Letters to the Editors

Reproductive disorders in homozygote and heterozygote familial Mediterranean fever patients and controls

Sirs,

Familial Mediterranean fever (FMF) is a hereditary, autoinflammatory disease characterised by recurrent fever and serositis, affecting the peritoneum, pleura, and joints (1). The gene associated with FMF, *MEFV*, was identified in 1997. It consists of 10 exons and contains about 400 genetic variants. The most common mutations in Middle Eastern and Armenian FMF patients are M694V, M680I, V726A, M694I, and E148Q. As FMF predominantly affects individuals in their reproductive years, fertility and pregnancy outcomes are of particular concern. Acute peritonitis in FMF patients may lead to peritoneal adhesions, and fallopian tube obstruction leading to mechanical infertility. Peritonitis during an acute FMF attack in a pregnant woman may induce uterine contractions and miscarriage or premature birth (2). Amyloidosis, the most devastating complication of FMF may theoretically thicken the ova resulting in difficulties in sperm penetration. Thus, FMF may seriously affect the reproductive function in women with the disease (3).

Previous studies showed a clear correlation between the patient genotype and FMF clinical severity (4, 5). However, no specific search looked for a direct correlation between the patient genotype and the reproductive system. This study aimed to compare the reproductive disorders in homozygote and heterozygote FMF patients and healthy controls. The study involved 249 women with reproductive disorders from a single gynaecology clinic at the National Centre of Medical Genetics and Primary Health Care (NCMG) in Yerevan, Armenia. They were divided into three groups: Group 1: 40 women with FMF carrying two identical *MEFV* mutations (homozygotes). Group 2: 47 women with FMF carrying one *MEFV* variant (heterozygotes). Group 3: a control group of women with reproductive problems but no other systemic disease, especially FMF.

All patients were recruited and examined successively by OA and PS, from a population of women who visited the same gynaecology clinic for reproductive problems. Informed consent was obtained from all participants. Reproductive issues assessed included menstrual dysfunction, primary and secondary infertility, endometrial hyperplasia, spontaneous miscarriages, ectopic pregnancy, and premature delivery. FMF diagnosis was confirmed using the Tel-Hashomer criteria in addition to genetic analysis of the 12 most common *MEFV* mutations: E148Q, P369S, F479L, M680I (G/C), M680I (G/A), I692del, M694V, M694I, K695R, V726A, A744S, R761H (6). A severity score was calculated for each FMF patient.

Most of the results are summarised in the Table. Groups 1 and 2 were significantly younger than the control group, probably because menstrual issues were more prevalent among the FMF patients. Homozygotes exhibited more severe FMF, with the M694V/M694V genotype found in 75% of these patients followed by M680I/M680I and V726A/V726A. The most common genotypes among heterozygotes patients were M694V/-, M680I/-, V726A/-, and E148Q/-. Primary infertility was significantly higher in homozygotes (79.4%) compared to heterozygotes (38.5%). The main cause of infertility in FMF patients was tubo-peritoneal. Adhesions in the pelvic, peri-tubal, and periovarian regions were more common in FMF patients compared to controls. Infertility was 1.54 times more frequent in homozygotes compared to heterozygotes and controls. Infertility causes among the control group included endometriosis, uterine fibroids, and endometritis. Homozygotes had a higher rate of spontaneous miscarriages and a lower pregnancy rate compared to heterozygotes. Live birth rates were higher in heterozygotes. Non-compliance or inadequate colchicine treatment was associated with higher infertility rates, with 38.2% of homozygotes and 84.6% of heterozygotes receiving insufficient treatment. Delayed colchicine use due to late FMF diagnosis or irregular usage also contributed to infertility issues.

We choose to study two FMF groups with clear definite diagnoses of FMF based on clinical features and carriage of 2 identical mutations (group 1) or based on clinical criteria, carriage of a single *MEFV* variant, and response to colchicine (group 2). By this choice, we searched for clear differences between the groups that could be related mainly to genotype-phenotype variations concerning their reproductive system.

In conclusion, FMF severity, genotype, and colchicine treatment adherence, impact pregnancy outcomes and reproductive health. This study underscores the need for improved patient education on strict colchicine adherence to mitigate FMF adverse effects on reproduction.

