INFERTILITY CAUSES AND PREGNANCY OUTCOME IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER (FMF) AND CONTROLS

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Key words: FMF, Pregnancy, colchicine, infertility

Short running title: Infertility, pregnancy in FMF

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Disclosures: The authors declare no conflicts of interest

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

ABSTRACT

Objective: Recurrent attacks of peritonitis of Familial Mediterranean fever (FMF), may lead to peritoneal adhesions and fallopian tube obstruction. Colchicine - 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 FMF patients. The aims of the study are to evaluate the causes of infertility and pregnancy outcome in FMF patients and to compare them with two groups: non-FMF patients with peritoneal female genital tuberculosis (FGTB) and normal healthy control.

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 FGTB patients and the normal control patients with reproductive problems were recruited successively from a large gynecology clinic in Yerevan. Genetic analyses for FMF were performed using ViennaLab Diagnostics GmbH Strip Assay.

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 (167patients). Infertility in FMF patients 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.

INTRODUCTION

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 (SAA) amyloidosis. In this condition amyloid fibers are deposited in kidneys, liver and intestines and later may involve the cardiovascular system too (3, 4). The gene associated with FMF (*MEFV*) was isolated in 1997 by two 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 via defective sperm and oocyte proliferation leading to difficulties in obtaining pregnancy and normal deliveries (8-11).

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. Thirteen (36%) women had infertility, 6 (46%) of whom had ovulatory dysfunction and 4 (31%) had peritoneal adhesions (11).

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 a 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 (13-16). Therefore, we decided to study the reproductive system and pregnancy outcomes in our FMF female patients in Armenia. We compared them with two additional groups: Non FMF patients with peritoneal female genital tuberculosis (FGTB) and normal 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 normal individuals can serve as a control for both groups (FMF and FGTB).

PATIENTS AND METHODS

FMF patients' group (Group 1). This group was chosen from the large data of the National Center of Medical Genetics and Primary Health Care in Yerevan, Armenia. During the years 1998 to 2018, 32,000 individuals were screened for *MEFV* mutations. Of this group we chose successively women in their reproductive years (18-49) who had a confirmed diagnosis of familial Mediterranean fever, 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 uterine 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 include: disease age of onset, attacks frequency, the 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).

Female genital tuberculosis (FGTB) group (Group 2). Since FMF is a prototype of a non-infectious 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 of us (PS and OS) conduct a large center for patients with FGTB peritonitis and fertility problems. Matched aged FGTB patients were recruited successively from this clinic during the years 2010-2018.

Normal control (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 (three groups) were interviewed and checked by OS and PS. For the FMF patients, a large chart containing demographic, clinical, laboratory and genetic data was filled (Supplement 1). In addition, a full gynecological evaluation was carried out for all the patients analyzed in the study (Supplement 2). 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, Yerevan, Armenia (ethics approval number №2/13, 11.02.2018).**

Molecular genetic methods for FMF diagnosis

All FMF patients 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 GmbH Strip Assay 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, R761H.

Statistical methods

Statistical analysis was performed using a complex data processing package - SPSS 21.0. Mean standard deviation and standard error were used to describe numerical data. For qualitative data, rates and proportions were applied. For comparison of continuous variables two-sided Student's test for independent groups was used. For comparison of quantitative outcomes between groups, we used Pearson's chi-square test (χ^2). It was also used to analyze inter-group differences on quantitative features. In case of quantitative limitations, two-side Fisher's exact test was used. In all cases, results were considered statistically significant at $p \leq 0.05$ value.

RESULTS

The studied groups.

Figure 1 depicts the flow chart for recruiting the patients with FMF and reproductive problems (Supplement 3)**.** 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 5,679 women in their reproduction period that carried *MEFV* mutations (one or two). Of this group 1,102 women were excluded since they were healthy carriers of a single mutation

(heterozygotes) without any clinical manifestation. From the remaining 4,577 patients with definite FMF (clinically and genetically), **211** patients were found with reproductive disorders.

