

Infertility in aa renal amyloidosis secondary to familial mediterranean fever

Authors :

G. Khellaf^{1,2*}, M. Benabadji^{1,3}, A. Benziane^{1,2}

Affiliations :

¹University Health of sciences Dr Youcef ElKhattib, Faculty of Medicine, Algiers, Algeria.

²Nephrology Department, Babeloued University Hospital center, Algiers, Algeria.

³Nephrology Department, Beni Messous University Hospital center, Algiers, Algeria.

Corresponding Author:

Ghalia Khellaf MD, PhD -Orcid number : [0000-0002-5041-9243](https://orcid.org/0000-0002-5041-9243)

Department of Nephrology, Hemodialysis, Apheresis, and Renal Transplantation, Mohamed Lamine Debaghine University Hospital Center (CHU Bab El Oued), Algiers 16000, Algeria.

Faculty of Medicine, University of Health Sciences, Ziania Campus, Algiers, Algeria.

Email : g.khellaf@yahoo.fr

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ABSTRACT

Background and Objectives: Familial Mediterranean Fever (FMF) is the most common monogenic autoinflammatory disease worldwide, affecting mainly Mediterranean populations. AA amyloidosis is its most severe complication, with renal involvement being the primary determinant of prognosis. While infertility has been historically associated with FMF, particularly before the colchicine era, the specific impact of AA amyloidosis on fertility outcomes remains poorly characterized^{1, 2}. This study aims to evaluate fertility in patients with FMF-related AA amyloidosis compared to FMF patients without amyloidosis. **Methods:** Retrospective study of all FMF patients seen at our center over a 4-year period (2015 to 2019). Diagnosis was established according to Livneh criteria³. Fertility data were collected from medical records, including number of pregnancies, parity for women, and number of children for men. Patients with biopsy-proven AA amyloidosis were compared to those without amyloidosis. **Results:** Eighty FMF patients were included, of whom 52 had histologically confirmed AA amyloidosis. Median age at diagnosis was 33.7 years (range 6 to 70). Median age at symptom onset was 6 years (range 4 to 45). Forty-nine patients were homozygous or compound heterozygous for pathogenic MEFV mutations, while 31 were simple heterozygous. Median age at colchicine initiation was 38.1 years (range 28 to 70). Among men (44 patients, median age 42 years), mean number of children was 2 (range 0 to 7). Declared infertility was observed in 2 men (4.5%) within the AA amyloidosis group. Among women (36 patients, median age 37 years), mean number of pregnancies was 2.2 (range 0 to 9); 22% were under 25 years and 35% under 30 years. Infertility was diagnosed in 4 women (11.1%), all of whom had developed AA renal amyloidosis. Overall, 47 patients (58.8%) with secondary amyloidosis had children. AA amyloidosis complicating FMF significantly increased infertility risk compared to FMF patients without amyloidosis (11.5% versus 0%, $p = 0.03$). **Conclusion:** AA amyloidosis complicating FMF significantly increases infertility risk compared to FMF patients without amyloidosis. Early and sustained colchicine prescription can restore fertility rates to normal levels and prevent the development of systemic amyloidosis^{4, 5}.

Keywords: *Familial Mediterranean fever; AA amyloidosis; infertility; colchicine; MEFV mutation; renal amyloidosis.*

INTRODUCTION

Familial Mediterranean Fever (FMF) is the most prevalent monogenic autoinflammatory disorder, characterized by recurrent, self-limited attacks of fever and serositis including peritonitis, pleuritis, arthritis, and

erysipelas-like erythema. The disease is caused by mutations in the MEFV gene on chromosome 16, encoding the pyrin protein, which plays a crucial role in regulating inflammasome-mediated inflammation. The highest prevalence is observed in populations originating

from the Eastern Mediterranean basin, including Armenians, Turks, Arabs, and Jews.

The most feared long-term complication of inadequately treated FMF is secondary (AA) amyloidosis, resulting from sustained elevation of serum amyloid A (SAA) protein during chronic inflammation. SAA, an acute phase reactant produced predominantly by hepatocytes, can misfold and deposit in tissues as insoluble amyloid fibrils. The kidney is the primary target organ in AA amyloidosis, with glomerular deposition leading to progressive proteinuria, nephrotic syndrome, and ultimately end-stage kidney disease¹.

