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ORIGINAL RESEARCH

Impact of rheumatoid arthritis and methotrexate on pregnancy outcomes: retrospective cohort study of the Italian Society for Rheumatology

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ABSTRACT

Objective To evaluate the impact of rheumatoid arthritis (RA) and methotrexate (MTX) on the probability of becoming pregnant, pregnancy losses, elective termination of pregnancy (TOP) and congenital malformations.

Methods A retrospective cohort study on administrative healthcare databases was conducted. Three patients' cohorts were enrolled among childbearing-age women. The first cohort included patients with RA starting MTX between July 2004 and December 2011. The second cohort included patients with RA without MTX treatment randomly selected from the same population (ratio 1:1). Finally, a cohort of subjects without RA was identified (ratio 1:4). Multivariate logistic regression models were implemented, ORs and 95% CI were reported.

Results The two matched RA cohorts included 3564 patients with MTX and without MTX. The cohort without RA included 14 256 subjects. In the three cohorts, the proportion of women achieving pregnancy during follow-up was 6.3%, 9.1% and 11.9%, respectively. Congenital malformations were very rare in all cohorts. RA women treated with MTX at any time before conception showed significantly higher risks of pregnancy losses than non-RA women (OR (95% CI) 2.22 (1.40 to 3.45)). We observed a significant positive relationship between the exposure to MTX in the 3 months window before conception and increased risk of elective TOP (OR (95% CI) 4.77 (1.08 to 19.40)).

Conclusion MTX-treated patients appeared to be the cohort with the highest risk of pregnancy losses. The positive association with elective TOP and exposure to MTX in the three months window before conception in patients with RA reinforces the need for adequate preconception counselling to avoid unplanned pregnancies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The current guidelines recommend avoiding exposure to methotrexate (MTX) in pregnancy because high doses of MTX are teratogenic in humans.

WHAT THIS STUDY ADDS

⇒ Patients with rheumatoid arthritis (RA) treated with MTX at any time before conception have significantly higher risks of pregnancy losses than non-RA women.

⇒ Taking MTX in the 3 months window before conception is significantly associated with elective termination of pregnancy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Adequate preconception counselling may be particularly important for patients with RA to avoid unplanned pregnancies.

⇒ MTX exposure should always be monitored in patients with RA of childbearing age.

BACKGROUND

Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disease globally characterised by an age-standardised prevalence rate higher in females and with a high number of incident cases in women in childbearing years.[1] The optimal management of RA requires prompt treatment and methotrexate (MTX) represents the anchor drug to start as soon as the diagnosis is defined.[2] If short-term use and past MTX use do not appear to reduce fertility in patients with RA, women in her fertile age should be counselled for using concomitant contraception during MTX treatment.[3 4] In fact, there is absolute contraindication to MTX use during pregnancy for the risk of spontaneous abortion and embryotoxicity.[5] The current guidelines strongly recommend avoiding exposure to MTX at any dose in pregnancy, and discontinuing the medication 1–3 months before attempting conception because high doses of MTX are teratogenic in humans.[6 7] The MTX embryopathy shows a typical embryofetopathy characterised by craniofacial dysmorphism, limb reduction defects, syndactyly and cardiopulmonary anomalies (tetralogy

of Fallot, pulmonary valve atresia).[8] Few data are available in the case of accidental pregnancy on low-dose MTX. One systematic literature review, one population-based study and one prospective multicentre cohort study reported an increased risk of major birth defects and spontaneous abortion with postconception MTX exposure at weekly dosages typically used in the treatment of rheumatic diseases.[9–11] Overall, the studies have considered varied rheumatic diseases including connective tissue diseases and inflammatory arthritis, conditions that have a different impact on pregnancy outcomes. Regarding elective termination of pregnancy (TOP), Weber-Schoendorfer *et al* reported increased rates in both preconception and postconception MTX-exposed cohorts, but these data were not confirmed in a nested case–control study using administrative databases that observed that women with RA exposed to MTX had a lower rate of TOP compared with unexposed women.[11 12] Based on the existing literature, the purposes of this study were to evaluate the impact of MTX exposure on (1) the probability of becoming pregnant, (2) the risk of pregnancy losses and elective TOP, (3) the risk of congenital anomalies occurring at birth. Another aim of the study was to evaluate the effect of the cumulative MTX dose on pregnancy losses. The analysis was performed on a large population-based sample of women exclusively diagnosed with RA by using an Italian administrative health database (AHD).