Table I. Demographic features and reproductive disorders of the studied participants.

Reproductive disorders Number of participants	Homozygotes n=40	Heterozygotes n=47	Controls n=162	*p*
Age (years)	29.5 (27; 36,3)	27 (24.5; 29)	32 (28; 36)	<0.001[1]
Age at primary diagnosis (years)	22 (5.8; 29)	25 (21; 27)	30 (27; 33)	<0.001[1]
Duration of infertility (years)	2 (1; 4)	3.5 (2; 7)	4 (3; 6)	0.02[1]
Delay in diagnosis of the underlying disease (years)	18.5 (5.5; 25.3)	5 (4; 10)	3 (2; 5)	<0.01[1]
Postponed repeated surgical interventions on the pelvic organs	15 (37.5%)	14 (29.8%)	29 (17.9%)	0.015[2]
Pregnancy rate per patient	13/40 (32.5%)	37/47 (78.7%)	117/162 (72.2%)	<0.001[2]
Spontaneous miscarriages	4/13 (30.8%)	5/37 (13.5%)	24/117 (20.5%)	<0.001[2]
Live birth rate per pregnancy	8/13 (61.5%)	26/37 (70.3%)	73/117 (62.4%)	0.057[2]
Free fluid in the pelvis	37 (92.5)	20 (42.6)	28 (17.3)	<0.001
Infertility	34 (85.0)	26 (55.3)	115 (70.9)	0.012[2]
Primary infertility	27/34 (79.4)	10/26 (38.5)	46/115 (40.0)	<0.001[2]
Pelvic adhesions/peri-tubal/ periovarian adhesions	33/34 (97.1)	21/26 (80.8)	40/115 (34.8)	<0.001
Severity score				
mild	1 (2.5%)	22 (46.8)	-	
moderate	15 (37.5%)	24 (52.2%)	-	
severe	24 (60%)	1 (2.2%)	-	

[1]*p*-values obtained using the Kruskal-Wallis test; [2]*p*-values obtained using Pearson's χ^2 test with Yates correction; [3]*p*-values obtained using Fisher's exact test.

P. Sotskiy[1], *PhD*
O. Sotskaya[1,2], *PhD*
T. Sarkisian[1,2], *MD*
H. Hayrapetyan[1,2], *MD*
E. Ben-Chetrit[3], *MD*
M. Safaryan[2], *MD*

[1]Center of Medical Genetics and Primary Health Care, Yerevan, Armenia;
[2]Yerevan State Medical University after Mkhitar Heratsi, Yerevan, Armenia;
[3]Rheumatology Unit, Hadassah-Hebrew University Medical Center, Jerusalem, Israel.

Please address correspondence to:
Eldad Ben-Chetrit
Rheumatology Unit,
Hadassah-Hebrew University
Medical Center, POB: 12000,
91120 Jerusalem, Israel.
E-mail: eldad@hadassah.org.il

Competing interests: none declared.

References

1. BEN-CHETRIT E, LEVY M: Familial Mediterranean fever. *Lancet* 1998; 351: 659-64. https://doi.org/10.1016/s0140-6736(97)09408-7
2. 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(7): 733-36. https://doi.org/10.3109/14767058.2013.837446
3. YANMAZ MN, ÖZCAN AJ, SAVAN K: The impact of familial Mediterranean fever on reproductive system. *Clin Rheumatol* 2014; 33(10): 1385-88. https://doi.org/10.1007/s10067-014-2709-9
4. OZEN S: Update in Familial Mediterranean fever. *Curr Opin Rheumatol* 2021; 33(5): 398-402. https://doi.org/10.1097/bor.0000000000000821
5. BABAOGLU H, ARMAGAN B, BODAKCI E *et al*.: Factors associated with damage in patients with familial Mediterranean fever. *Clin Exp Rheumatol* 2020; 38 (Suppl. 127): S42-S48.
6. LIVNEH A, LANGEVITZ P, ZEMER D *et al*.: Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997; 40(10): 1879-85. https://doi.org/10.1002/art.1780401023