

Supplementary material

Question 1

Could you please tell me what the changes were in Familial Mediterranean fever since the introduction of colchicine in 1972, regarding the complications of AA amyloidosis, renal failure, renal dialysis, and small intestinal obstruction?

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The answer

Since the introduction of colchicine in 1972, the natural history and prognosis of familial Mediterranean fever (FMF) have changed dramatically, particularly regarding its major complications:

AA amyloidosis: The incidence of AA amyloidosis, previously a leading cause of morbidity and mortality in FMF, has markedly decreased. Colchicine, when used at effective doses (typically 1–2 mg/day in adults), is highly effective in preventing the development of amyloidosis, especially when started early and taken consistently. This effect is well established in the medical literature, with multiple sources confirming that lifelong colchicine therapy prevents amyloidosis and can even reverse proteinuria in early stages (1–6). However, colchicine resistance or poor compliance remains a risk factor for amyloidosis development (5, 6).

Renal failure and renal dialysis: The reduction in amyloidosis has led to a significant decline in FMF-related end-stage renal disease (ESRD) and the need for renal dialysis. Colchicine is most effective in the preclinical and proteinuric stages of amyloidosis; once nephrotic syndrome or advanced renal failure develops, progression to ESRD may still occur despite optimal colchicine therapy (7). Thus, early and sustained colchicine use is critical for renal protection.

Small intestinal obstruction: Historically, recurrent peritonitis in FMF could lead to adhesions and small intestinal obstruction. With effective colchicine therapy, the frequency of acute attacks and subsequent serosal inflammation has decreased, resulting in a lower incidence of this complication (1–3).

In summary, colchicine has transformed FMF from a disease with frequent, severe complications (AA amyloidosis, renal failure, dialysis, and small intestinal obstruction) to one with a near-normal prognosis for compliant patients. The remaining risk is primarily in those with colchicine resistance or intolerance, for whom biologic agents (*e.g.*, IL-1 inhibitors) are now considered (4, 6, 8).

Chat GPT-4

The answer

Since long-term daily colchicine became standard (first reported effective in 1972) the big changes are: a huge fall in AA (AA = reactive) amyloidosis incidence among treated FMF patients, fewer patients progressing to end-stage renal disease (ESRD), fewer dialysis/transplant cases caused by untreated FMF, and (less clearly) fewer acute surgical emergencies from unrecognized FMF, while chronic adhesive small-bowel obstruction remains a rare, reported long-term complication. The size of the benefit depends a lot on diagnosis delay, colchicine dose/adherence, and patient population (ethnicity/genotype). [nephropathol.com+3New England Journal of Medicine+3Clinical and Experimental Rheumatology+3](#)

1) AA amyloidosis - big drop after colchicine

- Before colchicine was used regularly (reports from the 1950s–early 1970s), series reported very high cumulative rates of AA amyloidosis in some cohorts (many older series report 20–60%, with variation by country/centre). [ResearchGate+1](#)
- Colchicine prophylaxis proved to prevent the development of AA amyloidosis and to arrest progression in early cases. Classic controlled/observational reports showed prevention of new amyloidosis among compliant patients. For example, Zemer et al. (NEJM) and later series documented marked reductions. [New England Journal of Medicine+1](#)
- More recent reviews/meta-series report amyloidosis prevalence in the colchicine era, usually in the **single**

digits (commonly ~3–10% in many reported cohorts), although figures vary by country, adherence, and how early patients were started on treatment. A 2024–2025 literature summary confirms a prominent decline in AA frequency after widespread colchicine use. [OUP Academic+1](#)

2) Progression to renal failure (ESRD) and need for dialysis/transplant

- Because AA amyloidosis is the primary route to ESRD in FMF, the fall in amyloidosis translated into fewer patients developing ESRD and therefore fewer FMF-related dialysis starts. Observational cohort studies and registry analyses show improved renal outcomes and survival in the colchicine era. [New England Journal of Medicine+1](#)
- Colchicine also appears to **slow/stop progression** in some patients with early amyloidotic renal disease, reducing progression to dialysis in compliant patients. However, once advanced nephrotic/renal failure is established, colchicine's ability to reverse damage is limited. [Wiley Online Library+1](#)
- Transplantation: Colchicine prophylaxis also reduced recurrence of AA in kidney transplants and improved transplant outcomes when adequate colchicine dosing was used. [Karger Publishers](#)