PATIENTS AND METHODS

Study design and setting

This is a retrospective cohort study performed using data of the Record Linkage of Rheumatic Disease (RECORD) study (promoted by the Italian Society for Rheumatology), an observational study aimed to measure the impact of RA at population level, using AHD information.[13 14] The data sources for the RECORD study were the AHD of Lombardy, an Italian region with more than 10 000 000 inhabitants (about 16% of the Italian population). The entire Italian population is covered by the National Health Service (NHS), and in Lombardy, an automated system of AHD has been created to collect a variety of information. The system of AHD included: (1) an archive of residents who receive NHS assistance (with demographic data); (2) an archive of all hospital discharge forms (HDFs) including information on diagnoses and procedures coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Disease-Related Group; (3) a database providing information on outpatient NHS-refundable drug delivery, coded according to the Anatomical Therapeutic Chemical (ATC) classification system; (4) an archive containing all the certifications of chronic diseases for the exemption from copayment and (5) an archive of outpatient services (eg, diagnostic test, consultations). Subject-specific data contained in these databases are linked using a single anonymised identification code.[14] The ICD-9-CM and the ATC used in this study are reported in online supplemental material.

Participants

The target population in RECORD study included all Lombardy residents, aged 18 years and older, who were beneficiaries of the NHS between 2004 and 2013. For this study, we included only women of childbearing potential with age between 18 and 50 years.

We enrolled three cohorts of patients: two cohorts included patients with RA (with or without MTX treatment) identified through a validated algorithm developed in the RECORD study, and one included subjects recorded in the RECORD study without RA.[14] This approach was performed to try to disentangle the effect of MTX exposure from the effect of RA disease.

Patients with RA, starting with MTX treatment from July 2004 to December 2011, were eligible to be included in the first cohort. Prevalent MTX users were identified as patients with MTX prescription in the wash-out period January–June 2004 and they were excluded. The cohort entry date was defined as the first MTX prescription date. Each patient was followed from cohort entry date to 31 December 2013. The enrolment until December 2011 ensured at least 2 years of follow-up.

The second cohort of patients included subjects diagnosed with RA and without MTX prescription in the entire period. In this cohort, the prescription of other conventional synthetic DMARDs including leflunomide, cyclosporine A, hydroxychloroquine, sulfasalazine and azathioprine was analysed. To define a cohort entry date in these patients, we randomly matched them to the first cohort of patients, with a 1:1 ratio, ensuring the same follow-up time in the two cohorts.

The third cohort included subjects without a diagnosis of RA and without treatment with MTX in the entire period, matched by age, with a 4:1 ratio, with patients in the first cohort. Therefore, all the patients of the second and third cohort were matched to the patients of the first cohort and, each of them, entered the cohort (cohort entry date) at the entry date of matched RA woman treated with MTX. Accordingly, the three cohorts had the same period to reach a pregnancy; this allowed us to compare the probability of getting pregnant in the different cohorts. To assess the impact of MTX on pregnancy outcomes, only patients who became pregnant during follow-up were examined. The study design is shown in figure 1.