During the years 2010-2018, **127** patients with female genital TB (FGTB) and reproductive disorders were recruited for the study. Concomitantly, **162** women with reproductive problems but without FMF, FGTB, or any other systemic disease were recruited as a control.

Comparisons between the FMF group and the FGTB and control groups

Demographic features:

At the study period, the age of the patients in group 1 ranged between 18 and 45 years (average 21.3±6.4 years) while in group 2 between 20 and 46 years (average of 28.4±7.0 years). 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.

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

Infertility

According to the WHO recommendations, "infertility" was defined as the absence of clinical pregnancy following 12 or more months of regular sexual intercourse without protection. Table1 shows that 139 (66%) out of 211 FMF patients had infertility, of whom 116 (83.5%) had primary infertility. In the FGTB group infertility was diagnosed in 69 (55%) patients, of whom 58 (84.1%) had primary infertility. The control group included 115 (71%) infertile patients consisting of 47 (40.9%) patients with primary infertility. The most prevalent cause of infertility was tubo-peritoneal. 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 appendages, endometriosis, and operative interventions (cystectomy and salpingectomy).

The second cause of infertility in patients from the FMF group was dis-ovulation, found in 77 patients (55.4%). In many cases it was concomitant with tubo-peritoneal infertility. Dis-ovulation 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 organs resection. Dis-ovulation 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 (4%) in group 2 and in 73 patients (45%) 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 – anti thrombin fragments and serum D-dimer) and platelet aggregation . We have also looked for factor - V Leiden deficiency, mutation in the prothrombin gene C20210A and for mutations in the *MTHFR* gene.

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

In vitro fertilization (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 embryos procedures". 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% against 16.7% and 17.6% respectively).

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 (59.3%) ended up with normal outcome (Table 3). Forty pregnancies terminated as early spontaneous miscarriages (15.9%), 4 pregnancies ended as late miscarriages (1.6%), four newborns (1.6%) had congenital malformations. Ectopic pregnancy was observed in 17 patients (6.8%). In the control group, out of 312 pregnancies 190 (61.0%) ended successfully with live born babies, 51 pregnancies ended with early spontaneous miscarriages (16.3%), 10 (3.2%) as late miscarriages. Eight newborns had (2.6%) congenital developmental abnormalities.

In the FGTB group, of 133 pregnancies, 79 (59.4%) pregnancies terminated with child delivery (Table 3). Fourteen (10.5%) pregnancies ended in early spontaneous miscarriages, 11 (8.3%) ended as late miscarriage. 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 second group (Table 3).

Delivery types among patients with complicated pregnancies

Table 4 shows the types of delivery in complicated pregnancies among the three groups. In the FMF group 76 out of the 102 (74%) complicated pregnancies, deliveries were on time and in natural ways. Thirteen (12.7%) deliveries required cesarean section. In the FGTB group 36 out of 54 (66.6%) 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 (60.6%) deliveries were on time and in 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±790g in the FGTB group, 2800±500 g in the FMF group and 2770±580g 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 ($p \leq 0,001$).

Analysis of the FMF sub - groups

Of the 211 FMF patients, 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 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 peritoneal tubal 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 three groups: FMF patients (group 1), females with genital peritoneal tuberculosis (FGTB) (group 2) and normal women with reproductive problems without FMF or FGTB (group 3). Demographic data disclose that most patients in group 2 belonged to a low economic class whereas most patients in the control group were classified as middle class. The FMF group included patients from both classes in almost equal numbers. This observation may explain the presence of 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 tubal- 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 dis-ovulation problems, endometriosis or endometritis, following pelvic inflammatory disease (PID). Zayed at 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 FMF patients who are treated with colchicine which can prevent the complications leading to infertility.