3) Dialysis prevalence/mortality trends

- Historical series from countries with high FMF prevalence (Turkey, Armenia, Israel) document a clear relative decline in numbers/proportion of dialysis patients whose ESRD was caused by FMF/AA amyloidosis after colchicine became routine. Exact dialysis-rate reductions vary by registry and time period, but the direction is consistent (big drop). [nephropathol.com+1](#)

4) Small intestinal obstruction/abdominal surgery

- FMF causes recurrent peritonitis; before diagnosis, many patients underwent emergency laparotomy be-

cause attacks can mimic a surgical abdomen. Several older series report multiple abdominal operations per patient before FMF diagnosis. Colchicine (and earlier recognition) reduced attack frequency and thus the number of false surgical explorations. Kaşifoğlu *et al.* and others documented the frequency of abdominal surgery in FMF cohorts and emphasised diagnostic delay as a cause. [avesis.ogu.edu.tr+1](https://avesis.ogu.edu.tr/)

- **True mechanical small-bowel obstruction** in FMF is less common than transient obstructive episodes; long-term adhesive obstruction (from multiple attacks/operations or serosal inflammation) is reported but rare. There are case reports/series describing adhesive small-bowel stenosis/obstruction even in patients on colchicine, but overall the incidence is low, and many centres have seen fewer emergency laparotomies as recognition and prophylaxis improved. Data are less systematic than for amyloidosis, so the exact incidence change is harder to quantify. [PMC+1](#)

Important modifiers/caveats

- **Adherence and dose matter.** Protective effect is closely tied to regular, adequate colchicine dosing (studies show some dose-response, and failures are often linked to poor adherence or underdosing). [Karger Publishers+1](#)
- **Delay to diagnosis:** patients diagnosed late (after years of uncontrolled inflammation) remain at risk of amyloidosis and renal failure despite later colchicine. Geographic/ethnic differences in baseline risk still exist. [OUP Academic](#)
- Genotype and comorbid inflammation: certain MEFV mutations and persistent subclinical inflammation increase amyloidosis risk even on colchicine; some patients need adjunctive IL-1 blockers. [PMC](#)

Bottom line (one-line)

Since regular colchicine use began (1972→today) the major, proven public-health effect has been a large and sustained reduction in AA amyloido-

sis and its downstream consequences (ESRD, need for dialysis/transplant) in populations with early diagnosis and good adherence; abdominal surgical emergencies and adhesive obstruction are less common now but remain possible, especially with delayed diagnosis or repeated attacks. [New England Journal of Medicine+2OUP Academic+2](#)

Chat GPT-5.2

ChatGPT said:

Thought for 46s

Short version: continuous colchicine since the early 1970s has almost completely changed the natural history of FMF. The big shift is that AA amyloidosis, ESRD and dialysis due to FMF used to be common, and are now largely confined to patients who are undiagnosed, undertreated or colchicine resistant.

I will go item by item.

AA amyloidosis

Before colchicine (pre 1972)

- In classic pre colchicine series, renal AA amyloidosis was very frequent in adult FMF.
- A widely quoted figure is about 75% of FMF patients over age 40 developing amyloidosis in some high risk ethnic groups such as North African, Jews, Armenians and Turks. [njmonline.nl](#)
- Other cohort data from the pre colchicine era report amyloidosis in roughly **20 to 30%** of FMF patients overall. [OUP Academic](#)

After colchicine became standard (mid 1970s onward)

- Continuous colchicine prophylaxis at 1 to 2 mg per day prevents FMF attacks and, more importantly, prevents the development of AA amyloidosis in the great majority of patients when started early and taken regularly. [PubMed+1](#)
- Large cohorts from Turkey, Israel and other Mediterranean countries show a sharp fall in amyloidosis incidence over the colchicine era. For example:
- A Turkish cohort reported that after regular colchicine use became rou-

tine, the proportion of FMF patients with amyloidosis fell to about 2%. ectrx.org

- A recent editorial reviewing multiple series notes that older cohorts showed high rates of AA amyloidosis, whereas more recent data from international registries show prevalence around 10 percent or lower, reflecting earlier diagnosis and colchicine use, with marked variation by country and access to care. *Clinical and Experimental Rheumatology*+1
- Today, AA amyloidosis in FMF is mainly seen in patients who are
 - untreated or diagnosed late,
 - non adherent or intolerant to colchicine, or
 - truly colchicine resistant, for whom IL 1 inhibition is now used. [PMC+2Arthritis Research & Therapy+2](#)

So compared with the pre colchicine era, the risk of AA amyloidosis in a patient diagnosed in childhood and compliant with colchicine has gone from “common and expected” to “uncommon to rare”.

Renal failure and dialysis

Most of the renal burden is mediated through AA amyloidosis, so the trends largely mirror the above.

Before colchicine

- AA amyloidosis was the main cause of mortality in FMF, usually via progressive nephrotic syndrome and ESRD. [njmonline.nl+1](#)
- A significant fraction of FMF patients in their third to fifth decade progressed to ESRD and required dialysis or died without access to RRT.

After colchicine became standard

1. Progression of established amyloid nephropathy

- In patients who already have renal amyloidosis but still preserved renal function, colchicine can stabilise or even improve kidney disease:
- In a classic Tel Aviv series of 68 FMF patients with AA amyloidosis treated with colchicine and followed at least 5 years, kidney disease worsened in 31 patients, remained stable in 22 and proteinuria regressed in

15. Better outcomes were associated with starting colchicine earlier and using doses at least 1.5 mg per day. PubMed+2CRIS+2

- Later case series and reviews confirm that colchicine can reduce proteinuria and prevent progression to chronic renal failure when started before advanced renal impairment. ResearchGate+1

2. Incidence of ESRD and need for dialysis due to FMF

- Because amyloidosis incidence has dropped so sharply, new cases of ESRD due to FMF amyloidosis are far fewer than in the pre colchicine era.
- Contemporary nephrology series describe ESRD due to FMF as a recognised but relatively infrequent aetiology among RRT patients in Mediterranean centres, again mostly in those with late or inadequate treatment. nephropathol.com+2PMC+2
- For patients who do reach ESRD, outcomes on dialysis and after kidney transplantation appear similar to other ESRD causes, and colchicine is usually continued, often at reduced dose. nephropathol.com+2Karger Publishers+2

In practical terms: in an FMF patient diagnosed and treated from childhood with adequate colchicine doses, ESRD from AA amyloidosis has gone from a relatively common fate to a rare complication.

Small intestinal obstruction

Here the data are less numeric and more observational. Pathophysiology and pre colchicine situation.

- FMF causes recurrent peritoneal attacks, which can lead to peritoneal adhesions.
- These adhesions can cause adhesive small bowel obstruction, especially in children and young adults. ScienceDirect+2Asclepius Open+2
- Case series and reviews from the pre and early colchicine era describe small bowel obstruction as an important surgical pitfall, often initially misinterpreted as another FMF peritonitis attack. Israeli Medical Association+1

Since routine colchicine prophylaxis

- Continuous colchicine markedly reduces the frequency and intensity of peritonitis attacks, therefore it is expected to reduce the cumulative risk of adhesion formation and adhesive small bowel obstruction. PMC+2Turkish Archives of Pediatrics+2
- Modern reports describe acute small bowel obstruction in FMF as rare, usually as individual case reports or small case based reviews, again in patients with long standing, often sub-optimally controlled disease. Israeli Medical Association+2PMC+2
- Biologic agents such as anakinra or canakinumab are increasingly used in colchicine resistant FMF to control inflammation and prevent further peritonitis and adhesions in patients who already had surgical complications. ResearchGate+1

We do not have good population level “before versus after 1972” rates for small bowel obstruction, but the qualitative signal is that it has become a relatively rare, mostly case report level complication in the colchicine era.