Outcome

Data on pregnancy and the complications, during follow-up, were recovered from HDF applying a validated algorithm to identify pregnant women, pregnancy outcomes and estimated gestational age.[15] Only the first pregnancy after the entry date was considered in the analysis. In detail, we evaluated the number of women with a pregnancy, and among them, we considered the following as outcomes: pregnancy losses, which includes

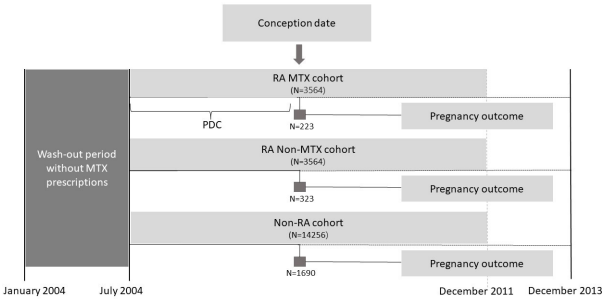

Figure 1 Study design. A total of 223 patients in the RA MTX cohort, 323 in the RA non-MTX cohort and 1690 in the non-RA cohort achieve pregnancy during the follow-up period. The proportion of days covered by MTX treatment was calculated by dividing the milligrams of active substance purchased by the subject by the defined daily dose (DDD) and then by the follow-up period before pregnancy. MTX, methotrexate; RA, rheumatoid arthritis; PDC, proportion of days covered.

early and late spontaneous abortions as well as stillbirths (occurring after 28 weeks of gestation[16]), elective TOP. Of note, only pregnancy losses requiring a hospital stay are included. Data on congenital malformations were only assessed in live births according to ICD9-CM codes listed in online supplemental material and reported in the mother HDF.

Exposure and covariates

Belonging to one of the three cohorts in analysis was considered as the main exposure. Therefore, having at least one prescription of MTX before pregnancy in patients with RA or having RA without a prescription of MTX or not having RA are the three exposure levels of interest.

To characterise the clinical profile of patients, in addition to age, health data from AHD relating to the period between 6 months before cohort entry date and 6 months after cohort entry date were considered. Concomitant comorbidities including diabetes, hypertension, thyroid diseases and chronic kidney failure were coded according to prespecified algorithms.[13 17] The concomitant use of glucocorticoids (ever use during the 6 months before and after estimated entry date) was used as a proxy of disease activity.

Statistical methods

Continuous variables were reported as mean (±SD) or as median (IQR) for non-normally distributed data. Categorical variables were reported as absolute and relative frequencies. To test the difference in the proportion of women with a pregnancy during follow-up among the three cohorts, a χ^2 test was performed.

Multivariate logistic regression models were applied, only in women with a pregnancy, separately for each outcome, including patients' cohort (RA with MTX, RA without MTX and no RA) as exposure variable and covariates (such as age, comorbidities and concomitant glucocorticoids treatment) as adjustment variables. To verify the robustness of the results of the main analysis, we also performed multivariate robust Poisson regression models with the same structure of the previous models.

Four sensitivity analyses were implemented: (1) the presence of cotreatments (with sulfasalazine or leflunomide), (2) the presence of oral contraceptive treatments, (3) the duration of MTX treatment before pregnancy and (4) whether the patient was taking MTX at conception.

For the first sensitivity analysis, all the patients with a prescription of drugs cited above in the period between 6 months before entry date and 1 year after entry date were excluded. The main analysis was repeated on this patients subset.

For the second sensitivity analysis, all the patients with a prescription of oral contraceptive treatments from entry date to the end of follow-up were excluded and the main analysis were repeated on the new sample of subjects.

The third sensitivity analysis included the patients treated with MTX (women with pregnancy belonging to the first cohort). For each patient, all prescriptions of MTX in the period between cohort entry date and 3 months before conception date were extracted from the database providing information on outpatient NHS-refundable drug deliver. We adopted this strategy because current recommendations suggest stopping MTX treatment at least 3 months before conception.[6 7] To quantify the amount of MTX, we calculated the number of days covered by each MTX prescription. We multiplied the number of milligrams of active substance contained in each drug box by the amount of drug boxes that were purchased by the subject. Finally, this quantity was divided by the defined daily dose and then by the follow-up before pregnancy (proportion of days covered). Multivariate logistic regression models of main analysis, one for each outcome, were performed substituting the patients' cohort with the proportion of days covered as exposure variable.