In vitro fertilization (IVF) was employed in the three 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 at al. 26 (35%) out of 74 infertile

women with FMF obtained successful pregnancy (19). Thus, the IVF success rate in the last two 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 (ICSI) 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 the three 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 (CD) 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 joints 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 healthy, 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 it resembles more 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 an adequate colchicine treatment. Low economic class may also have a similar impact due to a limited access to colchicine and a good health care. 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 FMF patients should start colchicine immediately at diagnosis and continue treatment even during pregnancy, in order to control the disease and prevent its potential obstetric complications.

Key messages

1. FMF and colchicine may potentially affect fertility and pregnancy outcome.

2. In vitro fertilization (IVF) success rate and pregnancy outcomes were poor in the TB group but were comparable between the FMF and control normal groups.

3. Infertility in FMF patients is in direct relationship with more severe disease

4. Adequate treatment with colchicine may prevent reproductive disorders and poor pregnancy outcome in FMF patients

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Table 1

Association between infertility types with FMF and Tuberculosis in comparison with the control group

	FMF n=139		FGTB n=69		Control n=115			
Types of Infertility	**N**	**%**	N	%	**N**	**%**	$\chi 2$	p-value
Tubal-peritoneal	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	**87.4**	10	8.7	23.7	0.001*
Dis-ovulation	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's 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*

Table 2

Structure of genital and extragenital diseases in the cohort of examined patients

	FMF		FGTB		Control		p
	№	%			№	%	
Chronic salping-oophoritis	77	36,5	81	**63,8**	59	36,4	P<0.001*
Uterine fibroids	6	2,8	6	4,7	19	**11,7**	P≤0.05*
Endometriosis	13	6,2	5	3,9	33	**20,4**	P<0.0001*
Ovarian cyst	38	18,0	27	21,3	21	13,0	P>0,29
Urogenital infection	27	12,8	25	19,7	74	**45,7**	P<0.001*
Polycystic ovary syndrome	7	3,3	3	2,4	15	**9,3**	P≤0.05*
Amyloidosis of the ovaries, peritoneum	3	**1,4**	0	0	0	0	P<0.001*
Premature ovarian failure	3	**1,4**	0	0	1	0,6	P<0.001*
Chronic endometritis	10	4,7	19	15,0	31	**19,1**	P<0,001*
Uterine abnormality	0	0	0	0	4	**2,5**	P<0.001*
Genetic factor infertility (karyotype change)	2	0,9	0	0	5	**3,1**	P≤0.01*
Hyperprolactinemia	6	2,8	12	9,4	8	4,9	P>0.05
Autoimmune thyroiditis, hypothyroidism	16	7,6	14	11,0	25	15,4	P>0.05
Fibrocystic mastopathy	9	4,3	8	6,3	10	6,2	P>0.05
Thrombophilia	31	14,7	5	4,0	73	**45,0**	P<0.0001*
Renal amyloidosis, amyloidosis of other organs	7	**3,3**	0	0	0	0	P<0.0001*
Chronic renal failure	3	**1,4**	0	0	0	0	P≤0.01*
Behcet's disease	2	**0,9**	0	0	0	0	P≤0.01*

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	59,3	79	59,4	190	61,0
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
χ^2	47.2					
p-value	0.001*					

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

Number of complicated pregnancies	FMF n=102		FGTB n=54		Control n=122	
	N	%	N	%	N	%
Delivery on time, Natural birth	76	74.5	36	66.6	74	60.6
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	12. 9	17	13.9
Premature Delivery (22-29 w)	0	0	3	5.5	8	6.5

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

	Infertility (N/%)	**Fertility (N/%)**	**p-value**
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 and more	29 (72.5)	11 (27.5)	
1-2	60 (80.0)	15 (20.0)	
<1	50 (53.2)	44 (46.8)	

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	**66,6**	4	**66,7**
Fertility	8	30,8	13	33,3	1	33,3	2	33,3
p-value	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-value	0.009*							