Low Dose Methotrexate in the First Trimester of Pregnancy: Results of a French Collaborative Study

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ABSTRACT. ***Objective.*** To assess the risk of major malformations in pregnant women with chronic inflammatory disorders treated with low dose methotrexate (MTX) during the first trimester of pregnancy. Secondary outcomes included the rate of miscarriage, birth weight, and gestational age at delivery.

Methods. Data from the French network of 31 pharmacovigilance centers and 2 teratology information services were analyzed. The outcome of pregnancy was prospectively assessed in women exposed during the first trimester of pregnancy. Data on maternal history and drug exposure were collected at the initial inquiry, and on the outcome of pregnancy at followup.

Results. Twenty-eight cases were available for analysis. MTX exposure ended before 8 weeks of gestation in 26 patients. Miscarriages occurred in 4 patients and 5 had elective termination of pregnancy. There were 19 live births, among whom 3 were premature. Birth weights in full-term children were within the expected range. One child exposed until 8.5 weeks of gestation had only minor anomalies (metatarsus varus and eyelid angioma).

Conclusion. Although no definitive conclusion can be drawn, our results and the analysis of the literature support the conclusion that no strong teratogenic risk is associated with low dose MTX provided that the drug is discontinued as early as possible in pregnant women. (J Rheumatol 2004;31:2360–5)

Key Indexing Terms:
METHOTREXATE PREGNANCY TERATOGENICITY

The folic acid antagonist methotrexate (MTX) is commonly used at high doses as a cytotoxic anticancer drug and at intermediate doses (usually 50 mg/m^2 as a single dose) as an abortifacient or for the medical treatment of ectopic pregnancies[1]. Since the 1980s, low dose MTX (5–20 mg weekly) has proven efficacious in the treatment of rheumatoid arthritis (RA), other inflammatory rheumatic disorders, and psoriasis, and is one of the first-line treatments for RA. As more women of reproductive age are thus likely to be exposed during the early stages of an unscheduled pregnancy, a careful assessment of the reproductive risks of MTX is a timely issue. Unfortunately, few data have been published and most of our knowledge regarding potential teratogenicity is based on animal studies, case reports, or small series.

Data from animal studies clearly indicate that MTX exerts variable embryotoxic and dose-dependant teratogenic effects depending on the species tested. Malformations were observed in the offspring of cats and rats at doses as low as 0.3 to 0.5 mg/kg that are equivalent to those used for rheumatic disorders in humans, whereas doses of 9.6 or 19.2 mg/kg in rabbits and 25 to 50 mg/kg in mice were required to produce a high percentage of malformations[2-4]. By contrast, no teratogenic effects were found in rhesus monkeys given intravenous doses of 30 mg/kg[5]. Cleft palate and limb defects were the most commonly observed malformations in sensitive species, but craniofacial, ocular, or neural tube anomalies were also reported. These teratogenic effects were prevented by folinic acid in rats and rabbits, but not in mice[6].

In humans, the teratogenicity of folic acid antagonists has been known since the early 1950s, and the typical features of the abnormalities were first described with aminopterin, an antifolic drug closely related to MTX. MTX was reported to produce abnormalities referred to as the aminopterin/methotrexate syndrome and were similar to those observed in animals. The most characteristic features of the syndrome include growth deficiency, dysmorphic facies, multiple skull and limb skeletal abnormalities, and less frequently, central nervous system abnormalities and congenital heart defects. Recently, developmental disabilities and mental retardation have been described in children or adults after *in utero* exposure[7-9]. Based on the time course of exposure in 6 published cases of the aminopterin/MTX syndrome, Feldkamp and Carey[10] suggested that the critical period for MTX-induced teratogenicity was from 8 to 10

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Submitted October 1, 2003; revision accepted June 22, 2004.

weeks of gestation (i.e., 6–8 weeks postconception) and that the estimated threshold dose was above 10 mg per week.