In the fourth sensitivity analysis, we included only the cohort of patients treated with MTX and we implemented the same models of the third sensitivity analysis. We added a dichotomous covariate that showed whether the woman was covered by MTX at the presumed date of conception (more specifically, in a period between 3 months before conception and the date of conception). We also added the interaction between this variable and the variable created for the third sensitivity analysis and related to the proportion of days covered by MTX treatment during the follow-up.

All hypothesis tests were two-sided and p values for statistical significance were set at 0.05. All the analyses were performed using R statistical software V.3.6 version (Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The two matched RA cohorts included 3564 patients with MTX and without MTX, while the cohort without RA included 14256 subjects. The three cohorts had a

Table 1 Demographic and clinical characteristics of the three cohorts at baseline and during follow-up

Baseline variables	RA with MTX (N=3564)	RA without MTX (N=3564)	No RA (N=14 256)
Age, mean (SD)	40 (7.2)	41.6 (7.5)	40 (7.2)
Age, median (IQR)	41 (35–46)	44 (37–48)	41 (35–46)
Diabetes, n (%)	64 (1.8)	53 (1.5)	24 (0.2)
Hypertension, n (%)	54 (1.5)	53 (1.5)	74 (0.5)
Thyroid diseases, n (%)	57 (1.6)	39 (1.1)	107 (0.8)
Chronic kidney failure, n (%)	5 (0.1)	4 (0.1)	0 (0)
Glucocorticoids, n (%)	1846 (51.8)	481 (13.5)	0 (0)
During follow-up			
Women with pregnancy, n (%)	223 (6.3)	323 (9.1)	1690 (11.9)

MTX, methotrexate; RA, rheumatoid arthritis.

similar average age at the entry date, but the two cohorts of patients with RA showed a higher number of comorbidities (table 1). 51.8% of patients in MTX cohort were treated with glucocorticoids while the percentage decreased to 13.5% for RA non-MTX cohort. No one in the group without RA took glucocorticoids. In the 2 years after the entry date, in the RA non-MTX cohort, 17% of women received antimalarials, 2% sulfasalazine, 1.5% leflunomide and 3% ciclosporin A or azathioprine. The MTX cohort had a median (IQR) duration of MTX exposure of 299 (88–813) days. 11.9% of women without RA achieved pregnancy during follow-up, 9.1% in the non-MTX group, and 6.3% in women taking MTX (p<0.001 both comparing non-RA patients with RA with/without MTX groups) (table 1).

Considering only pregnant women in all cohorts, we confirmed a similar mean age, and we observed a low frequency of comorbidities in all three cohorts. Patients with RA without MTX treatment during pregnancy predominantly took 8% antimalarials, 2% sulfasalazine, 1% other immunosuppressants, 12% glucocorticoids, in the 3% of the cases the patients were exposed to antimalarials and glucocorticoid in combination. Instead, patients with RA treated with MTX predominantly took 19% antimalarials, 3.5% sulfasalazine, 3% other immunosuppressants, 28% glucocorticoids, of these, 11% took glucocorticoids and antimalarials in combination. The risk of pregnancy losses among pregnant women was higher in RA women treated with MTX (22%) than RA women without MTX treatment (14.9%) and women without RA (14%). In the three cohorts, 43% of pregnancy losses occurred in the first 12 weeks of pregnancy and 0.3% occurred after the 28th week. The distribution of pregnancy losses was different between the three cohorts. No pregnancy losses were observed before gestational week 8 in the MTX cohort compared with the RA cohort without MTX and to the cohort without RA; in these last two cohorts, we recorded pregnancy losses from gestational week 5. The gestational week distribution of pregnancy losses is reported in online supplemental material. An extremely low number of congenital malformations was observed in each of the three groups (table 2).

Multivariate logistic regression models showed a significant relationship between MTX at any time before conception and pregnancy losses (OR (95% CI) 2.22 (1.40 to 3.45)) (table 3). The previous results were confirmed by multivariate robust Poisson regression models with an IRR of 1.91 (95% CI 1.25 to 2.76) for pregnancy losses. