Taiwanese Journal of Obstetrics & Gynecology 63 (2024) 900–903

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Retrospective evaluation of obstetric processes in patients with Familial Mediterranean Fever's disease: The three years experience of a tertiary rheumatology clinic

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ARTICLE INFO

Article history:
Accepted 10 September 2024

Keywords:
Familial Mediterranean Fever
Amyloidosis
Pregnancy
Colchicine
Anakinra

ABSTRACT

Objectives: Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disease affecting both genders in reproductive age. In this study, we aimed to investigate the relation between FMF and pregnancy on both maternal and fetal aspects.

Material and methods: In this retrospective, single-center, descriptive study we analysed total of 95 pregnancies of 40 FMF patients. Clinical and demographic data were obtained from patients' records. To prevent recall bias, only the last pregnancy of each patient was evaluated for disease activity and use or revision of medications during pregnancy.

Results: The median age of the patients at diagnosis was 22 and the first pregnancy age was 26 years. The median duration of FMF at last pregnancy was 8 (0–23) years. Eight (20%) patients had at least 1 pregnancy via assisted reproductive techniques (IVF), while 34 (85%) patients had at least 1 spontaneous pregnancy. While 32 patients were in remission (80%) before pregnancy, 8 were clinically active (20%). Improvement in clinical course and attack frequency during pregnancy was observed in 23 patients (57.5%), stable course in 10 (25.0%), and worsening in 7 (17.5%). The rate of live birth was 70.0%, abortus was 28.9%, preterm labor was 8.1%, pre-eclampsia was 5.0%, and only 1 achondroplasia as congenital fetal abnormality was observed.

Conclusion: FMF did not constitute a contraindication for pregnancy. The most important obstetric problems, complications, and negative fetal outcomes in the course of pregnancy are increased IVF requirement, abortion, and cesarean rates. There is no increase in the risk of congenital malformations due to FMF itself or use of colchicine.

Introduction

Familial Mediterranean Fever (FMF) is an autoinflammatory disease inherited with an autosomal recessive pattern and particularly affects Turkish, Arabic, Armenian, and Jewish populations [1]. Recurrent fever, serositis, arthritis-arthralgia, erysipelas-like erythema, and myalgia are the main symptoms [1]. While elevated acute phase values are expected as an indicator of the inflammatory response during the attack period, uncontrolled attacks lead to serious complications, especially amyloidosis, in the long term [2]. Clinical findings start in childhood and mostly affect patients of reproductive age.

In this study, we aimed to investigate the course, maternal and fetal outcomes of pregnant patients followed with FMF, in which our country is one of the endemic regions.

Materials and methods

In this retrospective, single-center, descriptive study the records of the patients who were diagnosed with FMF according to Tel

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https://doi.org/10.1016/j.tjog.2024.09.008

Hashomer criteria [3] between 01.06.2020 and 31.03.2023 in our clinic and followed up with at least one completed or continuing pregnancy were reviewed, retrospectively. We screened the data of 1080 female FMF patients and analyzed a total of 95 pregnancies of 40 FMF patients. The demographic, clinical, and obstetric data were recorded by using a standard data form. Diagnosis and gestational age, duration of disease before pregnancy, clinical findings, treatments received, obstetric history, clinical findings during pregnancy, treatment changes before and during pregnancy, obstetric and fetal complications, and pregnancy outcomes were analyzed. To avoid repeating data and recall errors, clinical findings during pregnancy, agents used in treatment and treatment revisions were analyzed only on the last or current pregnancy. Patients with insufficient data were excluded from the study.

The study protocol was approved by the Institutional Research Ethics Committee (file number 05.05.2023/685) and no informed consent was needed according to the nature of this retrospective record-based study. No funding was received for the study.

Statistical analysis

Since only patient group data were defined, median and range values were given for quantitative data and frequencies for qualitative variables. Statistical analyses were performed using SPSS Statistics for Windows, version 28.0 (SPSS Inc., Chicago, Ill., USA).

