Review

Systematic review on the safety of methotrexate in rheumatoid arthritis regarding the reproductive system (fertility, pregnancy, and breastfeeding)

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ABSTRACT

Objective. *To analyze the safety of methotrexate (MTX) in rheumatoid arthritis (RA) regarding the reproductive system (fertility, pregnancy, and breastfeeding).*

Methods. *Systematic review of studies retrieved by a sensitive search strategy in Medline (1961 – October 2007), Embase (1961 – October 2007), Cochrane Library (up to October 2007), and from the abstracts of the ACR (2005, 2006) and EULAR (2005 – 2007) annual scientific meetings. Selection criteria: a) population: studies had to include patients with RA; b) intervention and control: discontinuation of MTX or elective abortion* versus *continuation of MTX or continuing pregnancy; and c) outcomes: infertility, oligospermia, reversibility, miscarriages, malformations, premature babies, healthy newborn, percent of the dose of MTX that passes to human milk, adverse effects in the lactating child. There was no limitation regarding study design, except for case reports, or language.*

Results. MTX and pregnancy: *we selected 6 articles for detailed evaluation from 847 initial ones from the literature search. They were descriptions of cases obtained from searching retrospectively clinical databases of individual centers or from surveys. Patients had been exposed to MTX at doses used in rheumatology (5-25 mg/w), from conception to first trimester of pregnancy. Total number of MTX exposed pregnancies is 101, and the pooled outcomes (elective abortion not included): 19 miscarriages (23% of pregnancies); 55 live births (66% of pregnancies); and 5 of them had minor neonatal malformations (5% of pregnancies). The rate of induced abortions is 18%.* MTX and lactation and fertility: *no articles fulfilled the selection criteria. There is indirect evidence on the excretion of MTX in human milk and probably of reversible infertility from case reports.*

Conclusions. *This review exposes the shortage of data on the safety and risks of MTX during conception, pregnancy and lactation at the doses commonly used in rheumatology. MTX and pregnancy: there is not sufficient evidence to support whether it is MTX or the disease what underlies miscarriage in these patients. Pooling the data from the studies included, the rates of miscarriages and of birth defects are similar to the rates observed in healthy population. MTX and lactation and fertility: there is absence of confirming evidence.*

Introduction

Methotrexate (MTX) is the drug more frequently used by rheumatologists to control rheumatoid arthritis (RA) and other rheumatic diseases. MTX is a folic acid antagonist that impairs dihydrofolate reductase and interferes with the production of purines. In patients receiving MTX for the treatment of RA, the reported terminal half-life ranges about 3 to 10 hours (1). However, MTX is retained for several weeks at the kidneys and for months at the liver (2, 3). Due to its long presence in tissues the manufacturer recommends effective contraception in men and women during treatment and for at least six months thereafter (2). In animal studies (rats, mice and rabbits) MTX has been shown to cause embryotoxicity and teratogenicity (3). In humans, a severe malformation called the "aminopterin syndrome" has been described in outcomes of pregnancies exposed to MTX from four to 12 weeks. This syndrome consists of CNS abnormalities (spina bifida, mental retardation, hydrocephaly, anencephaly); skeletal abnormalities (synostosis of lambdoid sutures,

partial or absent ossification of bones, micrognathia, high or cleft palate, short extremities, wide set eyes, syndactyly of fingers, absent digits, club foot, large fontanelles, wide set nasal bridge); and cardiac abnormalities (dextrocardia) (4). The FDA has classified MTX as an X drug (fetal abnormalities in animal and human studies. The use clearly outweighs any possible benefit). It is contraindicated in women who may become pregnant.

MTX is often started in the early stages of the rheumatic disease, thus meaning that many of the patients are women still in their childbearing years. Women taking MTX for rheumatic diseases may thus be at risk during conception, pregnancy, and breastfeeding. Additionally, men exposed to MTX may also be at risk during conception (MTX affects spermatogenesis and oogenesis (2)), so are their partners if they conceived while their spouses were exposed.

Clinical trials in pregnant or lactating mothers for most drugs are lacking, and MTX is no exception. Most data available comes from animal studies and from case reports of accidental exposure with a negative outcome. Furthermore, MTX is used as abortifacient, although at higher doses than those utilized by rheumatologists (5). All in all, MTX is avoided or contraindicated in most guidelines and recommendations of disease due to abortive and teratogenic effects (6). However, very few rheumatologists would recall having problems related to outcomes of unexpected pregnancy or to male infertility in patients taking MTX. That is why it is so important to review the literature on how MTX should be used in RA when planning pregnancy (male and female patients), during pregnancy and after pregnancy.