Putting it together

Since continuous colchicine prophylaxis was introduced in 1972 and became standard of care:

- AA amyloidosis
- Previously, very frequent in untreated FMF, up to 20 to 30 percent overall and around 75 percent in some high-risk groups by age 40. njmonline.nl+1
- Now, uncommon in regularly treated patients, around 2 to 10 percent in recent series, largely confined to late diagnosed, undertreated or colchicine resistant patients. ectrx.org+2Clinical and Experimental Rheumatology+2
- Renal failure and dialysis
- Previously, AA amyloidosis causing nephrotic syndrome and ESRD was the major cause of death in FMF. njmonline.nl+1
- Now, progression to ESRD from FMF amyloidosis is rare in patients treated appropriately from early in the disease course, and RRT outcomes in those who do reach ESRD

are similar to other aetiologies. PubMed+2nephropathol.com+2

- Small intestinal obstruction
- Historically a recognised complication secondary to adhesions from repeated peritonitis. ScienceDirect+1
- In the colchicine era, acute adhesive small bowel obstruction is described as a relatively rare complication, mostly in patients with long standing, poorly controlled disease, often reported as single cases. PMC+2ResearchGate+2

Question 2

Could you please tell me what the changes were in familial Mediterranean fever since the introduction of colchicine in 1972, regarding the outcome of fertility and pregnancy?

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Since the introduction of colchicine in 1972, outcomes related to fertility and pregnancy in Familial Mediterranean Fever (FMF) have markedly improved. Colchicine is now established as the first-line therapy for FMF, and its regular use has led to a significant reduction in FMF-related infertility and adverse pregnancy outcomes. Untreated FMF is associated with recurrent peritonitis, leading to peritoneal adhesions, tubal obstruction, and secondary amyloidosis, all of which contribute to infertility and poor pregnancy outcomes. Colchicine prevents these complications by controlling disease activity and reducing the risk of amyloidosis (1, 3).

Current evidence demonstrates that colchicine does not increase the risk of major birth defects, miscarriage, or adverse maternal or foetal outcomes when used at therapeutic doses during pregnancy (3, 7). The miscarriage rate and incidence of congenital malformations in colchicine-treated FMF pregnancies are comparable to those in untreated FMF patients and healthy controls (5, 7). Furthermore, the rate of infertility among women with FMF who are regularly treated and followed is low, and pregnancy outcomes, including live birth rates, are similar to those of the general population (8, 9).

In men, colchicine may rarely cause oligospermia or azoospermia, but over-

all, it does not significantly impair fertility at recommended doses (2, 3, 5). The consensus in the medical literature is that colchicine therapy improves reproductive outcomes in FMF by controlling disease activity and preventing complications, and its use during pregnancy is considered safe and beneficial (3, 5, 7, 8, 10).

Would you like me to summarise the latest long-term data on colchicine safety and pregnancy outcomes in FMF, including any recent cohort studies or registry analyses published in the last few years?

Chat GPT-4

Short answer

Since colchicine became standard therapy for FMF (around 1972), the outcomes for fertility and pregnancy improved overall: female fertility and pregnancy outcomes (miscarriage, preterm birth, need for dialysis during pregnancy from amyloidosis) have generally become better, and continuing colchicine through conception and pregnancy is now considered safe and recommended in most patients. Male fertility is not significantly impaired by FMF itself; colchicine has been associated with rare, usually reversible, oligospermia/azoospermia in a small number of men. [e-lactancia.org+2PubMed+2](#)

What changed (more detail, evidence-backed)

- Before colchicine (pre-1972):** worse fertility and pregnancy outcomes. Recurrent serositis (peritonitis) caused pelvic adhesions and higher rates of female subfertility/infertility; pregnancies in untreated FMF had higher rates of miscarriage and preterm delivery. Colchicine was a major turning point because it prevented attacks and amyloidosis, reducing those complications. [e-lactancia.org+1](#)
- After colchicine:** improved female fertility and pregnancy outcomes. Multiple reviews and cohort studies report that regular colchicine reduces attack frequency, lowers miscarriage rates, and is associated with favourable pregnancy and perinatal

outcomes compared with historical untreated cohorts. Recent systematic reviews/meta-analyses conclude colchicine does not increase congenital malformations or miscarriage and may even reduce foetal loss in women with FMF. [OUP Academic+2PubMed+2](#)

