MOTHERISK *UPDATE*

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Safety of colchicine therapy during pregnancy

ABSTRACT

QUESTION A 27-year-old patient in our clinic with familial Mediterranean fever (FMF) has been treated with colchicine for the last decade. She is planning her first pregnancy. What recommendations should we give her regarding use of colchicine before and during pregnancy, bearing in mind that discontinuation of colchicine could lead to complications from amyloidosis?

ANSWER Colchicine passes through the placenta in humans, is teratogenic in animals, and raises rates of male and female infertility. Based on several patients with chromosomal anomalies, some authorities recommend that patients who require colchicine therapy during pregnancy undergo amniocentesis with karyotyping. In contrast, an increasing body of evidence suggests that colchicine use throughout pregnancy carries no substantial teratogenic or mutagenic risk when used at recommended doses. Its use prevents febrile attacks of FMF and reduces the frequency of renal complications.

RÉSUMÉ

QUESTION Une patiente de 27 ans de notre clinique souffre de la fièvre méditerranéenne familiale (FMF) et est traitée à la colchicine depuis 10 ans. Elle planifie sa première grossesse. Quelles recommandations devrais-je lui donner concernant l'utilisation de la colchicine avant et pendant la grossesse, tenant compte du fait que la cessation de la colchicine pourrait entraîner des complications dues à l'amylose?

RÉPONSE La colchicine traverse le placenta chez l'humain, est tératogène chez les animaux et augmente le taux d'infertilité chez l'homme et la femme. En se fondant sur plusieurs patients présentant des anomalies chromosomiques, certains experts recommandent que les patientes qui ont besoin d'une thérapie à la colchicine durant la grossesse fassent l'objet d'une amniocentèse avec caryotypage. Par ailleurs, un nombre croissant de données scientifiques font valoir que l'utilisation de la colchicine durant toute la grossesse ne pose aucun risque substantiel d'ordre tératogène ou mutagène lorsque la dose recommandée est respectée. Son utilisation prévient des attaques fébriles de FMF et réduit la fréquence des complications néphrologiques.

Colchicine, a microtubule growth inhibitor, affects mitosis and other microtubule-dependent functions of cells, including the phagocytic properties of polymorphonuclear cells. As a therapeutic agent, the drug has relatively few approved indications.[1] While familial Mediterranean fever (FMF) is the most common indication for colchicine therapy,[2] colchicine has long been used to prevent or mitigate acute and chronic gout. Less frequently, colchicine is used for treating liver cirrhosis; biliary cirrhosis; and certain skin disorders, such as psoriasis, palmoplantar pustulosis, Behçet's disease, dermatitis herpetiformis, scleroderma, and condyloma acuminatum.

Do you have questions about the safety of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at (416) 813-7562; they will be addressed in future Motherisk Updates. Published Motherisk Updates are available on the College of Family Physicians of Canada website (**www.cfpc.ca**). Some articles are published in *The Motherisk Newsletter* and on the Motherisk website (**www.motherisk.org**) also.

Familial Mediterranean fever is an autosomal recessive disease that primarily affects people of Jewish, Armenian, Arabic, and Turkish ancestry.[3] About half the patients affected have symptoms in their first decade of life; only 5% of patients develop FMF after the age of 30.[4] The

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disease manifests clinically by recurrent attacks of fever, peritonitis, pleuritis, arthritis, or erysipelaslike skin findings. Attacks, which generally last 1 to 4 days and occur every 3 to 4 months, are triggered by such factors as physical and emotional stress, menstruation, and a high-fat diet.[5] Between attacks, patients are healthy and usually free of symptoms.

Colchicine was introduced in the early 1970s to prevent and decrease the severity of FMF attacks.[6] Its anti-inflammatory properties made it a good therapeutic candidate, and up to 90% of patients had marked reduction or complete remission of symptoms during continuous treatment.[7-9] Because colchicine is teratogenic in animals[1] and passes through the placenta in humans,[10] it was contraindicated during pregnancy before the 1990s.

Effect on fertility

Colchicine was thought to affect fertility. Ehrenfeld et al[9] reported periods of infertility in 13 of 36 women with FMF taking long-term colchicine treatment (prevention of human cytotrophoblast differentiation into syncytiotrophoblasts following in vitro colchicine treatment suggested a possible mechanism for female infertility[11]). Azoospermia or impaired sperm penetration were found in 20% of men taking colchicine,[12] although the inconsistent sperm pathologies could be explained by variability in disease pathophysiology rather than by colchicine's effect on sperm production or function.[13] To date, no clear link between infertility and colchicine has been established.

Risk or benefit?

Even with these tentative risks of teratogenicity and infertility, discontinuing colchicine treatment before or during pregnancy appears to carry greater risk than maintaining it. Amyloidosis is the main complication of untreated FMF, and the resulting nephropathy[1] has been correlated with adverse maternal and fetal outcomes.[14] Evidence indicates that colchicine protects against amyloidosis in patients with FMF.[15] Proteinuria was found in 4 of 960 (0.42%) patients compliant with colchicine treatment compared with 16 of 54 (29.6%) noncompliant patients in a study of 1070 patients followed for 4 to 11 years. Results of another study indicated that colchicine increased survival of those with primary amyloidosis.[16] It is possible that pregnancy exacerbates amyloid nephropathy in patients with FMF.[17]

Several case reports support the safety of colchicine during pregnancy. Zemer et al[18] reported on three pregnant FMF-affected sisters. Two discontinued colchicine therapy during pregnancy and had subsequent nephropathy, amyloidosis, and febrile episodes; one of these two died within 2 years from end-stage renal failure. Nevertheless, both had delivered healthy children. The third sister continued colchicine therapy throughout pregnancy and had a healthy child with no reported complications. Two other pregnancies in FMF patients, complicated by ascites and amyloidosis, have ended successfully under continuous colchicine treatment.[19]

A successful pregnancy of a colchicine-treated FMF patient induced by in vitro fertilization[20] has been reported, and retrospective studies corroborate colchicine's safety during pregnancy. Among 84 colchicine-treated patients, three men and seven women had healthy children. One pregnancy ended in spontaneous abortion, possibly as a result of noncompliance with colchicine treatment and subsequent nephrotic amyloidosis.[21] Another review of 28 pregnancies in 36 FMF-affected women receiving long-term colchicine therapy[9] reported 16 healthy infants. Several other pregnancies ended in miscarriages at a rate similar to that in untreated FMF patients.

In a review of 116 colchicine-treated mothers with 225 pregnancies,[22] 40 were treated during the first trimester, 91 were treated to term, and 94 were untreated. Neither the colchicine-treated mothers nor their children were found to be adversely affected during 10 years of follow up. Spontaneous abortions were more prevalent in the untreated group (20.2%) than the treated group (12.2%), an outcome possibly related to attacks of fever and peritoneal irritation in untreated FMF patients.

Conclusion

Current evidence supports the safety of colchicine use throughout pregnancy at recommended doses. Discontinuing the drug during pregnancy might be detrimental for a woman with FMF. As yet, colchicine's link to infertility has not been fully established. Use of colchicine during pregnancy for gout and other diseases is not well documented, and risks of teratogenicity cannot be completely ruled out. If colchicine is to be used during pregnancy, caution should be exercised, and amniocentesis with karyotyping[9] should be considered due to the mutagenic risk shown in animals.

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