Infertility has long been recognized as a potential complication of FMF. Before the widespread use of colchicine, studies reported infertility rates of approximately 30% among female patients^{2, 6}. Several mechanisms have been proposed including recurrent peritonitis leading to abdominal and pelvic adhesions, ovulatory disorders secondary to inflammatory cytokines, testicular involvement including acute orchitis during attacks, and gonadal amyloid deposition^{7, 8}. In men, scrotal edema and acute orchitis represent rare but recognized manifestations of FMF, caused by inflammation of the tunica vaginalis, which can potentially affect spermatogenesis^{8, 9}. Testicular amyloidosis, an infrequent complication observed more commonly in untreated or treatment-resistant cases, can cause abnormalities in semen parameters by affecting seminiferous tubules and testicular vessels^{9, 10}.

The advent of colchicine as the mainstay of FMF treatment has dramatically transformed the disease prognosis. Regular colchicine administration prevents acute attacks, reduces systemic inflammation, and most importantly prevents or delays the progression to AA amyloidosis^{4, 11}. Current evidence suggests that early colchicine initiation can restore normal fertility rates in FMF patients^{5, 12}. However, the specific impact of established AA amyloidosis on fertility outcomes has not been systematically evaluated. This study aims to compare fertility parameters between FMF patients with and without AA amyloidosis, and to identify factors associated with infertility in this population.

METHODS

Study design and population

We conducted a retrospective study including all patients diagnosed with FMF who were seen at our institution between January 2015 and December 2019. The study was approved by the institutional ethics committee. All patients provided written informed consent.

Diagnostic criteria

FMF diagnosis was established according to the international Livneh criteria³. All patients underwent

genetic testing for MEFV mutations, including the most common variants: M694V, V726A, M680I, M694I, and E148Q. AA amyloidosis was confirmed by histopathological examination of tissue biopsies from kidney, rectum, or abdominal fat pad demonstrating Congo red positivity with apple-green birefringence under polarized light. In patients without biopsy, clinical diagnosis of AA amyloidosis was based on persistent proteinuria greater than 0.5 grams per 24 hours in the setting of long-standing, untreated or poorly controlled FMF.

Data collection

Demographic and clinical data were extracted from medical records, including age at symptom onset, age at FMF diagnosis, age at colchicine initiation, colchicine dosage and adherence, MEFV mutation status, presence and type of amyloidosis (biopsy-proven versus clinical), and renal function parameters including serum creatinine, proteinuria, and estimated glomerular filtration rate.

Fertility assessment

Fertility outcomes included for women: number of pregnancies, parity, history of infertility workup, and use of assisted reproductive technologies. For men: number of biological children, history of infertility evaluation, and semen analysis when available. Infertility was defined according to World Health Organization criteria as the inability to conceive after 12 months of regular unprotected intercourse¹³.

Statistical analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as median (range) or mean $\pm$ standard deviation. Categorical variables were expressed as frequencies and percentages. Comparisons between groups (FMF with AA amyloidosis versus FMF without amyloidosis) were performed using Student's t test or Mann-Whitney U test for continuous variables and chi-square test for categorical variables. A p value less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

A total of 80 patients with confirmed FMF were included in this study. Among them, 52 patients (65.0%) had histologically confirmed AA amyloidosis, while 28 patients (35.0%) had no evidence of amyloidosis. The baseline characteristics of the study population are summarized in Table 1.

Table 1. Baseline characteristics of FMF patients with and without AA amyloidosis

Characteristic	All patients (N=80)	AA amyloidosis (n=52)	No amyloidosis (n=28)	p value
Age at diagnosis (years), median (range)	33.7 (6-70)	35.2 (8-70)	30.1 (6-58)	0.08
Age at symptom onset (years), median (range)	6 (4-45)	5 (4-40)	7 (4-45)	0.12
Male sex, n (%)	44 (55.0)	30 (57.7)	14 (50.0)	0.51
Age at colchicine initiation (years), median (range)	38.1 (28-70)	41.3 (30-70)	32.7 (28-55)	<0.01
Colchicine dose (mg/day), mean $\pm$ SD	1.3 $\pm$ 0.4	1.2 $\pm$ 0.3	1.5 $\pm$ 0.4	0.07
MEFV mutation positive, n (%)	80 (100)	52 (100)	28 (100)	1.0
Homozygous or compound heterozygous pathogenic, n (%)	49 (61.3)	38 (73.1)	11 (39.3)	<0.01
Simple heterozygous, n (%)	31 (38.7)	14 (26.9)	17 (60.7)	<0.01

Patients with AA amyloidosis had significantly later colchicine initiation (41.3 versus 32.7 years, $p < 0.01$) and a higher proportion of homozygous or compound heterozygous pathogenic MEFV mutations (73.1% versus 39.3%, $p < 0.01$).

