

Effect of methotrexate treatment of ectopic pregnancy on subsequent pregnancy

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Abstract

Question My last pregnancy was diagnosed as ectopic, and I was treated successfully with intramuscular methotrexate (MTX) 8 weeks ago. I am currently planning for another pregnancy; however, I have read that MTX causes birth defects and that it stays in my body for a very long time, ranging from 1 to 12 months after treatment. When is it safe to conceive?

Answer We suggest that the outcomes of pregnancies conceived shortly after MTX therapy for extrauterine pregnancy are most likely to be favourable and similar to those pregnancies conceived 6 months after MTX treatment. However, as data are not sufficient to draw a definitive conclusion or to confirm the exact safe timing after MTX treatment, at least a 3-month waiting period is recommended for women who are planning pregnancy. Nevertheless, conception within 3 months of MTX treatment of extrauterine pregnancy should not be considered a definite indication of termination, and further targeted fetal anatomy assessment is recommended. Further retrospective and prospective studies are needed to define the safety period before 3 months and to solidify this recommendation.

Résumé

Question J'ai eu un diagnostic de grossesse ectopique et on m'a traitée avec succès, il y a 8 semaines, par injection intramusculaire au méthotrexate (MTX). Je planifie actuellement une autre grossesse, mais j'ai lu que le MTX cause des malformations congénitales et que la substance persiste dans le corps pendant une très longue période après le traitement, pouvant aller de 1 à 12 mois.

Réponse Nous sommes d'avis que l'issue d'une grossesse conçue peu après une thérapie au MTX pour une grossesse ectopique sera probablement favorable et semblable à celle d'une grossesse conçue 6 mois après le traitement au MTX. Par ailleurs, puisque les données ne sont pas suffisantes pour tirer des conclusions définitives ou pour confirmer un délai d'attente exact après un traitement au MTX, nous recommandons aux femmes qui prévoient une grossesse d'attendre au moins 3 mois. Néanmoins, la conception dans les 3 mois suivant un traitement au MTX pour une grossesse extra-utérine ne devrait pas être considérée comme une indication définitive pour y mettre un terme et il est recommandé de procéder à une évaluation plus approfondie de l'anatomie fœtale. Il faut un plus grand nombre d'études rétrospectives et prospectives pour déterminer les risques d'une conception dans les 3 mois suivant la thérapie, et renforcer cette recommandation.

Methotrexate (MTX), an immunosuppressive drug, is a folic antagonist that binds to the enzyme dihydrofolate reductase. This inhibits synthesis of thymidylate, serine, and methionine, which disrupts synthesis of DNA, RNA, and protein and leads to cell death.¹ Methotrexate is further metabolized to MTX polyglutamates, which are long-lived metabolites, inhibiting other folate-dependent enzymes. It is generally used to treat cancers, psoriasis, and rheumatic diseases, as well obstetric or gynecologic conditions, including extrauterine pregnancy (EUP), first-trimester terminations, and gestational trophoblastic disease.² A low-dose MTX treatment protocol introduced by Stovall et al³ 20 years ago is to date the treatment of choice for EUP when possible.

Exposure

Methotrexate is teratogenic or lethal to embryos of all animal species tested.⁴ In humans, MTX and aminopterin (another folate antagonist) have been associated with the following fetal malformations: central nervous system abnormalities, including spina bifida, hydrocephaly, anencephaly, and mental retardation; skeletal abnormalities, including synostosis of lambdoid sutures, partial or absent ossification of bones, micrognathia, cleft lip or palate, broad depressed nasal bone, hypertelorism, short limbs, syndactyly, absent digits, and clubfoot; and dextrocardia and intrauterine growth retardation.^{5,6} Feldkamp and Carey⁵ reviewed the literature about women exposed to MTX during pregnancy

and suggested that the minimal maternal dose necessary to induce defects was above 10 mg per week, and the postulated critical period was between 6 and 8 weeks after conception. This recommendation was supported by Donnenfeld et al,⁷ who reviewed information from 63 centres participating in the prospective evaluation of fetal abnormalities. However, owing to several different case reports of fetal malformations with low-dose MTX exposure after 8 weeks, this recommendation is considered controversial.⁶

