

REVIEW

Reproductive system in familial Mediterranean fever: an overview

E Ben-Chetrit, M Levy

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Familial Mediterranean fever (FMF), amyloidosis, and colchicine may affect the reproductive system of male and female patients. Colchicine treatment improves female fertility and the outcome of pregnancy and may prevent the development of amyloidosis. However, colchicine may induce oligospermia/azoospermia, but this effect is rare. Overall, colchicine treatment improves the prognosis of patients with FMF and increases their reproductive ability.

first is a suggestion for the underlying physiology for this relationship. It is proposed that hormonal changes may lead to the FMF attacks during menstruation. Support for this hypothesis may be found by two observations: (a) hormone replacement therapy significantly lowered the expression of intercellular adhesion molecules⁷; (b) oestrogen can inhibit tubulin assembly using a binding site analogous to colchicine sites.⁸ Based upon these two findings it is tempting to speculate that oestrogen may mimic the colchicine effect on tubuli and adhesion molecules. Colchicine inhibits the chemotaxis of neutrophils by inhibiting their microtubules and by suppressing the expression of adhesion molecules in granulocytes and endothelial cells.⁹ Because oestrogen levels decrease significantly in menstruation, their protective effect disappears leading to the acute attack.

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterised by recurrent attacks of fever, and peritonitis, pleuritis, arthritis, or erysipelas-like skin lesion.¹ The disease is common among Turks, Armenians, Middle-Eastern Moslems, and non-Ashkenazi Jews. One of the main complications of the disease is amyloidosis, which mainly affects the kidneys but may be accumulated in other organs and tissues, including the heart, intestines, and testes.² Colchicine is the preferred drug for FMF.^{3,4} It can control the acute attacks and prevent the development of amyloidosis. FMF is a systemic disorder that affects patients in their child-bearing years—a fact which raises concern about their reproduction system. This concern is further enhanced by the knowledge that the mechanism by which colchicine controls FMF attacks involves disturbance of the function of the microtubules.

Another hypothesis may be suggested based upon the finding that colchicine and oestrogens are substrates of the same cytochrome (3A4) in the liver.⁴ When levels of oestrogens are decreased (during menstruation), more enzymes are available for colchicine metabolism, thereby decreasing its concentration and its protective effect.

In the following we review the various repercussions of FMF and colchicine on the reproductive system of male and female patients, although update figures on these issues are missing.

“Only a few women have attacks of familial Mediterranean fever during menstruation”

Yet, these speculations do not explain why only a few women experience the attacks during menstruation and suggests that other factors have a role in this process.

FMF AND MENSTRUATION

Clinical observation has shown that familial Mediterranean fever attacks may be preceded by predisposing factors such as emotional or physical stress, cold exposure, or menstruation. It was reported that up to 15% of female patients with FMF experience perimenstrual attacks.⁵ Usually, patients have attacks also between menstruations. We have recently searched for patients whose attacks were restricted to the perimenstruation period.⁶ Only 10/141 (7%) women with FMF (over the age of 13) were found to have such attacks. This relatively rare presentation was not related to the age of the patients, the age of FMF onset, disease chronicity, or to the MEFV mutations they bear.

The second point is related to the therapeutic approach. Our experience shows that increasing the colchicine dose during the perimenstrual period or the use of contraceptives when indicated, may control these attacks.⁶

FMF AND FEMALE FERTILITY

In the early seventies it was assumed that peritoneal adhesions due to recurrent attacks of peritonitis, were the main cause of infertility in female patients with FMF.¹⁰ In a study by Ehrenfeld *et al* four of 13 patients with fertility problems had various degrees of pelvic adhesions or tubal disease which might have contributed to infertility.¹¹ Nevertheless, it was not clear whether FMF attacks were the only cause of these adhesions. These patients might easily have had

See end of article for authors' affiliations

Correspondence to:
Dr E Ben-Chetrit,
Department of Medicine A,
Hadassah University
Hospital, PO Box 12 000,
Jerusalem, Israel;
eldad@Hadassah.org.il

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Two additional points should be mentioned about the menstruation–FMF relationship. The

Abbreviations: BD, Behçet's disease; FMF, familial Mediterranean fever

pelvic inflammatory disease as a conceivable cause for peritoneal adhesions. In recent years our experience has shown that obvious peritoneal adhesions are quite rare and that this cause of infertility is unusual. One of the explanations for this observation is the current use of colchicine, which can reduce the production of peritoneal adhesions.¹²

In 1970 Mamou, who investigated ovarian function in 20 women with FMF, reported that ovarian insufficiency was the cause of infertility in most cases.¹³ Similarly, Ismajovich *et al* found ovulatory disturbances in 13 of 45 patients with FMF with primary sterility.¹⁴ Because these observations were made before the colchicine era it is possible that amyloidosis of the ovaries might have led to this complication. Since the introduction of colchicine, anovulatory ovulation as a cause of infertility is rare.

A patient with secondary sterility, in whom repeated in vitro fertilisation was unsuccessful, was seen in another hospital. It was found that the sperm could not penetrate the ovum. A careful examination of the ova from this patient showed that they were covered with a stiff substance which stained positively with amyloid (personal communication). This finding led to the use of the "X-technique" in which an external pore is made allowing the sperm to penetrate the ovum.

Thus, we see that FMF and amyloidosis may affect female fertility. However, this complication became a rare event after the introduction of colchicine treatment in FMF.

FMF AND PREGNANCY

The course of pregnancy in patients with FMF is variable. Some patients enjoy an attack-free period during pregnancy. However, other women may experience devastating attacks with high frequency. These patients may require a high dose of colchicine and yet remain active. Apart from the inconvenience and the pains during the attacks, there is an additional risk, because peritonitis may lead to early contractions of the uterus and eventual abortions. Therefore, it is necessary to control FMF attacks despite the need for a higher than regular dose and the potential adverse effects.

"FMF attacks during pregnancy must be controlled as they may lead to abortions"

In the era before colchicine was introduced, studies from the seventies reported that the rate of abortions and miscarriages (25–30%) was higher in women with FMF than in the general population.^{10, 15} Today, our experience is different and the course of pregnancies and their outcome in patients with FMF is much better and is almost comparable with that in the general female population (unpublished data). Conceivably, the improvement in pregnancy surveillance and colchicine treatment are responsible for this positive change.

Of special concern is the problem of pregnancy in patients with renal amyloidosis, because it may result in either abortion, stillbirth, or deterioration in renal function. Cabili *et al* who studied 29 pregnancies in 17 women with FMF and amyloidosis reported that in seven of them renal function deteriorated further. Based upon these observations, it seems that patients with renal amyloidosis should be advised not to conceive.^{16, 17} Nevertheless, sporadic cases of patients with FMF with amyloidosis who have had successful outcomes of their pregnancies, have also been reported.^{18, 19}

There are no new data about the outcome of the newborns of female patients with FMF. A single report by Rabinovitch *et al* found four newborns with trisomy 21 out of 2000 deliveries.²⁰ Because this ratio (1:500) is higher than expected in this age group (1:909), it is advisable to perform amniocentesis at 4–5 months of gestation. It is still not clear whether FMF by itself or colchicine may increase the risk for the development of this complication.

FMF AND MALE FERTILITY

Our knowledge about the effect of FMF on male fertility is quite limited. In patients with FMF with azoospermia, colchicine was considered to be the sole and direct cause. This was based upon a case report from the early seventies, in which Merlin described azoospermia in a patient with gout after chronic colchicine treatment.²¹ However, during the past few years, we have encountered several men with FMF with azoospermia, some of whom did not receive colchicine.^{22, 23} When we took biopsy samples from their testes we discovered marked germ cell aplasia or maturation arrest of the spermatocytes with amyloid deposition in the blood vessels. The association between testicular amyloidosis and secondary azoospermia is unclear. It is still unknown whether amyloid disturbs sperm transport by obliteration of intratesticular canaliculi, causing obstructive azoospermia, or disrupts sperm production by its direct effect on the seminiferous tubules. Based upon our findings, we recommend that a routine spermogram should be performed in young patients with FMF with renal or other organ amyloidosis. Furthermore, these patients should also be advised to have sperm cryopreservation, in case they develop azoospermia later in the course of the disease. Yet, a routine spermogram is not recommended for every male patient with FMF before colchicine treatment. Firstly, because this adverse effect is rare and, secondly, because most patients are diagnosed earlier than their age of puberty.

Another concern related to male fertility in FMF is the course and outcome of the pregnancies. This question is raised because the disease may theoretically affect the quality of sperms, leading to a potentially higher rate of abortions or fetal malformations. This concern may be greater, if the patients have received colchicine at the time of conception. In a study by Zemer *et al* who had been following up over 1000 patients, 24 identified pregnancies occurred while the fathers were receiving colchicine.¹⁵ However, no mention was made of fertility or delivery problems. To examine this problem we have recently completed a partially prospective study. We followed up 55 male patients with FMF, their wives' pregnancies (203), and the outcome of their deliveries. We compared 48 male patients with FMF who were receiving colchicine with 19 patients who did not receive colchicine during conceptions (some of the patients were analysed separately in two periods; with and without colchicine). Only healthy spouses with no medical or fertility problems were included. As a comparison group we interviewed 150 healthy men and 50 patients with various inflammatory diseases who shared similar ages and origin with the tested group. Our initial analysis showed that the rate of abortions, and/or malformations in patients with FMF was comparable with that of the general healthy population. Furthermore, we found no significant difference between the patients treated with colchicine and those who were not receiving this drug at the time of conception (manuscript in preparation).

COLCHICINE AND FEMALE FERTILITY

At the beginning of the colchicine era serious concern was raised about the potential for a teratogenic effect of the drug. In vitro, colchicine can induce polyploidy as a result of ultrastructural changes in spindle microtubules, leading to impaired mitotic function.²⁴ Indeed, aneuploidy has been reported in the offspring of patients with gout receiving colchicine.^{25–28} These findings led doctors to recommend that the drug should be stopped three months before conception and during pregnancy.

Thirty eight patients with FMF were investigated cytogenetically. Twenty one of them were examined before treatment with colchicine, 22 during treatment, and 5 of these during both periods. The measured parameters included mitotic rate, percentage of tetraploidy, and chromosome

breakage in short term lymphocyte cultures.²⁹ No statistically significant difference in these measures was found between the groups. In later studies, in which pregnant patients with FMF who conceived while receiving colchicine were followed up, their pregnancies and their outcome were uneventful. Our current policy is to recommend continuous colchicine before conception and during pregnancy and where feasible, it is advisable to perform amniocentesis at 4–5 months of gestation.

“Colchicine treatment can be continued during pregnancy, but an amniocentesis at 4–5 months is recommended”

Our current knowledge suggests that colchicine does not affect female fertility in patients with FMF. On the contrary, it may control FMF attacks during pregnancy and prevent abortions and inhibit peritoneal adhesions and prevent secondary infertility.

COLCHICINE AND MALE FERTILITY

In 1961 Yu and Gutman reported their experience with colchicine prophylaxis in 208 patients with gout over a mean period of 5 years.³⁰ None reported infertility. Later Merlin *et al* reported her case of a patient who developed azoospermia after long term treatment with colchicine.²¹ At about the same time, *in vitro* studies have shown that colchicine (in high concentrations) arrests mitosis through its inhibitory effect on microtubules.³¹ These observations raised serious concern about chromosomal and gonadal aberrations, on the one hand, and the risk for the development of azoospermia, on the other.

Bremner and Paulsen tested the effect of colchicine treatment on sperm counts and plasma testosterone, luteinizing hormone, and follicle stimulating hormone levels in seven healthy volunteers.³² No significant changes could be detected in these parameters during 3–6 months of treatment.

In another study 4 of 19 male patients with FMF had fertility problems while receiving long term colchicine treatment.³³ Three of these patients had had children while not receiving treatment, but their wives could not conceive when the patients were receiving colchicine. In one patient primary sterility remained one year after treatment had ended. In this and two other patients the spermogram was normal but the hamster zona-free ova penetration test was pathological. The fourth patient had azoospermia.

Because sperm motility (and hence ovum penetration) depends upon microtubular function we thought it was conceivable that colchicine might affect sperm activity. Accordingly, we studied the effect of colchicine on sperm motility in an *in vitro* system employing the “swim-up” technique for sperm selection.³⁴ It was found that sperm motility was significantly inhibited only after incubation with a minimal concentration of 10 µg/ml for at least 18 hours. Because with a therapeutic dose the plasma colchicine concentration is about 3 ng/ml, the amount of colchicine which would affect sperm motility *in vitro* is 3000-fold higher. Thus, it seems unlikely that regular colchicine treatment would inhibit sperm motility *in vivo*, unless the drug had a very high and special affinity to spermatozoa.

“Colchicine treatment is not likely to affect sperm motility”

In a study by Sarica *et al*, of 62 Turkish men with Behçet's disease (BD) who were receiving chronic colchicine treatment, oligospermia was evident in 23 (37%) patients and azoospermia in 2 (3%) patients.³⁵ This high number of affected patients

with BD compared with patients with FMF suggests that colchicine by itself may not be the only significant factor affecting sperm production. The pathophysiology of the underlying disease (in the case of BD—testicular vasculitis) may play an additional part in this complication.³⁶

In summary, colchicine may have the potential to affect sperm motility and production. However, with a regular therapeutic dose these complications are rare. As mentioned earlier, in cases of azoospermia the possibility of testicular amyloidosis should be excluded.

COLCHICINE AND LACTATION

A practical question which is often raised by nursing mothers with FMF is whether they are allowed—while receiving colchicine—to breast feed their infants. Pharmaceutical company leaflets and textbooks of pharmacology warn female patients not to do so. Milunsky *et al* have shown that breast milk in patients taking the drug contains traces of colchicine.³⁷ We determined colchicine levels in the sera and breast milk of four patients with FMF at various times after ingestion of the drug.³⁸ Colchicine was detected in all samples of sera and breast milk and its concentrations were similar in both fluids. However, the estimated daily amount of colchicine ingested by the infant is less than one tenth the therapeutic dose (per kg) given to adults. This rough estimate is concordant with our favourable clinical experience following up children of mothers who continued to nurse while taking colchicine. Therefore, we suggest that breast feeding is safe during this treatment.

SUMMARY

Familial Mediterranean fever, amyloidosis, and colchicine may affect the reproductive system of male and female patients. In the past FMF led to female infertility due to peritoneal adhesion which developed after recurrent attacks. The acute FMF episodes caused miscarriage and/or early delivery in pregnancy. However, colchicine treatment improved female fertility and the outcome of pregnancy by preventing the serosal adhesions and controlling the acute attacks.

Amyloidosis may lead to male and female infertility through its deposition in testes and ovaries. In cases of renal amyloidosis pregnant patients with FMF may progress to end stage kidney disease and dialysis. Again, colchicine administration may prevent the development of amyloidosis, thereby improving the chance of conception and successful termination of pregnancy.

On the other hand, colchicine by itself, may induce oligospermia/azoospermia in patients with FMF, but this adverse effect is relatively rare.

Breast feeding while taking colchicine is quite safe. Thus, overall, colchicine treatment improves the prognosis of patients with FMF and increases their reproductive ability.

Authors' affiliations

E Ben-Chetrit, M Levy, FMF Unit, Department of Medicine, Hadassah University Hospital, Jerusalem, Israel

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