Methods

Three systematic reviews were performed, one per question: a) Which are the effects of MTX on pregnancy, and its teratogenic effects? b) Which are the effects of MTX on male and female fertility? and c) Which are the effects of MTX on the newborn, and during lactation? The main reviewer (JAML) and a mentor (LC) established the protocol of the reviews. Further advice was obtained from the complete team of the 3E (Evidence Expertise Exchange) Initiative (7), including the program convenor, other mentors and other reviewers, regarding decisions on the population to be studied, and the type of studies to include.

Search strategy

The studies were identified by search strategies that were specific by question and by database (Appendix 1) in the following bibliographic databases up to October 2007: Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). Additionally, the abstracts of the American College of Rheumatology (ACR) (2005, 2006), and of the European League Against Rheumatism (EULAR) annual scientific meetings (2005, 2006, 2007), and the lists of references of the included studies were screened. The search strategies were based in those from the Cochrane pregnancy and childbirth group plus terms for RA and for methotrexate common to other reviews of the 3E initiative.

Studies selection

The studies retrieved by the above strategies were included if they met the following criteria: 1) Regarding the type of study, we accepted randomized controlled studies, cohort studies, longitudinal observation studies, and surveys; 2) the patients included in the studies had to be older than 18 and to have RA; 3) patients should be using MTX at the doses usually taken in rheumatology (7.5 - 25 mg/w); 4) the study had to give information on the following outcomes for the different questions: a) Male or female fertility; b) Pregnancy complications (effect on the first trimester), malformations, miscarriages, induced abortions, stillbirths; and c) Breast feeding complications, infections, immunosupresion, dose MTX in human milk.

Two reviewers (JAML, EL) screened the titles and abstracts of the retrieved studies for selection criteria independently. If the article did not have an abstract or the abstract suggested that the study might fulfil the selection criteria or was unclear, then a full copy of the article was obtained. The reviewers then screened the complete article for the selection criteria. When a discrepancy occurred, a consensus was reached by looking at the article together or with the mentor.

Data collection and analysis

The two reviewers collected the data from the studies included by using *ad hoc* standard forms. A double entry was carried out independently. One of the reviewers entered the data from the forms into spreadsheets. If, by doing this, the reviewer found any discrepancy between forms, again a consensus was reached by looking at the original article or by asking the mentor.

The information collected included the description of the study design, the sample studied, and the absolute numbers of patients and outcomes. This information permitted the reviewer to classify each study individually into a level of evidence that was used as a surrogate of the quality of the study. The level of evidence was the correspondent from the Oxford Centre for Evidence-based Medicine Levels of Evidence in the May 2001 adaptation (CEBM) (8), which grades the studies on harm as: 1a) Systematic reviews of randomized controlled trials with homogeneity; 1b) Individual randomized controlled trials with narrow confidence intervals; 1c) Trials in which all patients get harm or none does; 2a) Systematic reviews of cohort studies with homogeneity; 2b) Individual cohort study, or low quality randomized controlled trials; 2c) "Outcomes" Research and Ecological studies; 3a) Systematic reviews of case-control studies with homogeneity; 3b) Individual Case-Control study; 4) Case-series and poor quality cohort and case-control studies; and 5) Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles".

Evidence tables were produced in the case there were any studies included and a qualitative analysis carried out. After the first overview, which yielded very few results and of very low quality and high heterogeneity in designs, we did not anticipate any meta-analysis of the data.

Results

MTX and pregnancy

The three bibliographic databases threw 375 records plus 472 abstracts from the search from abstracts to meetings (Fig. 1). We excluded 786 of the 847 hits by reviewing title and abstract (See reasons in the Figure), what excluded all the abstracts from meetings. The remaining 61 articles were reviewed in detail. Of these, we excluded 57 articles, for which the reason of exclusion is detailed in an appendix. The main reasons were that the articles were narrative reviews, guidelines, or case reports. Additionally, we found two articles by hand search that were finally included in the review (9, 10).

Finally, we reviewed six articles in detail whose main characteristics are displayed in Table I. There were no true cohorts, only descriptions of cases obtained from searching retrospectively clinical records of patients followed at individual centers or from surveys. None of the studies reached a quality better than Level 4. The mean age of the included patients ranged from 28 to 35 years, and those whom received MTX did it at doses used commonly in rheumatology (5-25 mg/w). Exposure to MTX occurred from conception to first trimester of pregnancy.

In the study by Østensen (11) cases were collected from a survey to patients (both women and men), and then from a survey to doctors. The first survey was sent to 237 female and 189 male patients with rheumatic diseases, and it was returned by 170 women, 71 of whom had RA, and 77 men, 26 of whom had RA (response rate 35%). Østensen (11) reports 26 pregnancies in women with RA and 28 pregnancies in partners of men with RA. In three of the 26 pregnancies of women with RA there had been exposure to MTX, one of which ended up in a spontaneous abortion and two in which abortion was induced. In three of the 28 pregnancies in partners of patients the men were taking MTX and the outcome was: one induced abortion, one live birth, and a third one unknown. There were neither stillbirths nor birth defects. The survey to doctors was sent to 409 doctors and it was returned by 131 (response rate 32%). They report 19 pregnancies in women (five exposed to MTX) and ten pregnancies in partners of men with RA (eight exposed to MTX). In the female patient group there was one miscarriage and one live birth. The result of the other three pregnancies was unknown. All the partners of men exposed to MTX had live births, but two of these suffered congenital malformations (one with atrophy of one hand and a small fistula beneath the ear, the other with anomalies of the toes).

Kozlowski (12) described ten pregnancies in eight female patients taking MTX. He found no birth defects in five live born children. There were three miscarriages and two induced abortions.

Østensen (13) reviewed four cases of MTX exposure during pregnancy in 2000. She found three live born children without congenital malformations. The fourth pregnancy ended in a miscarriage.