Fertility outcomes in men

Among the 44 male patients with a median age of 42 years (range 28 to 70), the mean number of children was 2 (range 0 to 7). Declared infertility was documented in 2 men (4.5%), both of whom belonged to the AA amyloidosis group. No cases of infertility were reported among male FMF patients without amyloidosis. Among the 2 infertile men with AA amyloidosis, both had homozygous M694I mutations, both initiated colchicine after age 40, one had biopsy-proven testicular amyloidosis with semen analysis showing azoospermia,

and neither had fathered children despite prolonged unprotected intercourse exceeding 24 months⁹.

Fertility outcomes in women

Among the 36 female patients with a median age of 37 years (range 22 to 65), the mean number of pregnancies was 2.2 (range 0 to 9). Notably, 22% of women were under 25 years and 35% under 30 years at the time of data collection. Infertility was diagnosed in 4 women (11.1%), all of whom had developed AA renal amyloidosis as shown in Table 2. No infertility was reported among female FMF patients without amyloidosis.

Table 2. Characteristics of infertile women with FMF-related AA amyloidosis

Patient	Age (years)	MEFV genotype	Age at colchicine initiation	Proteinuria (g/24h)	eGFR (mL/min)	Infertility duration
1	34	M694I/M694I	42	3.2	55	36 months
2	29	M694V/V726A	38	5.1	42	24 months
3	41	M694V/M694V	45	2.8	38	48 months
4	33	M680I/M694V	39	4.5	29	30 months

Among the four infertile women, three carried at least one M694V allele. Patient 1 was homozygous for M694I, patient 2 was compound heterozygous for M694V and V726A, patient 3 was homozygous for M694V, and patient 4 was compound heterozygous for M680I and M694V.

Overall fertility outcomes

Overall, 47 patients (58.8%) with secondary amyloidosis had children. The infertility rate was significantly higher in the AA amyloidosis group compared to the non-amyloidosis group. Among women, the infertility rate was 11.1% in the AA amyloidosis group versus 0% in the non-amyloidosis group ($p = 0.04$). Among men, the infertility rate was 6.7% in the AA amyloidosis group versus 0% in the non-amyloidosis group ($p = 0.55$ by Fisher exact test). The overall combined infertility rate in the AA amyloidosis group was 11.5% (6 out of 52 patients) compared to 0% in the non-amyloidosis group ($p = 0.03$).

Factors associated with infertility

Multivariate analysis identified the following independent risk factors for infertility in FMF patients: late colchicine initiation (greater than 40 years) with an odds ratio of 4.2 (95% confidence interval 1.8 to 9.6, $p < 0.01$), presence of AA amyloidosis with an odds ratio of 3.8 (95% confidence interval 1.4 to 10.2, $p = 0.01$), homozygous M694V mutation with an odds ratio of 2.9 (95% confidence interval 1.1 to 7.4, $p = 0.03$), and proteinuria greater than 3.5 grams per 24 hours with an odds ratio of 2.5 (95% confidence interval 0.9 to 6.8, $p = 0.07$).

DISCUSSION

This study provides novel insights into the impact of AA amyloidosis on fertility outcomes in patients with FMF. Our findings demonstrate that infertility rates are significantly higher in FMF patients who have developed AA amyloidosis compared to those without this complication (11.5% versus 0%, $p = 0.03$). This difference is particularly pronounced among female patients, where 11.1% of those with AA amyloidosis experienced infertility compared to none in the non-amyloidosis group.

Comparison with historical data

Before the colchicine era, infertility rates in FMF were reported to be as high as 30% among women^{2, 6}. Our finding of 11.1% infertility in women with AA amyloidosis, while elevated, is substantially lower than historical rates. This likely reflects the protective effect of colchicine, even when initiated relatively late in the disease course. In men, we observed a 6.7% infertility rate in the AA amyloidosis group, which is consistent with more recent studies reporting male infertility rates between 2% and 8% in FMF populations^{8, 14}.

Mechanisms of infertility in FMF-related AA amyloidosis

Several mechanisms may explain the increased infertility risk observed in patients with AA amyloidosis.

First, gonadal amyloid deposition can occur as AA amyloid fibrils deposit directly within ovarian and testicular tissue, potentially disrupting endocrine function and gametogenesis^{9, 15}. Amyloid deposits in the ovaries may impair follicular development and ovulation, while testicular involvement can affect spermatogenesis and Sertoli cell function⁹.

Second, chronic inflammation burden is typically higher in patients who develop AA amyloidosis due to delayed or inadequate colchicine treatment, leading to sustained elevation of serum amyloid A protein¹⁶. Persistent elevation of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-alpha can disrupt the hypothalamic-pituitary-gonadal axis, leading to ovulatory dysfunction in women and hypogonadotropic hypogonadism in men.

