean section	4	3.9	7	13.0	17	13.9
Premature delivery (22–29 w)	0	0	3	5.5	8	6.6

FGTB: female genital tuberculosis; FMF: familial Mediterranean fever; w: weeks.

Table 5. Association between menstrual dysfunction, severity of disease, and infertility among patients with FMF.

	Infertility, n = 139	Fertility, n = 72	*P*
Menstrual dysfunction	103 (62.8)	61 (37.2)	0.067
Normal menstrual function	36 (76.6)	11 (23.4)	
Mild FMF	33 (50)	33 (50)	0.009
Moderate FMF	67 (70.5)	28 (29.5)	
Severe FMF	39 (78)	11 (22)	
No attacks	0 (0.0)	2 (100)	0.001
≥ 2	29 (72.5)	11 (27.5)	
1–2	60 (80.0)	15 (20.0)	
< 1	50 (53.2)	44 (46.8)	

Values are expressed as n (%) unless otherwise indicated. FMF: familial Mediterranean fever.

(Table 6). Further analysis revealed that infertility was significantly more common among patients homozygous for M694V and M680I. In addition, there was a clear correlation between the rate of infertility and delay in FMF diagnosis, irregular use of colchicine, or the use of low dose of the drug. Moreover, there was a higher rate of tuboperitoneal obstruction among FMF patients homozygous for *MEFV* mutations compared with the heterozygotes (Table 6).

DISCUSSION

In the present study, we compared the infertility causes and pregnancy outcome in 3 groups: FMF patients (group 1), FGTB (group 2), and healthy women with reproductive problems but without FMF or FGTB (group 3). Demographic data disclose that most patients in group 2 belonged to a low SES, whereas

Table 6. Distribution of infertile and fertile patients within the most frequent genotypes of FMF (n = 211).

	M694V/ M694V		V726A/ V726A		M680I/ M680I		V726A/E148Q	
	N	%	N	%	N	%	N	%
Infertility	30	90.9	1	25	3	100	2	50
Fertility	3	9.1	3	75	0	0	2	50
	M694V/ V726A		V726A/ M680I		M694V/A744S		E148Q/P369S	
	N	%	N	%	N	%	N	%
Infertility	18	69.2	26	66.7	2	66.7	4	66.7
Fertility	8	30.8	13	33.3	1	33.3	2	33.3
P				0.009				
	M694V/ E148Q		V726A/E479L		V726A/E369L		M694V/ M680I	
	N	%	N	%	N	%	N	%
Infertility	3	25	9	75	1	100	14	66.7
Fertility	9	75	3	25	0	0	7	33.3
	M694V/ -		V726A/-		M680I/-		E148Q/-	
	N	%	N	%	N	%	N	%
Infertility	9	64.3	7	43.8	6	66.7	4	50
Fertility	5	35.7	9	56.3	3	33.3	4	50
P				0.009				

FMF: familial Mediterranean fever.

most patients in the control group were classified as middle SES. The FMF group included patients from both classes in almost equal numbers. This observation may explain the presence of tuberculosis (TB) infection in the FGTB group, since their hygiene and access to medical services were probably limited.

Our study shows that primary infertility was more common among FMF and FGTB patients, while secondary infertility was predominant in the control group. This observation is quite expected since the most common cause for infertility was tubo-peritoneal obstruction. This complication occurred in FMF patients due to recurrent peritonitis and peritoneal adhesions, and in the FGTB group due to genital TB peritonitis. In the control group, the causes for infertility were either disovulation problems, endometriosis, or endometritis, following pelvic inflammatory disease. Zayed, *et al* reported that 18 out of 74 infertile women with FMF suffered from anovulation, whereas the majority, 56 (57.67%) patients, had excessive clear peritoneal fluid due to local inflammation[19]. These results are in accord with our observation. However, Nabil, *et al* claimed that the causes of infertility in patients with FMF are not different from those expected in the general population[15]. This observation is probably true in patients with FMF who are treated with colchicine, which can prevent the complications leading to infertility.