Concerns about the effects of MTX on subsequent pregnancies' outcomes arise mainly from the potent mechanism of action of the drug and its metabolites on pregnancy, as well as its detection in the kidney and liver weeks and even months after exposure. Although the half-life of MTX is 8 to 15 hours, its presence in the liver has been reported to last up to 116 days after exposure.^{8,9} Owing to concerns about MTX and its metabolites remaining in some organs and possibly affecting pregnancy or fetal development, manufacturers and several sources have arbitrarily recommended that women wait 3 to 6 months to become pregnant after stopping therapy.¹⁰ The specific question of "When is it safe to conceive after MTX treatment of EUP?" had not been studied until 2008.¹¹ Thus, it is not surprising that there is no consensus regarding this period. Most physicians follow the manufacturers' recommendations and advocate for a delayed period of 3 to 6 months. However this recommendation is based on animal models, sporadic human case reports, and various study designs. The goal of this update is to summarize the published data so far and to provide a scientific-oriented guideline.

Studies overview

A literature search regarding safety of pregnancy after MTX exposure yields various study populations, protocols, and study designs. A French collaborative study in 2004 concluded there was no increase of teratogenicity among 28 women who were treated with low-dose MTX for chronic inflammatory disorders, once the drug had been discontinued as early as possible in pregnancy.¹² In a 2009 systematic review, Martínez Lopez et al¹³ reported on 101 pregnancies exposed to low-dose MTX (5 to 25 mg/week) among rheumatic patients. The rates of miscarriages and of birth defects were found to be similar to those observed in healthy populations.

In a large retrospective study, 387 women were treated with combined therapy, including MTX, for gestational trophoblastic tumour; the incidence of abnormal outcome (eg, miscarriages, stillbirth, repeat mole) was found to be significantly higher in women who conceived within 6 months of completing chemotherapy (4 out of 15) than in those who conceived after 12 months (10 out of 95) ($P=.028$).¹⁴ In a similar study, Rustin et al¹⁵ reported a slightly increased

but non-significant incidence of stillbirth and congenital malformations compared with the expected background group. Rustin and colleagues¹⁵ recommended postponing further conception for 1 year after cessation of chemotherapy, even though no significant difference was detected. A prospective study indicated that therapy with MTX increased the rate of early miscarriages and malformation when conceiving within 1 year of therapy; however, this study included only 9 women and the exposure to MTX was prolonged, ranging from 1 to 12 months.⁷

The studies cited above provide indirect and conflicting information on the safety of MTX during pregnancy, and none of them addresses this topic specifically enough to help us to answer the woman's question.

Addressing the question

In 2008, Svirsky et al¹¹ addressed this topic in a retrospective study. They retrieved data on 314 women treated with MTX for EUP and evaluated the pregnancy outcomes among those who subsequently conceived. A total of 125 pregnancies were reported with complete information. Forty-five pregnancies occurred within 6 (mean [SD] 3.6 [1.7]) months of the last MTX treatment. The outcomes of those pregnancies were compared with those of 80 pregnancies that occurred more than or equal to 6 (mean [SD] 14.7 [23.6]) months after the last MTX treatment. The fetal malformations and adverse outcome rates, including miscarriages, for both groups were similar (odds ratio 1.003, 95% confidence interval 0.98 to 1.02). According to a logistic regression analysis, the interval between the last MTX treatment of EUP and the subsequent pregnancy had no effect on the outcome.¹¹

Based on the result of this study and given that the actual fetal exposure to MTX released from maternal organs is considered to be minimal, we suggest that the outcomes of pregnancies conceived shortly after MTX therapy for EUP are most likely to be favourable and similar to those conceived after 6 months. As data are not sufficient to draw a definitive conclusion or to confirm the exact safe timing after the MTX treatment, a recommendation of at least a 3-month waiting period for women who are planning pregnancy seems to be prudent. Nevertheless, conception within 3 months of the MTX treatment of EUP should not be considered a definite indication of termination, and further targeted fetal anatomy assessment is recommended. Further retrospective and prospective studies are needed to define the safety period before 3 months and to solidify this recommendation. 🌸

Competing interests

None declared

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Do you have questions about the effects 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.

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