3. Male fertility.

- FMF itself is not strongly linked to reduced male fertility in modern studies.
- Colchicine has been reported (rarely) to cause oligospermia/azoospermia in some men, but this effect is uncommon and often reversible on dose reduction/withdrawal; large recent analyses do not show a major paternal reproductive risk. [e-lactancia.org+1](#)

4. Assisted reproduction / IVF.

Studies of FMF patients undergoing IVF show colchicine treatment during ovarian stimulation does **not** significantly worsen IVF outcomes (clinical pregnancy rate, live birth). [FertSterT](#)

5. Safety in pregnancy and lactation: current consensus.

Contemporary guidelines and systematic reviews recommend continuing colchicine during attempts at conception, pregnancy and breastfeeding in most FMF patients because the benefits (attack control, prevention of amyloidosis and pregnancy complications) outweigh the low observed risks to the foetus or infant. Recent meta-analyses (including 2025 reviews) reinforce a good reproductive safety profile. Still, individual counselling is advised. [PubMed+1](#)

Practical takeaways

- If you or a patient has FMF and are planning pregnancy, do not stop colchicine without medical advice: stopping increases attack risk and may worsen fertility/pregnancy outcomes. [OUP Academic+1](#)
- For men worried about sperm effects, discuss dosage and, if there's concern about oligospermia, consider semen analysis and specialist advice; effects are uncommon and

often reversible. [e-lactancia.org+1](#)

- Pregnancies in women with FMF should have close obstetric follow-up (as with other high-risk conditions), but colchicine itself is not a reason to withhold standard prenatal care. [PubMed](#)

Chat GPT-5.2

In short, colchicine has changed FMF from a disease that commonly damaged fertility and pregnancy outcomes to one where, if the disease is controlled and colchicine is continued, fertility and obstetric outcomes are usually close to normal.

I will separate female fertility, male fertility, and pregnancy outcome, and contrast pre-colchicine with the colchicine era.

1. Female fertility

Before colchicine was standard (pre-1970s)

- Recurrent peritonitis often led to pelvic and tubal adhesions, so tubal factor infertility was a well described complication of FMF. [e-lactancia.org+1](#)
- FMF attacks during pregnancy were associated with spontaneous abortions and preterm delivery, probably via inflammatory flares and peritonitis. [e-lactancia.org+1](#)

So in the pre colchicine era, FMF itself was a significant cause of subfertility and adverse pregnancy outcome, especially in women with frequent abdominal attacks.

Since colchicine prophylaxis became routine

- The 2003 Ann Rheum Dis review explicitly notes that colchicine treatment improved female fertility and the outcome of pregnancy by preventing serosal adhesions and controlling acute attacks. [e-lactancia.org+1](#)
- More recent cohort data of women with FMF on colchicine show:
 - Infertility rates similar to background, with most infertility due to usual gynaecologic causes rather than FMF itself. [JRHEUM+2JRHEUM+2](#)
 - No signal that colchicine itself

impairs ovarian function, response to COS, or IVF outcomes. FertSterT+1

- change: from a disease that often caused tubal infertility and miscarriage to one where, under continuous colchicine, female fertility is generally preserved, and obstetric risk is mostly driven by standard factors rather than FMF per se.

2. Male fertility

Before colchicine / in uncontrolled FMF

- FMF associated AA amyloidosis can involve the testes and cause azoospermia, so severe, longstanding disease could cause male factor infertility. e-lactancia.org+1
- Early case reports suggested colchicine might cause azoospermia or chromosomal problems, which led to caution about use around conception in the 1960s to 1970s. e-lactancia.org

Colchicine era data

- Larger cytogenetic and clinical series found no significant increase in chromosomal aberrations and no consistent impairment of spermatogenesis with therapeutic colchicine doses in FMF. e-lactancia.org+1
- A 2004 series of 60 wives of men with FMF, most on colchicine, found no increased rate of abortions or congenital malformations and concluded there is no need to stop colchicine in men before conception. PubMed+1
- A 2025 cohort of 180 male FMF patients attempting conception reported:
 - 98.3% achieved pregnancy
 - 85% of pregnancies ended in live births
 - Miscarriage, stillbirth and ectopic pregnancy rates were similar to population averages
 - Conclusion: FMF does not decrease male fertility, and colchicine is safe during conception, with no paternal effect on pregnancy outcomes. PubMed+1

Net change: azoospermia now occurs mainly in the context of severe amyloidosis, which is much rarer because of

colchicine. In the typical treated male FMF patient, fertility and pregnancy outcomes of partners are essentially normal, and stopping colchicine before conception is not recommended.