IVF was employed in the 3 studied groups. In the FMF and control groups, take-home baby indices were almost equal: 36.4% and 37.5%, respectively. Ozgur, *et al* reported that in their hands, the rate of take-home baby index was significantly higher, 58.3%[20]. Yilmaz, *et al* reported that successful pregnancy following IVF was achieved in only 3 out of 10 (30%) infertile FMF patients[21]. In the study of Zayed, *et al*, 26 (35%) out of 74 infertile women with FMF obtained successful pregnancy[19]. Thus, the IVF success rate in the last 2 studies resemble our results. The high success rate reported by Ozgur, *et al* was due to a higher number of treatment cycles, and the use of intracytoplasmic sperm injection when conventional IVF had failed[20]. The take-home baby index was much lower in the FGTB patients due to TB endometrial damage affecting successful implantation of the embryos.

The rate of successful deliveries was similar among all 3 groups (60%; Table 3). However, the rate of ectopic pregnancies was significantly higher in the FMF group. Frequent FMF attacks due to a lack of colchicine treatment can lead to strong uterine contractions, which may end up with ectopic implantation of the gestational sac.

The rate of early miscarriages and congenital malformation was quite similar in the FMF and control groups, whereas late miscarriages were more common in the FGTB group. Neonatal height and weight were also similar in groups 1 and 2, and significantly lower in the FGTB group. Nabil, *et al* reported a favorable pregnancy outcome in 26 patients with FMF treated with colchicine before and after pregnancy[15]. Their neonatal outcome was similar to that expected in the general population. Yasar, *et al* evaluated retrospectively, the outcome of pregnancy in 46 FMF patients and compared them with 138 control individuals[16]. They observed higher rates of cesarean delivery and low birth weight infants in the FMF group. However, rates of stillbirth did not differ between the groups. Preterm delivery rate was also higher in the FMF group, but this difference was not statistically significant[16]. In a population-based study, Ofir, *et al* compared the outcome of all pregnancies of women with and without FMF[22]. They found that FMF was an independent risk factor for preterm delivery. However, their perinatal outcome was comparable to the general population. Most of their FMF patients were treated with colchicine during pregnancy. In our study, higher rates of recurrent miscarriage occurred mainly in patients with FMF who were not on colchicine treatment. Thus, it seems that our results are in line with most observations of the above studies. However, the remaining differences may be explained by the different sizes of the studied groups, different study design, and different treatment regime with colchicine.

Comparing fertile and infertile FMF patients disclosed that infertility was clearly associated with carriage of M694V or M680I mutations (homozygotes). These genotypes are associated with more severe disease as early onset of the disease, more frequent attacks, and more joint involvement. In addition, infertility and bad pregnancy outcome were more common among females who did not take colchicine or were treated inadequately.

Many FMF patients are afraid to take colchicine during pregnancy due to the theoretical teratogenic potential of the drug. Ben-Chetrit, *et al* reported no difference in early abortions, late abortions, and congenital malformations between FMF patients who took colchicine during pregnancy and health-, age- and ethnicity-matched controls[12]. In a study by Diav-Citrin, *et al*, 238 colchicine-exposed pregnancies were compared with 964 pregnancies without colchicine exposure[23]. The results showed again that colchicine use did not cause increased cytogenetic risk.

The major drawbacks of this study are those inherent in all retrospective studies. However, the relatively large size of the groups studied and the large amount of data recruited may further strengthen our conclusions.

In summary, our study results show that the FMF group resembles the FTGB group regarding the etiologies for infertility. However, regarding IVF and pregnancy outcomes, the FMF group more resembles the control group. We observed that FMF has no significant effect on the frequency of early or late abortions, congenital malformations, or late obstetric complications. The slight predominance of early miscarriages and preterm delivery reported by others may be explained by a lack of adequate colchicine treatment. Low SES may also have a similar effect due to a limited access to colchicine and good healthcare. In a recent study, Atas, *et al* show that FMF disease onset (< 20 years), disease severity, and colchicine nonresponse were independent risk factors for FMF-associated infertility[24]. This observation is in line with our findings and supports the recommendation that patients with FMF should start colchicine immediately at diagnosis and continue treatment even during pregnancy, in order to control the disease and prevent its potential obstetric complications.