The expected malformation rate after *in utero* exposure to MTX is not known. In a review of the literature, congenital anomalies were identified in 2 of 19 children born to women exposed to high dose MTX for malignant conditions during the first trimester of pregnancy[11]. Data on the effects of lower doses of MTX in nonmalignant patients are scarce. Congenital anomalies compatible with the aminopterin/MTX syndrome have been described in at least 11 children[7-9,12-18], and there is a single case report of a normal child born after exposure to low dose MTX[10]. However, it is well known that retrospective case reporting favors the description of malformations rather than favorable outcomes, and no inference on the incidence of malformations can be drawn from these data. Only 4 small series have prospectively included patients exposed to low dose weekly MTX during early pregnancy[11,19-21]. Of the 23 documented exposures, 5 resulted in elective abortions (including one malformed infant), 4 in first-trimester miscarriage, 13 in healthy infants, and the last infant, born prematurely, had a respiratory distress syndrome, ileal perforation, and a positive sweat test for cystic fibrosis, but no gross malformations. Overall, one case of congenital malformations consistent with the aminopterin/MTX syndrome was observed among 15 assessable fetuses or living infants[11].

The current data are therefore largely insufficient to reliably assess the teratogenic risk of low dose MTX during early stage pregnancy. In a collaborative study we investigated the risk of major congenital malformations in patients with chronic inflammatory disorders who inadvertently continued MTX until or after the date of conception.

MATERIALS AND METHODS

A specific questionnaire was sent to each of the 31 centers of the French pharmacovigilance network and to 2 French teratology information services to analyze the data on MTX exposure during pregnancy that they collected from 1993 to 2001. As described for teratology information services in Europe, several of these centers specifically provide information on the safety of medicinal drugs during pregnancy and evaluation of risk in exposed patients[22]. In France, most inquiries received by these centers originate from physicians.

Similar procedures are routinely used by all these centers. Briefly, data on demographic, medical, obstetric, and drug exposure history are obtained through telephone interviews using a standardized questionnaire during the initial request. The exact time course of exposure is assessed using the date of the last menstrual period or the date of conception evaluated on ultrasound examination. Information on the course and outcome of pregnancy is obtained later using standardized forms sent within 2 months of the expected date of delivery to the inquiring physician or the designated obstetrician. Two or 3 contacts are sometimes necessary to obtain complete followup. The questionnaire at followup records additional data on drug exposures since the initial contact, details on the course of pregnancy and possible complications or adverse events, and complete data on the newborn.

Patients were considered eligible for evaluation if (1) they had pregnancy confirmed on ultrasound; (2) they underwent a prospective assessment of the outcome of their pregnancy, i.e., the MTX exposure was documented before delivery; and (3) they were exposed to at least one dose of MTX after the last menstrual period for rheumatic or chronic inflammatory disorders. Indeed, although the estimated half-life of low dose MTX is 5–8 hours, the terminal elimination half-life is subject to interindividual variability and can reach 50 hours[23]. Moreover, MTX or its pharmacologically active metabolites can be retained for several weeks in various human tissues, so that continued fetal exposure can result even when the drug has been stopped immediately before conception[24]. Low dose MTX was defined as any dose ≤ 50 mg per week.

The primary outcome of interest was the rate of major malformations (i.e., those having an adverse effect on either the function or social acceptability of the individual)[25]. Secondary outcomes included the rate of spontaneous abortion, defined as fetal loss before 20 weeks after the last menstrual period, still-births (fetal death at 20 weeks or later after the last menstrual period), elective abortions, and neonatal complications. Prematurity was defined as any birth occurring before 37 gestational weeks and low birth weight as less than 2500 g. Gestational weeks are calculated from the date of the last menstrual period or by date-confirmation of pregnancy by ultrasound examination, and this definition will be used in this report.

RESULTS

All centers that were contacted returned our questionnaire, but only 10 received at least one inquiry to counsel a pregnant patient exposed to low dose MTX during the first trimester of pregnancy over a 9-year period. Of a total of 33 pregnancies enrolled for followup, data were available for analysis of 28, one was still continuing, and 4 were lost to followup. The 28 pregnancies with fully documented followup occurred in 27 patients (one woman had 2 successive pregnancies) and the mean age of patients at conception was 32.9 ± 4.8 years. Only 4 patients had not been previously pregnant. Nine already had one child and 12 had 2 or more children (obstetrical status unknown in 2 patients). No woman had previously given birth to a malformed child. One patient was a regular smoker and none were alcohol abusers, but these data were missing in 12 patients. The therapeutic indications for MTX were RA in 22 patients, Takayasu's arteritis in one (2 pregnancies), psoriatic arthritis in 2, and dermatomyositis or ankylosing spondylitis, each in one patient. The weekly dosage of MTX was less than 15 mg in 26 patients (mean dose 10.5 mg/wk), and one patient with Takayasu's arteritis received 50 mg per week. Data on folic acid supplementation were available for only 4 patients, of whom 2 received folic acid before pregnancy.

The stage of pregnancy was confirmed by ultrasound examination. The mean gestational age at the time of inquiry was 9.0 ± 3.7 weeks of gestation. Sixteen patients discontinued MTX during the first 4 gestational weeks. Ten were still being treated between 5 to 8 gestational weeks, and one discontinued MTX after gestational week 8 (Figure 1). One patient started MTX during gestational week 6 for a 5-week period, whereas all other patients initiated treatment before pregnancy. The mean cumulative MTX dose since the beginning of pregnancy was 30.7 ± 23.3 mg. Nineteen patients had received concomitant medications at the time of inquiry (mostly nonsteroidal antiinflammatory drugs and corticosteroids).

Pregnancy outcomes included 5 elective abortions, 4

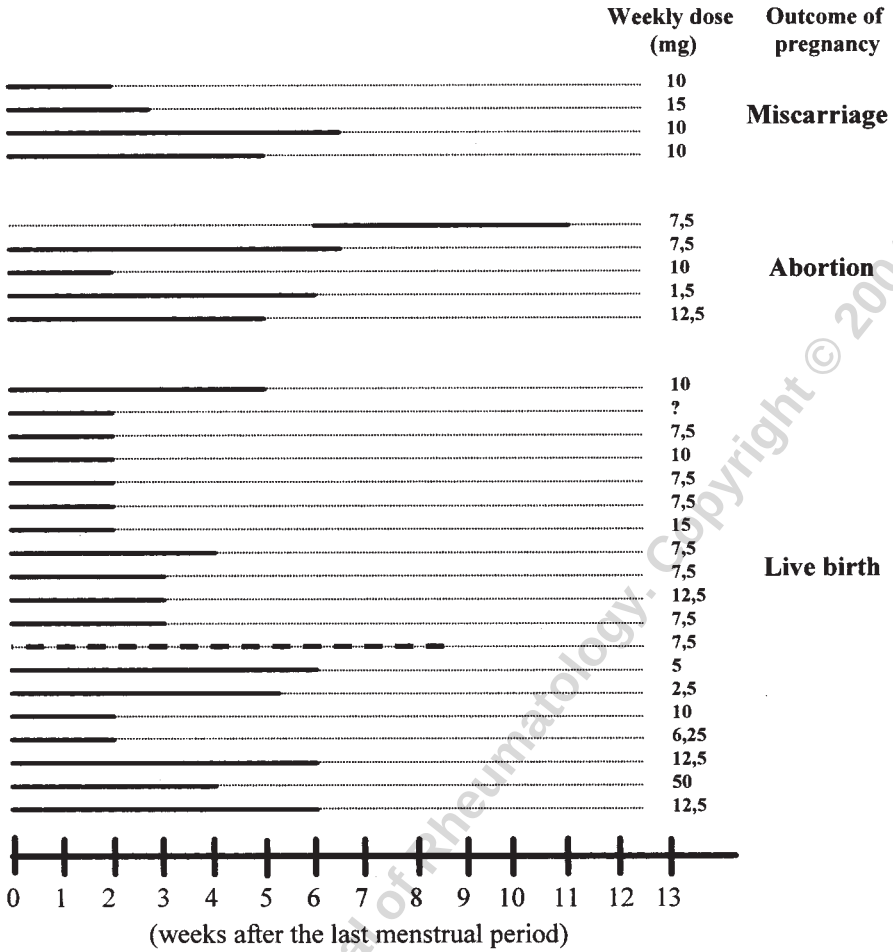

Figure 1. Dose and timing of MTX exposure in relation to pregnancy outcome in our series (broken line indicates the case with minor congenital anomalies).

spontaneous abortions, and 19 live births. No pathological examination of the 9 aborted fetuses was performed. Among the 19 live births, the mode of delivery consisted of 12 vaginal and 4 cesarean deliveries (unknown in 3 patients), and preterm birth occurred in 3 patients. The mean gestational age at birth for the 16 full-term babies was 39.2 ± 1.2 weeks. There were twice as many male as female babies. The mean birth weight (14 children), height (9 children), and head circumference (8 children) in full-term children were 3179 ± 465 g, 49.7 ± 2.3 cm, and 34.2 ± 0.9 cm, respectively.