Results

The data of a total of 95 pregnancies of 40 patients with a median age of 29 years (22–42), with at least 1 pregnancy detected during our follow-up were analyzed. The median age of symptom onset was 11 (5–30), the median age of diagnosis was 22 (5–37), and the median age at first pregnancy was 26 (19–41) years. The median duration of FMF at last pregnancy was 8 (0–23) years. While 57.7% of the patients had at least 1 FMF patient in their family, the comorbidities of the patients were as; 1 systemic lupus erythematosus, 1 chronic renal failure, 1 atypical HUS, 1 amyloidosis, 1 hypothyroidism, 1 previous cerebrovascular disease, 1 asthma, 1 epilepsy, 1 ulcerative colitis, 1 ankylosing spondylitis, 1 factor V leiden mutation carrier, 1 idiopathic thrombocytopenic purpura and 2 hypertension.

The disease and attack characteristics of the patients were given in Table 1. The attack was defined as the one or more of acute onset fever, serositis presented as abdominal pain, pleural pain, pericardial pain, arthritis, and erysypelas like erythema, lasting at least 24 h and up to 5 days. The remission state was defined as the decrease in attack frequency during pregnancy and 2 or less attack during 6 months. Stable state was defined as the similar attack frequency before and during pregnancy period. Wosening was defined as the increase in attack frequency during pregnancy and 3 or more attack during 6 months. Clinically active patients were defined as 3 or more attack in 6 months before pregnancy indicating uncontrolled FMF disease activity. While 32 patients were in remission (80%) before pregnancy, 8 patients were clinically active (20%) at the last pre-pregnancy visit. Improvement in clinical course and attack frequency during pregnancy was observed in 23 patients (57.5%), stable course in 10 patients (25.0%), and worsening in 7 patients (17.5%). The number of patients who had at least 1 attack during pregnancy was 14 (35%), and the median number of attacks during pregnancy was 2 [1–10]. Three of nine patients who were not under any colchicine during pregnancy had at least one attack (33.3), while 11 of 31 patients who used any colchicine during pregnancy had at least one attack (35.5%). The treatments received by the patients during the overall follow-up period before the last pregnancy and at the last visit before the last pregnancy were given in Table 2. Treatment revision was required in one patient during pregnancy and anakinra was added to colchicina lirca due to the high attack frequency as 9 attacks during pregnancy under 2 mg per day of colchicina lirca. She had history of one successful pregnancy and 1 abortus. The last pregnancy was completed at 38th week of gestation via cesarean section. Her comorbidities were chronic renal failure, atypical hemolytic uremic syndrome and previous attack of HELLP. The baby had no congenital abnomality or malformation.

Table-1
Clinical findings and attack characteristics of the patients during all follow-up.

Variable (n = 40)	Frequency n, %
Attack frequency (n = 35)	
2 per month	5/35 (14.3)
1 per month	9/35 (25.7)
6 per year	4/35 (11.4)
4 per year	3/35 (8.6)
3 per year	1/35 (2.8)
2 per year	3/35 (8.6)
1 per year	10/35 (28.6)
Attack duration, median, day	3 (2–7)
Fever	29 (72.5)
Peritonitis	37 (92.5)
Pleuritis	16/40 (40.0)
Pericarditis	1/40 (2.5)
Pelvic attack	9/40 (22.5)
Erysipelas like erythema	6/40 (15.0)
Artralgia/Arthritis	24/40 (60.0)
Prolonged febrile myalgia	1/40 (2.5)
Neurologic symptoms	0
Proteinuria	2/40 (5.0)
Amyloidosis	1/40 (2.5)

The obstetric histories of the patients, and maternal and fetal complications during pregnancy were given in Table 3. Eight (20%) patients had at least 1 pregnancy via assisted reproductive techniques (IVF-in vitro fertilization), while 34 (85%) patients had at least 1 spontaneous pregnancy history. According to declaration of patients, none of them underwent any surgical intervention to relieve pelvis adhesions during infertility work-up of IVF process.

Among patients who continued to use any kind of colchicine before the last pre-pregnancy visit and during pregnancy a total of 74 pregnancies of 31 patients were recorded, while a totally of 21 pregnancies of 9 patients were recorded among patients who is not under any kind of colchicine before pregnancy. Among those 9 patients, only one of them has not used colchicine in every time. Considering the extremely small size of these subgroups no comparison was performed for maternal and fetal outcomes.

While 5 out of 95 pregnancies were ongoing, 63 of 90 completed pregnancies resulted in live births (70.0%). In our study, preterm labor that occurred before 37 weeks of gestation was found with a frequency of 8.1% in 4 of the last completed pregnancies. All of these patients had used any type of colchicine during pregnancy. While at least 1 FMF attack was detected during pregnancy in three of them, the course of the disease worsened during pregnancy in two. Perinatal mortality was not detected as a result of pregnancies with or without treatment. Achondroplasia, unassociated with FMF and treatment, with FGF3 mutation in only 1 infant was found, and no other congenital anomalies were observed. Other maternal and fetal complications and detailed obstetric history are given in Table 3.

Discussion

The clinical findings of FMF are usually manifested by recurrent fever, serositis, and joint findings in childhood and pubertal period,

Table-2
Treatments received during all follow-up and last pre-pregnancy visits of the patients.

Treatment (n = 40)	Overall n, (%)	Last visit before pregnancy n, (%)
Not receiving colchicine or alternative therapy	1 (2.5)	9 (22.5)
Native colchicine (dispert)	39 (97.5)	23 (57.5)
Imported colchicine (colchicina lirca, colchicine opocalcium or colchicine seid)	9 (22.5)	8 (20.0)
Corticosteroid	0 (0)	0 (0)
Anakinra	1 (5.6)	1 (2.5)
Canakinumab	0 (0)	0

considering that attacks tend to go into remission after the fifth decade. Therefore, it is seen that the affected female patient group consists of fertile-age women [4]. The data showing that infertility and oligomenorrhea increase in FMF patients had been reported especially in the era when the number of untreated patients was high, and it was thought that there was a tendency to ovulatory dysfunction with an unclear pathogenesis in addition to intra-abdominal adhesions occurs via inflammatory reactions during attacks [5,6].

Colchicine has become the main treatment agent in not only the prevention and control of attacks but also complications, namely amyloidosis and related end-stage renal disease, with its introduction in treatment since in 1972. In particular, pelvic adhesions due to inflammation and serositis decrease with the regular use of colchicine, and it improves reproductive capacity, also [6–9]. Interleukin-1 blockade is additionally used effectively with an increasing frequency in case of resistance or inadequate response to colchicine [10,11]. Although there is safety and usage data for the use of colchicine and IL-1 blockade during pregnancy and lactation, still there is a concern about their use by rheumatology and gynecology practice [2,10,12]. Especially, considering the anti-mitotic effect of colchicine, its effect on pregnancy and fetal outcomes is still a hot topic [13].

On the other hand, uncontrolled disease activity results in many complications, especially peritoneal adhesions, amyloidosis, and end-stage renal disease [14]. Therefore, effective attack prophylaxis and treatment, prevention of unplanned pregnancies during an active stage of FMF, and giving close follow-up during pregnancy are important issues.

The duration of the disease at pregnancy, which is one of the factors that can affect the disease activity, is around 7 years in the literature, and it was similar to our data [15]. While the number of patients with at least 1 attack during pregnancy was 35% in our study, clinical improvement was found in 57.5% of the patients and clinical worsening was found in 17.5% of the patients. Quite similar to previous studies, Bodur et al. showed no attacks were detected during pregnancy in 61.4% of the patients [15]. Again, Akar et al. examined a total of 73 pregnancies and no attack was found in 62.5% of the patients, and the disease course worsened in 17.5% of the patients [16]. The median frequency of attacks during pregnancy was 2 in our study, which was similar to the literature [15]. In our study, the frequency of at least one attack was similar in pregnancies with and without colchicine, while İskender et al. found that patients who received colchicine treatment had more frequent attacks than those who did not (59.5% vs 18.2%, p = 0.012) [17].

Obstetric history was similar to previous cohort analyses and the rate of live births was reported about 65–70% in almost all studies [15,18]. The most important obstetric complications and fetal adverse outcomes in the course of pregnancy were increased IVF requirement, abortion, and cesarean section rates. There is no risk of congenital malformations from the use of FMF or colchicine. FMF itself has been associated with pelvic adhesions, subfertility, and oligomenorrhea, and the frequency of IVF is increasing in FMF patients, similar to our cohort [13].

In our study, the increase in the frequency of abortion and cesarean section was found to be higher in the FMF group compared to healthy pregnant women in previous studies. When healthy pregnant women and pregnant women with FMF disease were compared, a 15–20% increase in abortion frequency was observed in the FMF group compared to healthy pregnant women in previous studies [15,19]. While the frequency of cesarean section was found to be quite high as 63.5% in our study, it is around 15–40% even though it is found to be higher than healthy pregnant women in the literature [18,19].

The data on preterm birth are contradictory, and it was found with a frequency of 8.1% in our study. In previous studies, the presence of FMF was shown as an independent risk factor for preterm birth and was found to be 7% in the general FMF group and 59% in the colchicine group [15,18–20].

