Female reproductive dysfunction in familial Mediterranean fever patients with and without colchicine treatment

Sirs,

Familial Mediterranean fever (FMF) is an autosomal-recessive inherited disease characterised by recurrent episodes of fever, abdominal pain and serositis. Colchicine is effective in preventing attacks that can be stimulated by various stimuli such as stress, cold exposure or infections. In the literature there are many evidences about FMF and female reproductive system dysfunctions: ovarian failure and efficacy of colchicine in infertility prevention, due to ovarian dysfunction and peritoneal adhesions, are described (1-3). It has also been reported an increase of spontaneous abortion incidences in FMF-affected women two-fold more than the general population (25–30% *vs*. 15%) (4-6). Indeed, frequent peritonitis, as seen in untreated or unresponsive-to-treatment FMF, may determine premature uterine contractions with abortion risk or premature birth (2, 3, 7).

We aimed to verify the prevalence and type of infertility among FMF women, and the prevalence of spontaneous abortions and premature deliveries in FMF patients with or without colchicine treatment.

We evaluated, retrospectively, a cohort of female patients diagnosed with FMF at our Periodic Fever Research Center between January 1998 and July 2008. A questionnaire was administered to obtain data concerning the presence and type of infertility (if studied), number of pregnancies carried to term, progress and therapy taken during pregnancy, spontaneous abortions, premature deliveries and congenital malformations.

Among 221 FMF patients, there were 108 women, of whom 73 in fertile age and therefore eligible for our study. Thirty-eight patients had not had a voluntary pregnancy yet; 7/35 (20%) patients who had tried to get pregnant were sterile: 2 patients because of peritoneal adhesions, 1 patient because of endometriosis, 1 patient for both causes, and 3 women without an apparent cause. The total number of pregnancies was 61 (in 28 women), segregated by symptoms and colchicine treatment (results in Table I). The majority of patients (27/28) had become pregnant after FMF onset, 2 before disease onset, while one patient had been pregnant before and after disease onset. Fifty out of 61 pregnancies were carried to term and 11/61 ended in spontaneous abortion. The highest number of pregnancies (48/61) occurred in 21 women with FMF symptoms but not in colchicine: 1 patient because of drug-resistance, 3 patients were doubtful regarding drug side-effects, and all others because they had been not diagnosed as FMF yet. In this last group, 38/48 (79%) pregnancies were carried to term, and 10/48 (21%) ended in miscarriage at different periods of pregnancy. None of those patients had diabetes or other conditions associated with miscarriage. Among 6 patients treated with colchicine, there were 9 pregnancies: 8 carried to term, and only one abortion occurred two weeks after amniocentesis. There were 2 premature deliveries in 2 patients treated with colchicine (the first one had a gestosis, the other showed placental abnormality). There were no foetus malformations in the group of patients in therapy or in those without it.

Table I. Periodic Fever Center cohort.

No. of patients with certain FMF diagnosis	221
No. of female patients with certain FMF diagnosis	**108**
No. of patients excluded due to lack of data	26
No. of patients younger than 14 years old	9
No. of female patients in review	73
Attacks and menstruation relation	20
No. of no voluntary pregnancies in female patients	38
No. of female patients with infertility	7
No. of patients with foregoing pregnancies	28
No. of pregnancies (carried to term or not)	61
No. of pregnancies carried to term	50
with no symptoms or treatment	4
with symptoms, without treatment	38
with symptoms, with treatment	8
No. of abortions	11
with no symptoms or treatment	0
with symptoms, without treatment	10
with symptoms, with treatment	1
No. of premature deliveries	2
No. of congenital malformations	0

In our study, the infertility prevalence was about two-fold compared to the general population (20% *vs*. 8–10%) (8); the largest number of pregnancies (48/61) occurred without colchicine and 21% of them ended in miscarriage, with an increased prevalence compared to the general population (10–15%) as already reported in pre-colchicine era data (4-5). Those observations might be due to the considerable diagnosis and treatment delay in Italy (14.8 years). Thus, we can assume that the lack of therapy over a long period of time increases the risk of infertility/abortions compared to the general population. Another interesting issue arising from this study is the absence of congenital foetus malformations in patient groups under colchicine treatment; therefore colchicine seems, currently, a relatively safe drug that should be continued throughout pregnancy (9).

Further studies with a larger FMF population would be helpful in confirming those data.

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