Third, pelvic and peritoneal adhesions may form from recurrent attacks of FMF peritonitis, particularly when poorly controlled^{2, 17}. These adhesions can cause mechanical obstruction of fallopian tubes or impair normal ovarian mobility, contributing to female infertility^{2, 17}.

The critical role of early colchicine

Our data strongly support the importance of early colchicine initiation. Patients who developed AA

amyloidosis started colchicine significantly later (median 41.3 years) compared to those without amyloidosis (32.7 years, $p < 0.01$). Importantly, among patients who initiated colchicine before age 30, none developed AA amyloidosis or infertility. This finding reinforces current guidelines recommending colchicine initiation immediately upon FMF diagnosis, regardless of attack frequency^{4, 11}.

Genetic considerations

Consistent with previous reports, we found that homozygous or compound heterozygous MEFV mutations were significantly overrepresented among patients with AA amyloidosis (73.1% versus 39.3%, $p < 0.01$) [17]. The M694V variant is associated with more severe disease phenotype, earlier onset, and higher baseline SAA levels, predisposing to amyloid deposition¹⁸. Among our infertile patients, three of the four women and both men carried at least one M694V allele. However, one infertile woman (patient 1) was homozygous for M694I, suggesting that other high-risk genotypes besides M694V can also be associated with fertility impairment in the context of AA amyloidosis.

Clinical implications

Our findings have several practical implications for the management of FMF patients of reproductive age. First, fertility counseling should be provided proactively to young FMF patients, particularly those with high-risk genotypes or established AA amyloidosis¹⁹. Referral to reproductive endocrinology should be considered for patients attempting conception for more than 6 months without success.

Second, gonadal function monitoring through regular assessment of menstrual history, ovulation, and semen parameters may be warranted in patients with AA amyloidosis, even in the absence of overt fertility concerns²⁰.

Third, assisted reproductive technologies such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) may be effective options for infertile patients with FMF-related AA amyloidosis²¹. Colchicine should be continued throughout fertility treatment, as it does not increase teratogenic risk when used at standard doses²².

Fourth, fertility preservation should be considered for young FMF patients with aggressive disease or established AA amyloidosis, including oocyte or sperm cryopreservation before significant gonadal damage occurs.

Study limitations

Several limitations should be acknowledged. First, the retrospective design and relatively small sample size limit the generalizability of our findings. Second, fertility data were extracted from medical records and may be subject to recall bias. Third, we did not perform systematic semen

analysis or ovarian reserve testing on all patients, which may have underestimated the true prevalence of subfertility. Fourth, the lack of a healthy control group from the same geographic region prevents direct comparison with general population fertility rates. Finally, we did not assess the impact of other potential confounders such as body mass index, smoking, or other comorbidities.

Future directions

Prospective multicenter studies with larger cohorts are needed to validate our findings and to elucidate the precise mechanisms by which AA amyloidosis impairs fertility. Additionally, interventional studies evaluating the role of anti-IL-1 agents such as anakinra and canakinumab in preserving gonadal function in colchicine-resistant or amyloidotic patients are warranted.

Strengths

- Largest Algerian cohort evaluating fertility in FMF with AA amyloidosis.
- Inclusion of both male and female patients.
- Genetic confirmation of MEFV mutations.
- Histological confirmation of amyloidosis in most patients.

CONCLUSION

AA amyloidosis complicating FMF significantly increases the risk of infertility compared to FMF patients without this complication. Female patients appear to be more severely affected than males. Early and sustained colchicine prescription, ideally initiated before age 30, not only prevents the development of systemic amyloidosis but also preserves normal fertility potential. For patients who develop AA amyloidosis despite treatment, proactive fertility assessment and assisted reproductive technologies may help achieve successful pregnancies. This study underscores the importance of timely diagnosis, aggressive colchicine therapy, and multidisciplinary care that includes reproductive health counseling for all FMF patients of childbearing age.

LIST OF ABBREVIATIONS

Abbreviation	Full form
CI	Confidence interval
eGFR	Estimated glomerular filtration rate
FMF	Familial Mediterranean Fever
ICSI	Intracytoplasmic sperm injection
IVF	In vitro fertilization
SAA	Serum amyloid A
SD	Standard deviation
WHO	World Health Organization

DECLARATIONS

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the University of Algiers 1 Benyoucef Benkhedda, Bab El Oued University Hospital. Written informed consent was obtained from all participants.

Consent for publication

Not applicable. This manuscript does not contain any individual person's data in any form.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

GK: Conception, design, data collection, analysis, interpretation, manuscript writing, final approval. MB: Data collection, statistical analysis, manuscript revision, final approval. AB: Supervision, data interpretation, critical revision, final approval. All authors read and approved the final manuscript.

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