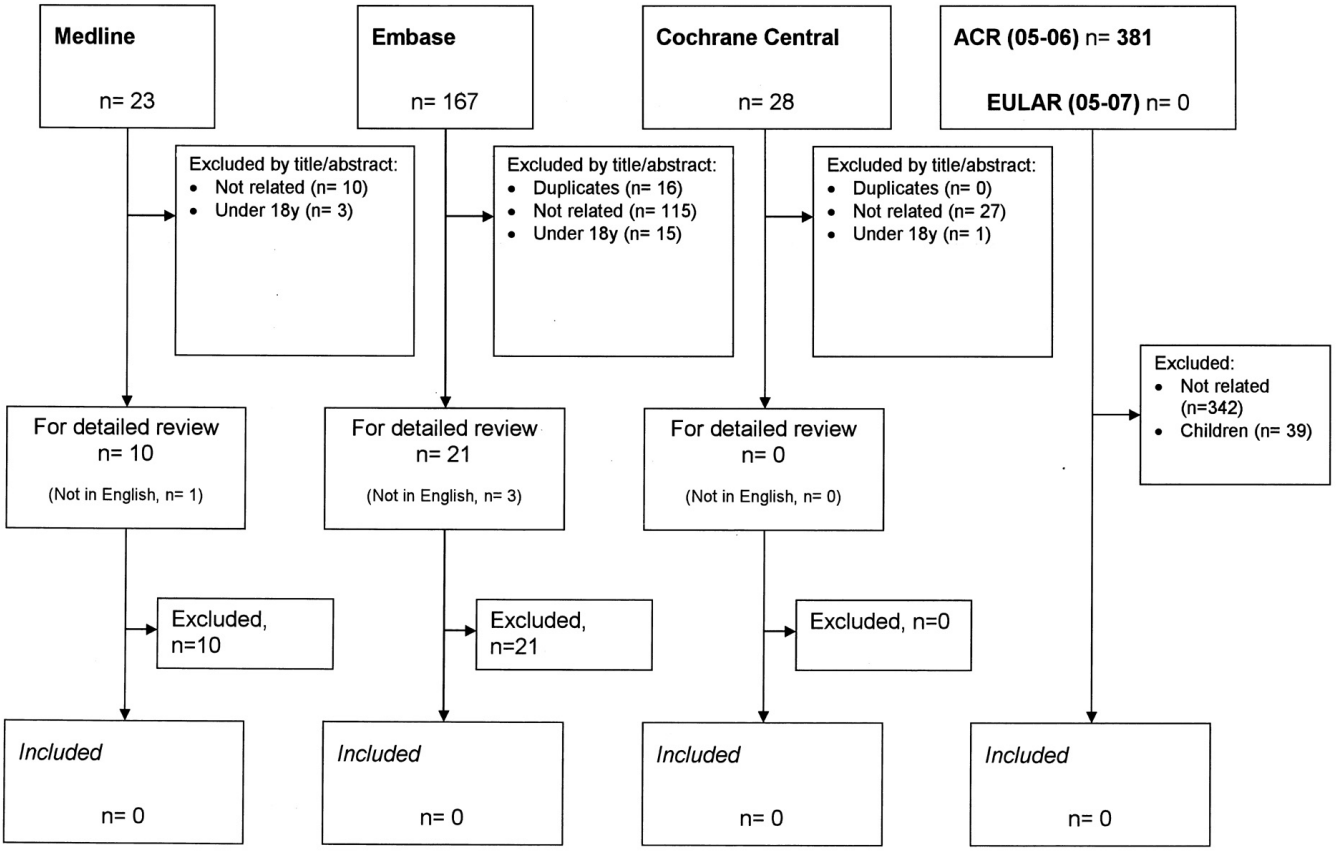

Fig. 1 A. Effects of methotrexate on male or female fertility.

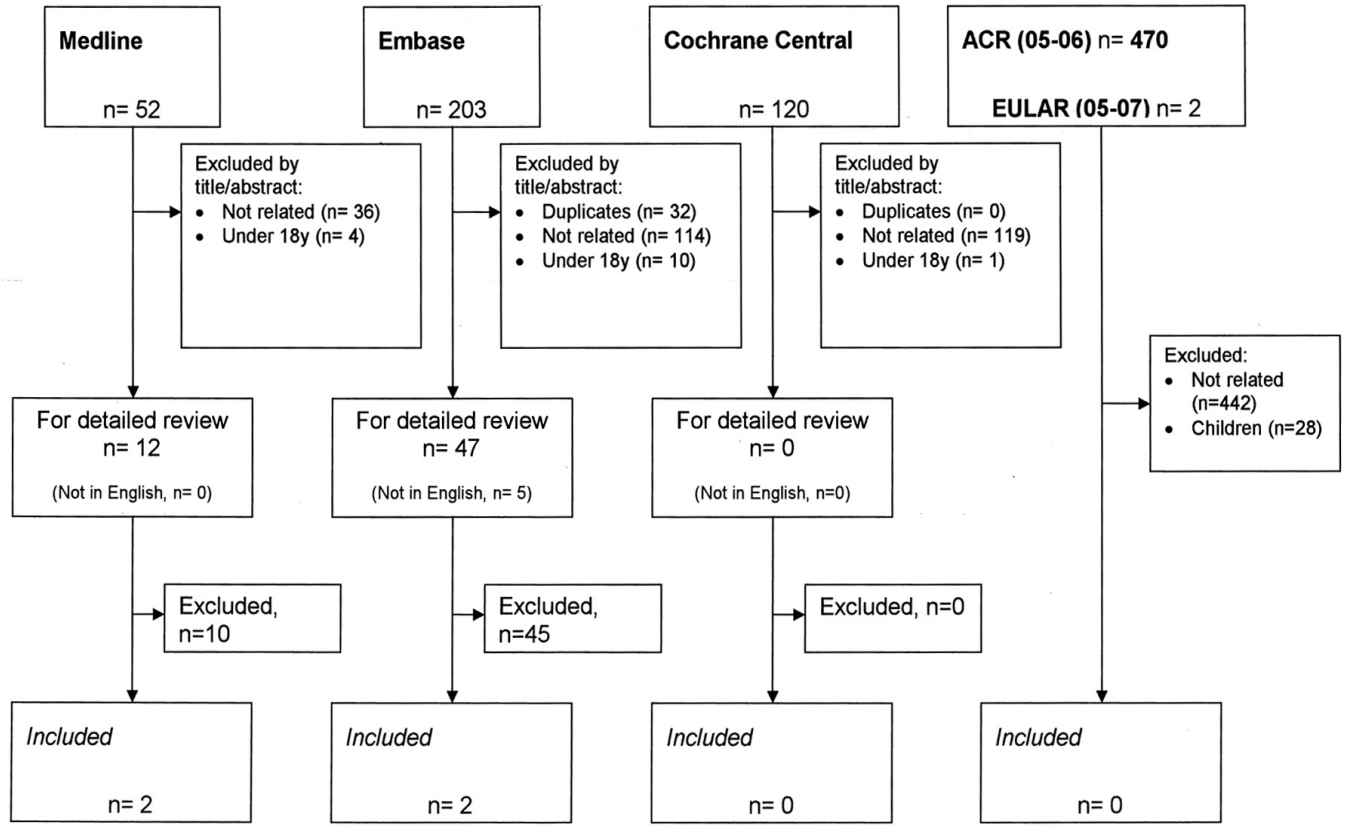

Fig. 1 B. Methotrexate on pregnancy and teratogenic effects.

