

## EDITORIAL

## Methotrexate in pregnancy: still many unanswered questions

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Methotrexate (MTX) is a folate antagonist with known teratogenicity including abortifacient effects that interfere with DNA synthesis. We want to discuss on which findings teratogenicity is based and which open questions still exist. In this context, we introduce a recent Italian study by Zanetti *et al*<sup>1</sup> on pregnancy outcomes after therapeutic use of MTX in women with rheumatoid arthritis (RA).

MTX is on the WHO list of essential medicines. In addition to the approved indications for the drug treatment of malignancies and inflammatory disorders, it is used for the non-surgical treatment of ectopic pregnancy and elective termination of pregnancy (TOP). The dose differs according to indication and also plays a role in teratology. Paracelsus already pointed to the fact that the ‘dose makes the poison’.

**FINDINGS TERATOGENICITY OF MTX IS BASED ON**

As often, teratogenicity in humans was discovered by case reports describing a similar phenotype of malformations (MTX embryopathy), at first after failed TOP. Already in the 50th, the teratogenic effects of aminopterin,<sup>2</sup> a structurally similar but more potent folate antagonist was described. In 1968, the first case of an infant with MTX-induced congenital malformations after failed attempted TOP was published.<sup>3</sup> Since then, multiple similar case reports have been reported,<sup>4</sup> also after misdiagnosed ectopic pregnancies.<sup>5</sup> The guideline dosage for the indication of ectopic pregnancy is a single intramuscular administration of 50 mg/m<sup>2</sup>.

**UNANSWERED QUESTIONS**

Even though the teratogenicity of MTX is indisputable, not every malformation in an infant after intrauterine exposure is attributable to the drug. The following considerations should be taken into account:

- ▶ **Background risk:** One should consider the 3%–5% major malformation baseline risk. Birth defects may represent the baseline risk rather than result from MTX, especially true for relatively common malformations such as septal defects.<sup>6</sup>
- ▶ **Genetic aetiology:** If an infant has combinations of malformations similar to those of MTX embryopathy, it is important to consider genetic causes. This was not possible in the past. Martin *et al*,<sup>7</sup> for example, thought their small study was unique as it described ‘for the first time a prospectively ascertained case of MTX embryopathy in a woman exposed to a typical low dose of 7.5 mg/week for rheumatoid arthritis’. However, no genetic test for mutations causing *FGFR* (fibroblast growth factor receptor) craniosynostosis syndromes was carried out; they may resemble MTX embryopathy.
- ▶ **Exposure time:** The information that an exposure occurred during the first trimester, the time of organogenesis, is insufficient to assume causality as the development of the different organs follows a determined schedule. Neural tube defects (NTDs), for example, appear early in embryogenesis. Hyoun *et al*<sup>8</sup> discuss a report on failed TOP with aminopterin. The fetus had an NTD with meningomyelocele.<sup>9</sup> However, exposure took place 3 weeks after neural tube closure had been completed. Causality thus seems unlikely in this case.
- ▶ **Concomitant drugs:** In order to terminate a pregnancy, MTX is often combined with the teratogen misoprostol.<sup>10–15</sup> If pregnancy continues and results in a malformed infant, the malformation may be caused by MTX, misoprostol or both.

In summary, MTX is not the cause for all malformations in offspring with intrauterine MTX exposure. Thus, not every malformation associated with intrauterine MTX exposure expands the phenotype of the MTX

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embryopathy, which, unfortunately, is neither well understood nor adequately described. However, at least craniosynostosis, limb deficiencies and cardiovascular defects seem to be part of the embryopathy.<sup>4,8,16</sup>

### LOW-DOSE MTX

It is of special clinical interest to know if a typical rheumatic weekly low-dose of MTX leads to an MTX embryopathy. No characteristic MTX embryopathy was observed in the case series,<sup>17,18</sup> in a prospective study from France with 28<sup>19</sup> and in a multicentre prospective cohort study with 324 treated patients.<sup>20</sup> In this study, 188 pregnancies were MTX-exposed post conception and 136 preconception. In the preconception cohort, the risk of neither major malformations nor spontaneous abortions was increased. However, in the postconception cohort, the rate of overall major malformations was 6.6%. This was significantly higher compared with the non-autoimmune disease cohort but not with the disease-matched comparison group. The risk of spontaneous abortion was also significantly increased in the postconception group (42.5%), suggesting that low-dose MTX may also be an abortifacient.