One child presented with minor neonatal anomalies that consisted of bilateral metatarsus varus and right eyelid angioma. The mother had been exposed to MTX 7.5 mg/week and sulfasalazine 3 g/day for RA until 8.3 gestational weeks. Two children had documented neonatal pathological conditions: one premature child born at gestational week 30 experienced hyaline membrane disease and neonatal jaundice, and the second child had transient respiratory distress and jaundice.

DISCUSSION

The potential teratogenicity of low dose MTX is of concern because it is increasingly used in rheumatic women of childbearing age. Whereas MTX and other related folic acid antagonists have been clearly recognized as potential teratogens, there are still insufficient data to correctly assess the reproductive consequences of low dose MTX. In particular, quantitative data are insufficient to make an estimation of the risk. Although the available prospective studies in pregnant women treated with low dose MTX for rheumatic disease are reassuring, with only one case consistent with the aminopterin/MTX syndrome among 15 pregnancies, the number of patients studied is very small. In addition, estimates of the critical period of exposure (8 to 10 gestational weeks) and the threshold dose (> 10 mg/wk) were based on analyses of only 6 malformed infants, and the exact timing of exposure in these pregnancies was not always carefully stated in the original report[10]. It should also be stressed that any attempt to define a critical period of MTX teratogenicity in humans should be regarded cautiously. Indeed, MTX

has known abortifacient properties and severely malformed embryos may be potentially aborted early in pregnancy. In addition, given the potential inaccuracies in dating pregnancies by last menstrual period, it is unclear whether the exposure truly fell within this proposed critical time period.

On the other hand, the possible role of the maternal rheumatic disease on adverse pregnancy or fetal outcomes has been carefully explored in only a few studies. In their comprehensive review, Nelson and Ostensen[26] were unable to find studies suggesting an association between RA and an increased risk of spontaneous abortions, premature births, low birth weight, and congenital abnormalities. More recently, the same group analyzed the data from the Norwegian Medical Birth Registry, and suggested that women with rheumatic disease had a modest but significantly higher rate of preterm births and a higher number of low birth-weight children or children with birth defects compared to a reference group[27]. Overall, a possible negative influence of rheumatic disease on perinatal outcome cannot be ruled out.

Nineteen live infants were included in our series, and only one had minor anomalies (bilateral metatarsus varus and right eyelid angioma), which are not considered major malformations according to the commonly accepted definition. In addition, even though these anomalies were compatible with the time course of MTX exposure, there were not typical features of the classical aminopterin/MTX syndrome. The absence of major malformation in this series should be interpreted very cautiously, because the number of exposed pregnancies was small. In addition, no pathological examination of the 9 aborted fetuses was available, and the possibility that one or more of the aborted fetuses displayed this syndrome cannot be ruled out. Because the limited number of our patients prevented any reliable estimate of the malformation rate, our data were combined with those of other prospective series according to the proposed critical period of MTX exposure and after exclusion of spontaneous and voluntary abortions when no information on the fetus was available[11,19-21]. Overall, 34 pregnancies were assessable (19 from our series and 15 from the literature), and MTX exposure ended after gestational week 8 in only 5. There was only one case of malformation, corresponding to an overall malformation rate of 2.9% (95% CI 0.7–15.3%). That was a medically aborted fetus exposed until 19 weeks of gestation (20 mg weekly) that presented with brachycephaly, depressed nasal bridge, and short right femur bone[11]. No congenital malformations were noted among the 29 patients who discontinued MTX before gestational week 8 (0%; 95% CI 0–12%).

Since the proposed critical period of exposure and threshold dose for teratogenicity were suggested by Feldkamp, *et al*[10], 9 additional cases consistent with the fetal aminopterin/methotrexate syndrome and providing detailed information on the time course of MTX exposure during the first trimester of pregnancy have been described[7-9,11,13,15,17,18]. The therapeutic indication for MTX treatment was psoriasis or arthritis in 5 patients, termination of pregnancy in 3, and breast cancer in one, and the doses ranged from 10 mg weekly to a total dose of 1200 mg over 13 weeks. None of these patients received doses of MTX lower than 10 mg weekly. The period of exposure was within 8 and 10 gestational weeks in 5 cases. In 3 patients, drug exposure occurred between 5 and 7 gestational weeks[13,15,18] (Figure 2). In the last patient, MTX was given from 13 to 25 weeks of gestation, and the child presented a milder form of the syndrome[8]. These recently published case reports suggest that the critical period of MTX teratogenicity begins before gestational week 8 and extends beyond week 13. In addition, no definitive dosage threshold can be correctly defined. Indeed, one patient received only 2 single injections of MTX 10 mg at the end of weeks 4 and 5 of gestation[13], indicating that even low total doses should be considered in risk evaluation.

The rate of spontaneous abortions in our study, determined as the number of spontaneous abortions divided by the total number of documented outcomes excluding elective termination of pregnancy, is 17.4% (95% CI 5.0–38.8%), which is comparable to other series including 4 spontaneous abortions among 18 pregnancies exposed to MTX[11,19-21] or to the expected rate of miscarriage in the general population of 10% to 20% of recognized pregnancies[28]. However, a correct estimation of the spontaneous abortion rate requires early inclusion of patients after conception, as the estimated percentage of pregnancies that spontaneously abort may be minimized if the request is received after several weeks of gestation[29]. In our study, the first inquiry occurred after a mean of 9 weeks of gestation, which is rather late. Therefore, an underestimation of the spontaneous abortion rate cannot be ruled out. Data from 2 large controlled studies with a similar assessment of patients found 7–8% incidence of spontaneous abortions in the control groups, which included more than 1380 patients exposed to nonteratogenic agents, an incidence significantly lower than in our study[30,31]. Although it is impossible to demonstrate a direct causal relationship between spontaneous abortion and MTX exposure, a possibly increased risk of spontaneous abortion cannot be definitely ruled out and remains compatible with the use of MTX as an abortifacient[1]. In a recent population based cohort study, nonsteroidal antiinflammatory drug (NSAID) use at the time of conception or during pregnancy was also associated with an increased risk of miscarriage[32]. Thus, a possible role of concomitant exposure to NSAID should also be considered, and 2 of our 4 patients who had spontaneous abortions were indeed exposed to NSAID before and during the early stages of pregnancy.

The rate of preterm births in our study is 16.7% (95% CI 3.6–41.4%). This rate is relatively high in comparison with