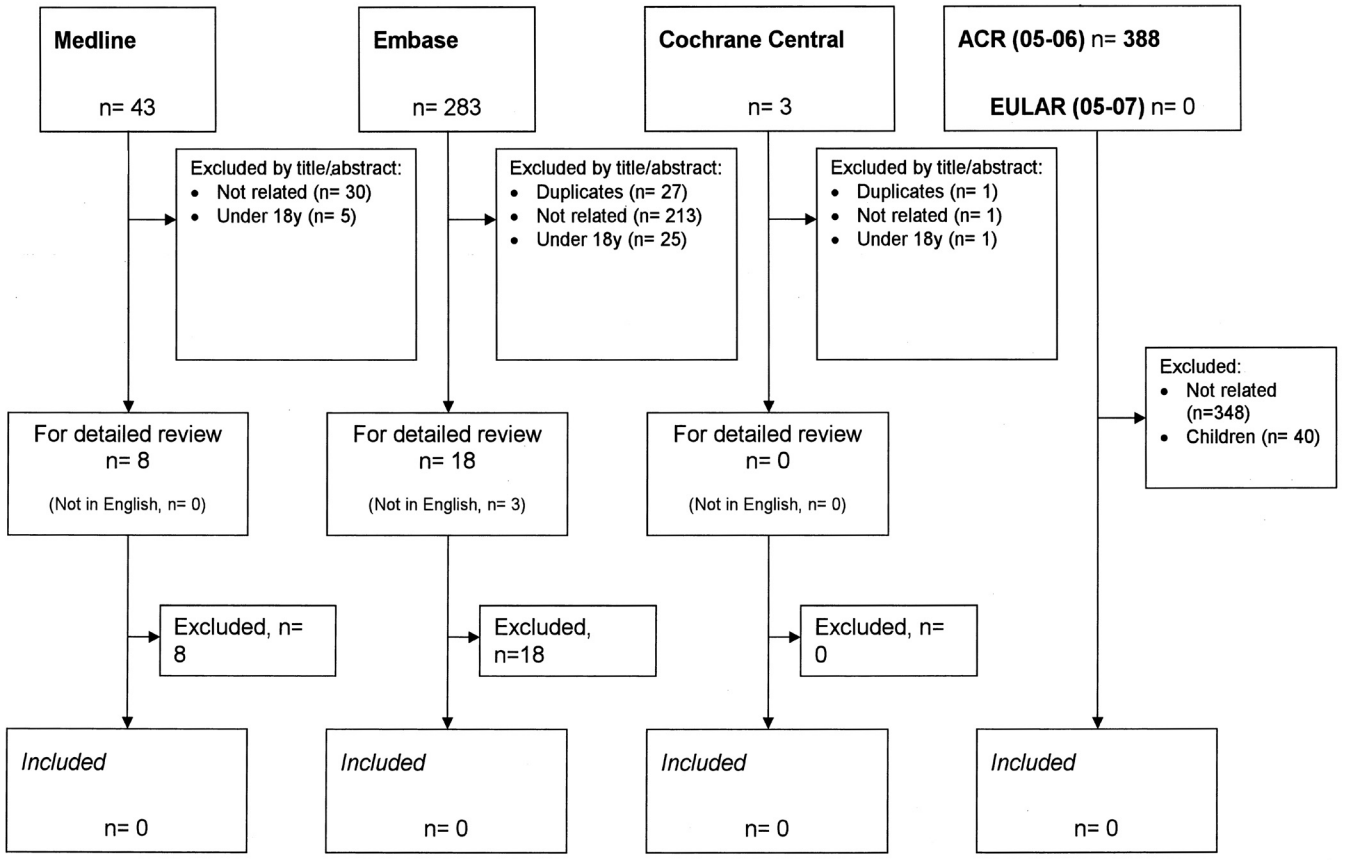

Fig. 1 C. Effects of methotrexate on lactation and newborn.

Lewden (14) described 28 pregnancies while using MTX. He found 19 live newborns, one of whom had minor birth defects, a metatarsus varus and eyelid angioma. There were five elective and four spontaneous abortions (14%).

Chakravarty (9) got the data from a survey to doctors. It was sent to 600 doctors and was answered by 175 of them (response rate 29%). They reported 65 pregnancies in RA patients taking DMARD at conception. There were 39 pregnancies in patients exposed to MTX. He found 21 (54%) live born healthy children. One pregnancy resulted in congenital malformations (bilateral metatarsus varus and right eyelid angioma). Other two children had neonatal pathological conditions (one premature child had hyaline membrane disease and neonatal jaundice; the other had transient respiratory distress and jaundice). There were eight elective and seven spontaneous abortions (18%).

Donnenfeld (10) obtained the information on patients from a survey to Teratology centres. They had registered 14 pregnancies of which seven were in RA patients. Nine of the patients were exposed to MTX one year prior to conception. The other five patients were exposed during pregnancy. There were nine healthy newborns (64%). One pregnancy resulted in a baby with cavernous hemangioma. There were four miscarriages.

The total number of MTX exposed pregnancies in these studies is 101 (Table II), and the pooled outcomes:

Table I. Included studies for methotrexate on pregnancy and teratogenic effects.

Study	Participants	Intervention	Outcomes measured	Quality
Chakravarty (9) USA Survey to doctors	n=65 100% women with RA Exposed at conception	MTX 7.5-15 mg/w	• Abortion • Stillbirth • Live birth • Birth defects	4
Donnenfeld (10) USA Survey to teratology centres	n=14 Mean age 30.2; 50% women with RA, any duration	MTX 7.5-12.5 mg/w	• Abortion • Stillbirth • Live birth • Birth defects	4
Østensen (11) Switzerland Survey to patients	n=247 Mean age 35; 68.8% women with any rheumatic disease, any duration	MTX 7.5-25 mg/w (27.6 % female; 59.6% male)	• Abortion • Stillbirth • Live birth • Birth defects	4
Kozlowski (12) USA Exposed case series	n=8 Mean age 28.4; 100% women (6 RA) Pregnancy while using of MTX	MTX 7.5-10 mg/w	• Abortion • Stillbirth • Live birth • Birth defects	4
Østensen (13) Norway Exposed case series	n=4 Mean age 29; 100% women with RA Pregnancy while using of MTX	MTX 5-15 mg/w	• Abortion • Stillbirth • Live birth • Birth defects	4
Lewden (14) France Exposed case series	n=28 Mean age 32.9; 100% women with any rheumatic diseases Pregnancy while using of MTX	Mean dose MTX 10.5 mg/w	• Abortion • Stillbirth • Live birth • Birth defects	4

Table II. Summary of results from the studies on pregnancy outcome. Only the data referring to rheumatoid arthritis patients are displayed.

Outcomes	Chakravarty 2003	Donnenfeld 1994	Kozlowski 1990	Lewden 2004	Ostensen 2000	Ostensen 2007	
Exposed prior to conception	–	9	–	–	4	–	
Exposed during pregnancy	39	5	8	28	4	3F	M
Weeks of exposure (range)*	1.5 – 15	3 – 5	0 – 15	0 – 9‡	3 – 6	–	–
Pregnancies	39	14	10	28	4	3F	3M
Induced abortions, n (%)	8 (21)	0	2 (20)	5 (18)	0	2 (67)	1 (33)
Miscarriages, n (%†)	7 (23)	3 (21)	3 (38)	4 (17)	1 (25)	1 (100)	0
Live births, n (%†)	23 (74)	4 (29)	5 (63)	19 (83)	3 (75)	0	1 (100)
Congenital malformations, n (%†)	3 (10)	0	0	1 (4)	0	0	0

F: female patient exposed; M: male patient exposed.
*Only in patients exposed during pregnancy, not prior to pregnancy.
†Percentage of outcome from all pregnancies except those in which abortion was induced electively.
‡One patient was exposed from week 6 to week 11.