The overall rather low malformation risk is good news for women who unintentionally conceive during low-dose MTX treatment. However, there are some main shortcomings: The high proportion of TOPs might have falsely mitigated the magnitude of teratogenic effects. In addition, the median duration of MTX administration was 4.3 weeks after the last menstrual period (LMP) (IQR 3–6). This does not cover the entire first trimester. However, 27 of 188 were still taking their medication between weeks 8 and 10 (after LMP). This number is not high enough to rule out an MTX embryopathy after low dose. The median weekly dose was 10 mg (IQR 8.8–15.0). Would the results be different with a higher median dosage and longer exposure duration?

### ITALIAN STUDY ON LOW-DOSE MTX AND PREGNANCY

In view of these questions and uncertainties, it is to be welcomed that the Italian Society of Rheumatology published a retrospective cohort study evaluating the impact of low-dose MTX in patients with RA on pregnancy outcomes, namely, the risks of spontaneous abortion and elective TOP, the rate of congenital anomalies and the probability of becoming pregnant.<sup>1</sup> The study was performed using administrative healthcare data of the Record Linkage of Rheumatic Disease. Antirheumatic comedication was included, and the study provides a lot of thorough statistical testing and sensitivity analyses. Of note, there was no pregnancy with MTX exposure during pregnancy. In the vast majority, MTX was discontinued even earlier than 3 months before conception. This may indicate that education about the potential risks of MTX therapy is very effective in Lombardy, Italy.

Of 3564 women with RA in the MTX cohort, 223 conceived. This is a significantly lower percentage (6.3%)

compared with the RA-without-MTX cohort (9.1%) and with the no-RA cohort (11.9%). However, as it is unknown how many women tried to conceive, this finding is difficult to interpret.

The recommendation is to withdraw MTX treatment 1–3 months before conception.<sup>21,22</sup> At least in the past, women often chose TOP when low-dose MTX was discontinued within this preconception time window. The study could confirm a significant positive relationship between the exposure to MTX in the 3 months' window before conception and an increased risk of TOP (OR 4.77, 95% CI 1.08 to 19.40).

There were few infants with congenital abnormalities. The rate was under 1% in all three groups, a rate which is below the background risk, suggesting underascertainment.

The risk of spontaneous abortion was not increased when MTX was discontinued in the preconception period of 3 months. However, there was a statistically significantly increased risk when MTX treatment was halted at any time before conception and there was some dose relationship. This means that, in the majority of cases, MTX treatment was stopped long prior to pregnancy. There is no biologically plausible explanation yet on how MTX could cause this. The authors rightly discuss this result as probably not related to the past drug exposure but to a supposedly higher disease activity and other unmeasured factors. More research is necessary to prove or refute the higher risk of miscarriage after an MTX therapy discontinued long before pregnancy and to include further variables such as disease activity.

### PROSPECTS

It will be difficult to close the information gaps in the future because, fortunately, not many women unintentionally conceive while taking MTX. Before prescribing low-dose MTX to women with RA in their reproductive age, the physician should address the issue of pregnancy and contraception. In this context, it is important to know that about 40% of pregnancies are unintended worldwide.<sup>23</sup> If MTX was discontinued within the 3 months preconception, the risks of adverse pregnancy outcomes do not seem to be increased.<sup>24</sup> Therefore, preconception counselling should not advise or encourage TOP due to prepregnancy MTX.

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