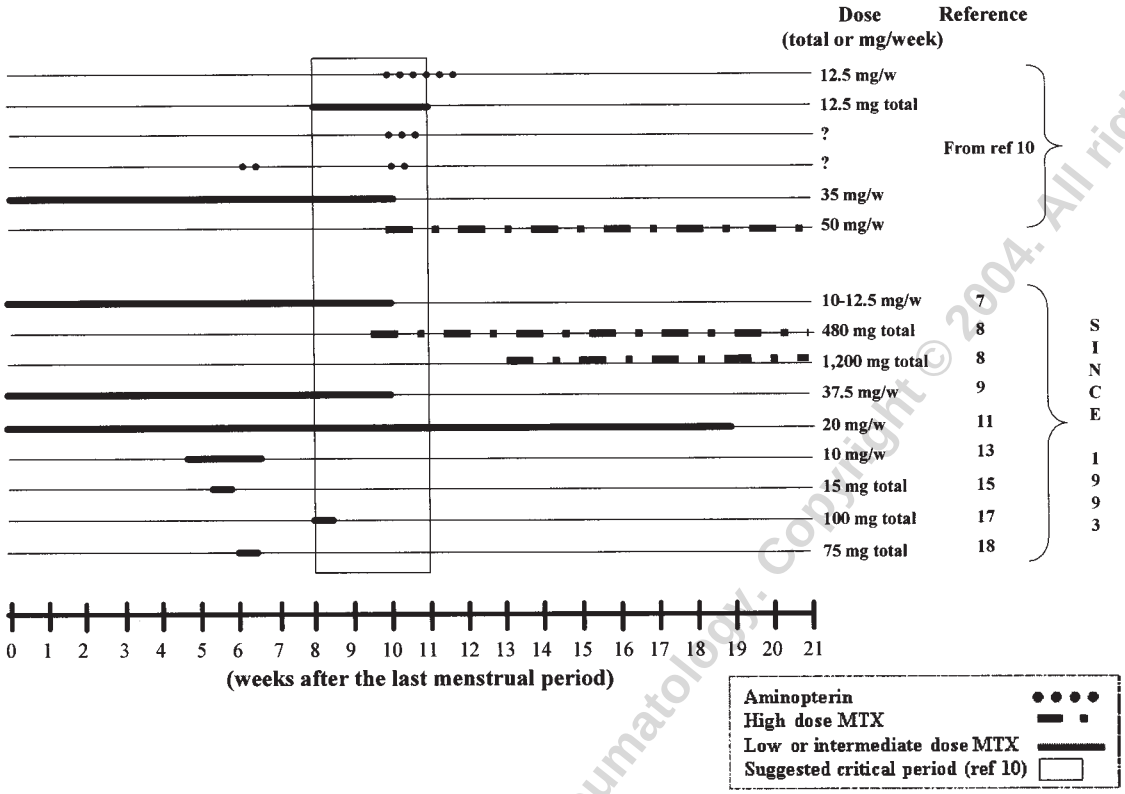

Figure 2. Case reports of aminopterin/MTX syndrome in relation to dose and proposed critical period of exposure (data organized by year of publication).

the 5.4% rate in all singleton births reported in France[33]. Unfortunately, data we collected provided no information on disease activity during pregnancy, but none of our patients had received corticosteroids or NSAID after the first trimester of pregnancy. Although it is usually accepted that rheumatic disease is not associated with premature labor, recent findings indicate an increased rate of preterm birth in these patients[27]. Consequently, a possible role of maternal disease cannot definitely be excluded. Finally, biometric characteristics were in the range of expected values found in the normal newborn population, and only one of our 15 full-term infants weighed less than 2500 g.

Owing to the limited data available, it is still premature to draw a definitive conclusion on the effect of inadvertent exposure to low dose MTX in pregnancy, and counseling patients and physicians remains difficult. Based on our findings and those of other prospective series, and taking account of the limitations of such risk evaluations, we suggest that discontinuation of low dose MTX as early as possible after last missed menses does not appear to strongly increase the teratogenic risk over the background rate and does not require a medical abortion. However, the size of our sample only allows us to rule out a higher than 6-fold increase in the risk of major malformations in patients who discontinued MTX before gestational week 8. In addition, recent isolated reports suggest that the critical period of MTX teratogenicity may begin before gestational week 8. A careful ultrasound examination should therefore be proposed to all patients, whatever the dose or the period of exposure.

The mechanisms of MTX developmental toxicity are unknown, but are presumably related to its antifolic effects. Although there are no clinical data to suggest a beneficial effect of preconception folic acid to prevent the teratogenic risk of MTX, it seems reasonable to advise women of reproductive age to take folinic acid before a planned pregnancy. This recommendation also applies to patients without preconception folinic acid supplementation who have inadvertently continued MTX after the beginning of pregnancy. However, reduction of the incidence of malformed fetuses when folinic acid was injected up to 24 hours after MTX was only seen in rats and rabbits[6]. Even when they are given folate supplementation, women exposed to MTX should have a prenatal diagnostic ultrasound.

Even though our series included a relatively small number of patients and was not controlled for exposure and disease, this is the largest series with prospective assessment of pregnancy outcomes after low dose MTX during the first trimester of pregnancy. Nevertheless, it is important to continue prospective collection of data on pregnant women

inadvertently exposed to MTX, to provide more definitive and hopefully reassuring data for counseling patients who have been exposed during the first stages of pregnancy.

ACKNOWLEDGMENT

We warmly thank the French Pharmacovigilance Network for contributing to this study.

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