19 miscarriages (19% of all pregnancies; 23% of pregnancies in which abortion was not induced); 55 live births (54% of all pregnancies; 66% of pregnancies in which abortion was not induced); and only five of them had neonatal malformations (4% of all pregnancies; 5% of pregnancies in which abortion was not induced), none of which were the described aminopterin syndrome. The rate of induced abortions is 18%.

MTX and lactation

We found 717 studies in the different databases. There were 28 duplicates and 663 were excluded by title or abstract (see Figure 1c). We reviewed 26 studies in detail. No study fulfilled the selection criteria. We only discovered a case report truly referred to lactation (15).

MTX and male fertitility

We obtained 599 studies from Medline, Embase, Cochrane Central, and abstracts from the ACR (2005-2006) y EULAR (2005-2007). After we eliminated the duplicates, we retained 583 studies. We excluded 552 studies by title or abstract (see 1a). We reviewed 31 studies in detail. All of them were excluded because they did not meet the inclusion criteria.

Discussion

This review exposes the shortage of data on the safety and risks of MTX during conception, pregnancy and lactation at the doses commonly used in rheumatology. We found only six articles, five surveys to patients or doctors and a case series. We found also many reports on individual patients that were excluded because of publication bias. Most data on the use of MTX during pregnancy come from patients treated for cancer with multiple therapies or from the use of MTX as an abortifacient. In these cases, the doses of MTX exceed the low weekly dose we use in rheumatology.

Rheumatology guidelines do not recommend the use of MTX during pregnancy (6). They do recommend contraception, but once the patient has conceived, guidelines do not specifically recommend elective abortion. However, besides discontinuing MTX, elective abortion is common, as we have seen in the review (18%). We do not know which could have been the outcome of these pregnancies.

However, there is not sufficient evidence to support whether it is MTX, or the disease, or just chance, what underlies miscarriage in women accidentally exposed to low-dose MTX during pregnancy. In the general population, it has been shown that about 12 to 15 percent of pregnancies end-up in a miscarriage some time before 20 weeks (16). In our review, the percentage of miscarriages obtained from pooling all the studies together is 23%, discarding induced abortions. Not a very different result or just slightly higher. Also, it has been studied that with each pregnancy, all women have a 3% to 5% chance of having a baby with a birth defect (17, 18). Pooling the data from the studies included, again subtracting the induced abortions, the prevalence of birth defects in our review was 5%, and none of the congenital abnormalities were related to the aminopterin syndrome previously described.

It can be argued that there were not many miscarriages or malformations because MTX was stopped early after awareness of the pregnancy. Only in two studies there is enough information on individual patients regarding the length of exposure and the specific outcome (10, 14). No clear trend is seen in these studies; basically the mean of weeks of exposure is the same for pregnancies that ended in miscarriage and in live birth. Moreover, a patient – whose data is not included in the table as she had no rheumatic disease – was exposed as much as 38 weeks to MTX in doses high enough to treat an intraductal breast cancer (10). This patient delivered a healthy 3.350 g newborn after 41 weeks of pregnancy. In the rest of the studies, data is presented aggregated and it is not possible to assess whether the weeks of exposure have any association with outcome.

We only discovered a case report referred to lactation in a patient exposed to MTX (15). The excretion of methotrexate into breast milk was studied in a 25 year old woman, one month post partum, under treatment for choriocarcinoma at a dosage of 22.5 mg per day. MTX was detectable in milk and serum 2 hours after oral administration. The peak milk level of MTX reached a maximum after 10 hours, at a concentration that was less than 10% of that in plasma. This dose, which would be equivalent to the full dose of MTX in an adult, could be avoided if breastfeeding is precluded in that period of time after dosage to the lactating mother.

Regarding the effect of MTX on male fertility, we found two good narrative reviews (3, 19) although they were not included in the systematic review given the design. One limitation to several of the studies reviewed in both articles – in which MTX was used in other indications and doses – is the concurrent administration of other chemotherapeutic agents. When MTX is used alone studies suggest no increased infertility. In Lloyd's (3) review the risk of infertility appears low even after high-dose MTX treatment (up to 400mg) for osteosarcoma.

This review exposes the shortage of data about the risk of using low dose weekly MTX during conception, pregnancy and lactation. On light of the low level of evidence available, rheumatologists should dissuade patients exposed to MTX from continuing MTX in case pregnancy is desired. If a patient becomes pregnant while exposed to MTX it is not clear that induced abortion is a better choice than following the pregnancy closely. MTX is excreted into breast milk, although at low concentrations.

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