The frequency of preeclampsia was found to be similar to the literature in our study, and it did not increase in the FMF group compared to healthy individuals [18]. No evidence has been shown that FMF poses a risk for perinatal mortality and congenital fetal anomalies, and similar to our study, polyhydramnios, oligohydramnios, congenital malformations, and placental anomalies

Table-3
Obstetric history, maternal and fetal complications of the patients.

Total pregnancies, (n, %)[a]	95
Ongoing pregnancy	5
Total live births	63/90 (70.0)
Normal vaginal delivery	*23 (36.5)*
Cesarean section	*40 (63.5)*
Abortion	26/90 (28.9)
Curettage	0/90 (0)
Ectopic pregnancy	2/95 (2.1)
In vitro fertilization	8/40 (20)
Multiple pregnancies	27/40 (67.5)
Week of birth, median (range)	39 (29–41)
Maternal complications, n (%)[b]	
Threatened abortion	6/40 (15.0)
Bleeding before 20 weeks gestation	3/40 (7.5)
Placenta abruptia	0
Placenta previa	1/40 (2.5)
Preeclampsia/HELLP	2/40 (5.0)
Ovarian torsion	0 (0)
Fetal complications, n (%)	
Preterm birth[c]	4/37 (8.1)
Oligohydramnios	1/90 (2.22)
Polyhydramnios	0 (0)
Fetal chylothorax	0 (0)
Fetal distress	1/90 (1.11)
IUGR	1/90 (1.11)
Congenital anomaly (achondroplasia)	1/90 (1.11)
Perinatal mortality	0

[a] Calculation was made based on terminated pregnancies. Gravida was entered as 1 because one fetus of twin pregnancy of 1 patient was born and one fetus was terminated with abortion.
[b] Calculated over the number of patients since preeclampsia and miscarriage threat recur in recurrent pregnancies.
[c] Complications are calculated based on patients the last terminated pregnancy of 37 patients, remaining 3 had their first pregnancy which still ongoing.

were found to be around 4–5% and similar to the healthy population [17,19].

Although colchicine is a mitotic inhibitor and shows transplacental transmission, it is an agent that is used safely during pregnancy [13,20–22]. In amniocentesis studies, it has been shown that there is no increase in chromosomal anomalies or miscarriages in pregnancies that occur under the colchicine use of any of the partners [23]. Again, in patients using colchicine for any indication, live birth (around 91%), miscarriage, ectopic pregnancy, major anomaly frequencies, and postpartum growth and development retardation were found to be similar compared to healthy individuals [13,20,24]. However, preterm birth was found to be 15%, and cesarean section 24.4% more frequently than the healthy group [20]. Therefore, untreated patients seem to be at higher risk than the use of colchicine and it was thought that routine amniocentesis is not required [13].

While 22.5% of our patients were followed without any treatment during pregnancy, this rate varies between 11 and 85% in previous studies [15,16,19,20]. The data on the use of anti-IL-1 agents in pregnancy is increasing with their use in FMF and other autoinflammatory diseases, and the number of patients who are using IL-1 blockage, namely anakinra or canakinumab during an attack or in insufficient response to colchicine is increasing [10,11,25]. In our study, anakinra was used in addition to colchicine in one patient due to the increased frequency of attacks, and no maternal or fetal complications were observed.

The limitations of the study were the small sample size, restriction in a single center, and the reliability of data regarding the number of attacks and clinical findings which were based on patient statements with risk of recall bias.

Conclusion

In conclusion, in our study, it was thought that FMF did not constitute a contraindication for pregnancy. The most important obstetric problems, complications and negative fetal outcomes in the course of pregnancy are increased IVF requirement, abortion, and cesarean rates. FMF or the use of colchicine was not associated with an increase in the risk of congenital malformations. It seems important to have a planned pregnancy after achieving disease remission, if possible, and to reduce maternal and fetal risks frequent and close follow-up of pregnant patients should be advised.

Ethics committee approval

The study protocol was approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (no: 03.03.2023–404).

Financial disclosure

The authors reported that they have received no financial support.

Informed consent

This is a retrospective study and informed consent was not needed.

Data availability statement

Data available on request from the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request and all authors have access the all data.

Declaration of competing interest

No conflict of interest was declared by the authors and the study has not been presented in any platform before.

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