
Use of methotrexate in young patients with respect to the reproductive system

E. Gromnica-Ihle¹ and K. Krüger²

¹Private Practice of Rheumatology, Berlin, Germany; ²Rheumatology Center St. Bonifatius, Munich, Germany.

Erika Gromnica-Ihle, MD, Professor
Klaus Krüger, MD, Professor

Please address correspondence
and reprint requests to:

Prof. Dr. Erika Gromnica-Ihle,
Majakowskiring 11,
D-13156 Berlin, Germany.

E-mail: erika@gromnica-ihle.de

Received on July 23, 2010; accepted in
revised form on August 20, 2010.

Clin Exp Rheumatol 2010; 28 (Suppl. 61):
S80-S84.

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EXPERIMENTAL RHEUMATOLOGY 2010.

Key words: Methotrexate,
rheumatology, reproductive system.

ABSTRACT

Methotrexate (MTX) is one of the most commonly used drugs in the treatment of inflammatory rheumatic diseases. Unfortunately, MTX is an FDA Pregnancy Category X medication, which means it is contraindicated during pregnancy. The following review of the literature, with international guidelines, gives in addition an overview of current scientific knowledge on the topic.

MTX is a teratogenic substance. It accesses the placenta and, for the dosage of 5 to 25mg per week normally used in rheumatic diseases, can lead to both habitual abortions and anomalies in the neonate. Folic acid antagonism of MTX is the reason.

In the rheumatologic setting, small case reports are available for the usage of MTX of 101 pregnant women at the time of conception or during pregnancy, mostly during the first trimester. Individual casuistry also exists. An abortion rate of 23% was found to result from these case reports. The anomaly rate for neonates was >5%. Only a few pregnancies with neonatal anomalies are described with the child's father taking MTX at the time of conception. MTX is taken up (in small amounts) by the mother's milk, and breast feeding under MTX therapy, therefore, is also contraindicated.

Detailed and exact information on female patients taking MTX during the reproduction phase, but also for the father-to-be of the child if treated with MTX, with reference to the required contraception until at least three months before a planned conception and stopping of MTX at least at that time, is essential.

Introduction

Due to advances in antirheumatic pharmacotherapy, quality of life has significantly improved for many patients with rheumatic diseases. Although one part-

ner may be suffering from an inflammatory rheumatic disease, today most couples are still able to fulfil their desire to have children. Given that the age of conception has shifted into the fourth decade of life among many women in industrial nations, rheumatoid arthritis frequently appears in women who have not yet finished their family planning. In addition to the rheumatic disease itself, antirheumatic drug treatment may also have an impact on reproduction. Therefore, a modification of standard drug therapy and careful counselling are necessary during the reproductive phase to avoid damage to the foetus, neonate and/or breast-fed child.

Methotrexate (MTX) is among the drugs most often used in the treatment of inflammatory rheumatic diseases. Methotrexate is a US Food and Drug Administration (FDA) Pregnancy Category X medication that is contraindicated during pregnancy (1).

Data collection for this assessment

The available data for this assessment were based on: a) studies of patients who had been given MTX therapy for the treatment of neoplasms; b) studies in which MTX was employed as an abortifacient; c) small case studies in which women on MTX therapy for autoimmune diseases became pregnant unintentionally; and d) studies in which men on MTX therapy fathered children.

Compared with the treatment of neoplasms or its use as an abortifacient, MTX is administered in significantly lower doses in rheumatology.

The use of MTX in ectopic pregnancy (2) was not a topic of this review.

Folic acid deficiency and teratogenicity

The first suggestions that folic acid antagonists could be teratogenic in humans were based on the reports of failed terminations in mothers given aminop-

Competing interests: none declared.

terin in the first trimester of pregnancy (3). As a folate analogue, aminopterin competes for the folate binding site of the enzyme dihydrofolate reductase and blocks tetrahydrofolate synthesis. Inhibition of tetrahydrofolate synthesis results in depletion of nucleotide precursors as well as the amino acids methionine and serine, and this leads to inhibition of DNA, RNA and protein synthesis.

The anomalies observed in newborn children were described as aminopterin syndrome. This syndrome is characterised by the following features:

- craniostenosis
- flat orbital margins
- exophthalmus
- prognathism
- epicanthus
- large nose
- low-set ears
- short limbs / micromelia
- club foot/ skew foot
- general dysostosis
- anencephaly
- hydrocephalus
- mental /psycho-motor retardation
- antenatal delayed growth

Methotrexate is a methyl derivate of aminopterin that is a less toxic successor to aminopterin. In the 1970s, animal studies showed that MTX was embryotoxic in early pregnancy and caused skeletal abnormalities and cleft palate later in pregnancy (4). All reports of abnormality included neural tube, skull or limb problems with gestational ages at exposure ranging from four to twelve weeks (5).

Methotrexate is a folic acid antagonist that impairs dihydrofolate reductase and interferes with the production of purines. The mean values for the elimination half-life of MTX have been shown to range from about 5 to 8 hours (6). Interestingly, MTX distributes to extravascular compartments (synovial fluid) and different tissues, especially liver, kidney and joint tissues.

Methotrexate is also transported into blood cells. Indeed, MTX is transported intracellularly via the reduced folate carrier and is retained within cells long after it has been eliminated

from serum. The median time for methotrexate-glutamate to become undetectable in red blood cells was 15 weeks (the range was 3–32 weeks) from the time MTX treatment was ceased (7). Feldkamp and Carey (8) reviewed published cases of foetal aminopterin-like syndrome under MTX treatment and suggested that the critical period for the development of malformations was 6 to 8 weeks post-conception (*i.e.* 8 to 10 weeks of gestation), and that the estimated threshold dose was above 10mg MTX per week. Foetal malformations, however, have also been described before the 5th and after the 11th week of gestation (9), and current, no definite dosage threshold for foetal risk can be defined (10).

Foetal abnormalities in humans have been observed in women treated for cancer (5) and when MTX was unsuccessfully used to terminate a pregnancy (11). Abnormalities included such as hydrocephalus, hypoplasia of frontal and orbital bones, micrognathia and hypertelorism (12), or microcephaly, hypertelorism, low-set ears and up-sweep of the frontal hairline (9).

Some rheumatologic studies have observed foetal abnormalities with dosage between 7.5 and 25mg MTX/week. One report described an infant with multiple congenital anomalies born to a 20-year-old mother with juvenile rheumatoid arthritis who had been taking weekly low-dose MTX during the first trimester of pregnancy (the foetus was exposed to a total MTX dose of ca.100mg over a period of 8 weeks). The abnormalities were consistent with those associated with maternal ingestion of MTX at levels used to induce abortions (*i.e.* the group of abnormalities referred to as the “aminopterin syndrome”) (13).

MTX and teratogenicity

MTX teratogenicity in rheumatoid arthritis cannot be addressed by randomised controlled studies, for obvious ethical reasons. A systematic review of studies examining the safety of MTX on the reproductive system of patients with rheumatoid arthritis, retrieved by a sensitive search strategy in Medline (January 1961 to October 2007), Embase (January 1961 to October 2007),

Cochrane Library (up to October 2007), the abstracts of the American College of Rheumatology (ACR) (2005, 2006), and of the European League Against Rheumatism (EULAR) (2005–2007) annual scientific meetings, was published in 2009 by Martínez Lopez *et al.* (14). They analysed six publications based on case series and surveys of patients or doctors. Many reports on individual patients were excluded because of publication bias (cases also included in case series).

Table I summarises key details from these analysed studies, including the survey of rheumatologists by Østensen *et al.* (15). In the 101 pregnancies analysed by Martínez Lopez *et al.* (14), the patients had been exposed to MTX using doses of 5–25mg/week. A total of 13 women and 1 man were exposed prior to conception, and 87 women were exposed following conception. The pooled outcomes were: 18 women had induced abortions, 19 pregnancies ended in miscarriages (23% of pregnancies in which abortion was not induced) and 55 live births were registered (66% of pregnancies in which abortion was not induced). In 4 of these cases neonatal malformations were observed.

MTX and miscarriages in rheumatic diseases

The abortion rate of 23% in the cited summary by Martínez-Lopez *et al.* (14) significantly exceeds the rate seen in the general population. It has been shown that about 12–15% of pregnancies in the general population are terminated by spontaneous miscarriage before 20 weeks (21).

MTX and congenital malformations in rheumatic diseases

In the review by Martínez Lopez *et al.* (14), the malformation rate for newborn children was 7.3% of live births. None of the anomalies were as severe as those described for aminopterin syndrome. A case report by Buckley *et al.* (13), however, also described one case of aminopterin syndrome with anti-rheumatic therapy. Østensen estimated a 5–10% risk of congenital anomalies after first-trimester exposure of low-dose MTX therapy in rheumatic patients based on

Table I. Case series including mainly rheumatoid arthritis patients (14).

Study	Source	MTX dose	Time after conception before MTX was stopped	Pregnancies	Outcomes
Kozlowski 1990 (16) USA	Case series	7.5–10mg/week	2–15 weeks	n=10 (6 patients rheumatoid arthritis)	2 x elective abortions 3 x spontaneous abortions 5 x live birth
Donnenfeld 1994 (17) USA	Survey of teratology centres	7.5–12.5mg/ week (only RA)	4 x 2–6 weeks 1 x 37–38. week 9 x <1 year prior to conception	n=14 (7 patients rheumatoid arthritis)	4 x spontaneous abortions 9 x healthy live birth 1 x live birth with cavernous hemangioma
Østensen 2000 (18) Norway	Exposed case series	2.5–15mg/week	3–6 weeks	n=4	1 x spontaneous abortions 3 x live birth
Chakravarty 2002 (19) USA	Survey of doctors	unknown	Exposed at conception	n=39 (39 patients rheumatoid arthritis)	8 x elective abortions 7 x spontaneous abortions (1 x with congenital malformation) 23 x live birth (2 x with congenital malformations) 1 x still pregnant
Lewden 2004 (20) France	Exposed case series	mean dose 10.5mg/week	16 x stop <4 weeks 10 x stop 5–8 weeks 1 x >8 weeks 1 x MTX week 6 for a 5-week period	n=28 (27 patients) (22 patients rheumatoid arthritis)	5 x elective abortions 4 x spontaneous abortion 19 x live birth (1 x with minor neonatal anomalies)
Østensen 2007 (15) Switzerland	Survey of patients	unknown	“in pregnancy” or at the time of conception	n=6 (3 partner with MTX)	3 x elective abortions (1 x partner with MTX) 1 x spontaneous abortion 1 x live birth 1 x unknown
	Survey of rheumatologists	unknown	“in pregnancy”	n=5	1 x spontaneous abortion 1 x live birth 3 x unknown
		unknown	at the time of conception	n=8 (partner with MTX)	8 x live birth (2 x with neonatal anomalies)

experience and knowledge of the literature (10). Based on published data, a 2–4% chance of having a baby with a birth defect is assumed in women in general (22). Therefore, although the increased risk of birth defects is high, the absolute level appears less than 10%.

MTX and paternal exposure

No impact on fertility among men has been described for the MTX doses used in rheumatology (23, 24). A single case report described an oligospermia in a man treated with MTX for psoriasis, with restoration of normal sperm concentration after discontinuation of MTX (25). Measurements of serum gonadotropin and testosterone levels were normal during and after MTX treatment (25). Another case of oligospermia has been described in a patient who received higher doses of MTX for tumour therapy in combination with other cytostatic agents (26).

Information on paternal drug exposure at the time of conception is scarce. However, a variety of teratology information and clinical consultation services on drug safety during pregnancy and lactation exist (27), and they also include paternal exposure. The Berlin Institute for Clinical Teratology and Drug Risk Assessment during Pregnancy prospectively documented 58 pregnancies involving paternal exposure to MTX. The authors documented one major birth defect of trisomy 16 (28). Østensen *et al.* (15) reported, among 11 men who received MTX at the time of conception, 2 children with birth defects were born. One had atrophy of one hand and a small fistula beneath the ear, and the other had anomalies of the toes (15). Taken together, it is far from clear from published data if any connection between paternal exposure and malformations exists.

MTX and breastfeeding

The excretion of MTX into breast milk was studied in a 25-year-old woman, one month postpartum, who was undergoing treatment for choriocarcinoma (29). The peak milk level after an oral dose of 22.5mg MTX was reached after 10 hours with a milk/plasma ratio of 0.08 and a maximum milk concentration of 0.26µg/100ml. The significance of this concentration for the nursing child is unknown. No studies on the excretion of polyglutamate metabolites of MTX exist. Because MTX is detectable in breast milk, and studies have not definitively determined its effects on the nursing child, MTX is regarded as contraindicated during the lactation period.