REFERENCES

1. Ben-Chetrit E, Levy M. Familial Mediterranean fever. Lancet 1998;351:659-64.

2. Ben-Chetrit E, Levy M. Reproductive system in familial Mediterranean fever: an overview. Ann Rheum Dis 2003;62:916-9.
3. Zemer D, Pras M, Shemer Y, Sohar E, Gafni J. Daily prophylactic colchicine in familial Mediterranean fever. In: Amyloid and amyloidosis. Proc 3rd International Symposium on Amyloidosis. Amsterdam-Oxford-Prinston: Exerpta Medica 1980:580-3.
4. Kasifoglu T, Bilge SY, Sari I, Solmaz D, Senel S, Emmungil H, et al. Amyloidosis and its related factors in Turkish patients with familial Mediterranean fever: a multicentre study. Rheumatology 2014;53:741-5.
5. French FMF Consortium. A candidate gene for familial Mediterranean fever. Nat Genet 1997;17:25-31.
6. The International FMF Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. Cell 1997;90:797-807.
7. Taylor EW. The mechanism of colchicine inhibition of mitosis. Kinetics of inhibition and the binding of H3-Colchicine. J Cell Biol 1965;25:145-60.
8. Ehrenfeld EN, Polishuk WZ. Gynecological aspects of recurrent polyserositis. Isr J Med Sci 1970;6:9-13.
9. Mamou H. [Periodic disease and endocrine disorders.] [Article in French] Semin Hop 1970;46:2024-9.
10. Ismajovich B, Zemer D, Revach M, Serr DM, Sohar E. The causes of sterility in females with familial Mediterranean fever. Fertil Steril 1973;24:844-7.
11. 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; 94:1860-91.
12. Ben-Chetrit Eli, Ben-Chetrit A, Berkun Y, Ben-Chetrit Eldad. Pregnancy outcomes in women with familial Mediterranean fever receiving colchicine: is amniocentesis justified? Arthritis Care Res 2010;62;143-48.
13. Uzunaslan D, Saygin C, Hatemi G, Tascilar K, Yazici H. No appreciable decrease in fertility in Behçet's syndrome. Rheumatology 2014;53:828-33.
14. Sarı İ, Birlik M, Kasifoğlu T. Familial Mediterranean fever: an updated review. Eur J Rheumatol 2014;1:21-33
15. Nabil H, Zayed A, State O, Badawy A. Pregnancy outcome in women with familial Mediterranean fever. J Obstet Gynaecol 2012;32:756-9.
16. Yasar O, Iskender C, Kaymak O, Yaman ST, Uygur D, Danisman N. Retrospective evaluation of pregnancy outcomes in women with familial Mediterranean fever. J Matern Fetal Neonatal Med 2014;27:733-6.
17. Mor A, Shinar Y, Zaks N, Langevitz P, Chetrit A, Shtrasburg S, et al. Evaluation of disease severity in familial Mediterranean fever. Semin Arthritis Rheum 2005;35:57-64.
18. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997;40:1879-85.
19. Zayed A, Nabil H, State O, Badawy A. Subfertility in women with familial Mediterranean fever. J Obstet Gynaecol Res 2012; 38:1240-4.
20. Ozgur K, Bulut H, Berkkanoglu M, Erdemir R, Coetzee K, Kay G. Colchicine treatment for FMF does not affect IVF outcome [abstract]. Fertility Sterility 2013;100:S507.
21. Yilmaz NK, Kara M, Kaba M, Coskun B, Erkilinc S, Erkaya S. Effect of Familial Mediterranean Fever on IVF outcome: a retrospective case series. Acta Clin Croat 2016;55:254-8.
22. Ofir D, Levy A, Wiznitzer A, Mazor M, Sheiner E. Familial Mediterranean fever during pregnancy: an independent risk factor for preterm delivery. Eur J Obstet Gynecol Reprod Biol 2008;141:115-8.
23. Diav-Citrin O, Shechtman S, Schwartz V, Avgil-Tsadok M, Finkel-Pekarsky V, Wajnberg R, et al. Pregnancy outcome after in utero exposure to colchicine. Am J Obstet Gynecol 2010;203:144.
24. Atas N, Armagan B, Bodakci E, Satis H, Sari A, Bilge NSY et al. Familial Mediterranean fever-associated infertility and underlying factors. Clin Rheumatol 2020;39:255-61.