3. Pregnancy outcomes under colchicine

Here the key evolution is that we now keep colchicine on, instead of stopping it out of fear of teratogenicity.

Earlier era concerns

- Because colchicine interferes with microtubules, early reports raised concern about chromosomal abnormalities and malformations. That led some clinicians to stop colchicine during pregnancy, which then allowed FMF flares, with consequent miscarriage and preterm labour. e-lactancia.org+1

Data accumulated since the 1970s

1. Cohorts in women with FMF

- Classic Israeli and other Mediterranean series following more than 200 colchicine-exposed pregnancies in FMF showed:
 - Malformation rates comparable to controls
 - No increase in miscarriage or stillbirth when FMF was controlled
 - Worsening outcomes when colchicine was withdrawn and attacks recurred. e-lactancia.org+2CRIS+2
- Ben-Chetrit *et al.*, *Arthritis Care Res* 2010, and similar cohorts:
 - Colchicine during pregnancy did not worsen pregnancy outcome, and helped keep attacks under control
 - Authors concluded there was no justification for routine amniocentesis solely because of colchicine exposure. Ovid+2Advanced Cellular Research+2
- Other retrospective series from Turkey and elsewhere describe generally favourable perinatal outcomes in FMF women on colchicine, though FMF itself may be a modest independent risk factor for preterm birth.

TJR+2DergiPark+2

2. General teratogenicity data

- Large teratology cohort: 238 colchicine-exposed pregnancies, mostly first-trimester, compared with 964 controls
 - Major congenital anomaly rate was similar to controls
 - No specific malformation pattern identified. Am J Obstet Gynecol+1
- A 2025 systematic review and meta-analysis of 25 studies (FMF and other colchicine uses) reported:
 - Relative risk of miscarriage or foetal loss in FMF with colchicine 0.87, 95 percent CI 0.67 to 1.12
 - Congenital malformation rates 0.6 to 4 percent, comparable to FMF women not taking colchicine
 - No clear adverse effect on male or female fertility. ScienceDirect+2PubMed+2

3. Guidelines and contemporary recommendations

- EULAR and other FMF management recommendations now explicitly state that colchicine should not be discontinued before conception, during pregnancy or lactation, for either women or men, except in rare cases of toxicity. Arthritis Research & Therapy+2SpringerLink+2

Net change:

- Pre colchicine or when colchicine was stopped, FMF itself increased risk of miscarriage, preterm birth and infertility.
- With continuous colchicine:
 - Miscarriage and congenital anomaly rates are similar to the general population
 - FMF flares are fewer, so there is less preterm labour and maternal morbidity
 - Obstetric outcomes in most series are described as favourable, provided disease is controlled and amyloidosis is absent or mild. TJR+2JRHEUM+2

4. Bottom line in “before versus after colchicine” terms

Since colchicine became standard therapy for FMF in the 1970s:

• Female fertility

- Before: substantial tubal infertility and recurrent pregnancy loss due to repeated peritonitis and uncontrolled inflammation.
- Now: in adherent patients started early, fertility is usually preserved, and infertility is more often due to usual gynecologic causes; colchicine itself does not appear to impair fertility and likely improves it by preventing adhesions. e-lactancia.org+1

• Male fertility

- Before: significant risk of azoospermia in those with severe testicular amyloidosis.
- Now: amyloidosis is much less common, and large cohorts show normal or near normal male fertility, with colchicine considered safe during conception and no detectable paternal effect on pregnancy outcomes. PubMed+2PubMed+2

• Pregnancy outcome

- Before or when colchicine was withheld: FMF flares during pregnancy increased risk of miscarriage and preterm birth.
- Now: continuous colchicine is associated with good pregnancy and perinatal outcomes, malformation and loss rates similar to background, and better maternal disease control. ScienceDirect+3Ovid+3TJR+3

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Chat GPT-4

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