Long-term effects of MTX treatment in children exposed *in utero*

In a study by Kozlowski *et al.* (16), children exposed to MTX *in utero* were

subsequently monitored by a telephone interview with the mothers. There were no significant pathological findings up to the mean age of 11.5 years. Even after administering higher MTX doses for haematological malignancies in pregnant women, the 84 children studied did not reveal any distinctive characteristics in long-term follow-up (30). No other data have been published.

Educating patients on the use of MTX

Unfortunately, the education of patients on MTX treatment for rheumatic diseases during the reproductive years is far from optimal, and/or frequently the patients do not comply with the recommendations. The results from a patient survey (15) revealed that a reference was made to the necessity for contraception in 24 out of 26 women taking MTX, but only 16 women followed this advice. Out of 28 men on MTX therapy, only 13 received advice on the necessity for contraception, but 14 men used contraception. As a result, less than two thirds of women and only half of men taking MTX practiced contraception during the reproductive years.

In an academic Division of Rheumatology in Boston (Beth Israel Deaconess Medical Center), a Quality Improvement and Patient Safety Program was implemented. This included pregnancy counselling for women with rheumatoid arthritis taking MTX. Since the initiation of this project, the percentage of female patients of reproductive age with rheumatoid arthritis who received documented pregnancy counselling before starting MTX increased from 44% to 100% over the course of 2 years (31). Based on the linkage of two nationwide databases, the use of antirheumatic drugs in pregnant women and expectant fathers has been studied in a population-based cohort study in Norway (Norwegian Prescription Database and Medical Birth Registry of Norway) (32). Data on 106,000 pregnancies from 2004–2006 were collected. Four women filled prescriptions for MTX during the 3 months prior to conception (total prescriptions of antirheumatic drugs: n=637), and two women also filled prescriptions for MTX during the first

(total prescriptions: n=392) and second (total prescriptions: n=251) trimesters. In the whole period of the study, 38 women were given MTX prescriptions (total: n=1411), and 36 prescriptions were dispensed to fathers-to-be in the 3 months before conception (total: n=1,212). The authors concluded that there was a high level of awareness about maternal MTX use in pregnancy in Norway. Information about MTX use in expectant fathers shortly before conception, however, is lacking (32).

International recommendations on the use of MTX during pregnancy and lactation

1. United States Food and Drug Administration (FDA):

Methotrexate is an FDA Pregnancy Category X medication that is contraindicated during pregnancy.

2. The following conclusions were published by a panel of 29 international experts following a consensus workshop on anti-rheumatic drugs during pregnancy and lactation, which was held in Stresa, Italy in September 2004 (33):

The level of evidence for the recommendations was presented in accordance with the classification by Miyakis *et al.* (34).

- MTX is contraindicated during pregnancy and should be prescribed to fertile women only under the cover of safe contraception (evidence level III).
- MTX must be withdrawn prophylactically 3 months before a planned pregnancy (evidence level IV).
- After stopping MTX folate supplementation should be continued throughout pregnancy (evidence level I).
- Given the minute amounts excreted into the breast milk, it is not known whether once-weekly administration of MTX has any significance for the nursing child. The American Academy of Pediatrics (AAP) does not recommend breastfeeding because of theoretical risks (evidence level IV).

3. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis (35):

Methotrexate should not be used for at least 3 months before planned pregnancy for men and women, and should not be used during pregnancy or breast feeding. Level of evidence: 4. Grade of recommendation: C. Agreement (Delphi vote) mean (SD) 8.2 (2.7) (methods by 36).

Summary assessment

1. MTX during the child-bearing years
Methotrexate is contraindicated during pregnancy and is not considered safe in lactation. Therefore, all women of childbearing potential should be strongly counselled and advised to use reliable forms of contraception while taking MTX. The same applies to women whose male partners are treated with MTX.

2. Pregnancy during MTX treatment

If a woman unintentionally becomes pregnant during MTX therapy, she should immediately stop the MTX medication. A consultation must be held with the patient to discuss her options.

3. How long MTX should be withdrawn before a planned pregnancy?

Methotrexate must be withdrawn at least 3 months prior to conception for both women and men.

4. Folic acid supplementation

Folic acid supplementation should be continued during the preconception period after methotrexate is stopped and throughout pregnancy. The recommended dose is 800µg of folic acid daily to reduce the risk of neural tube defects (37).

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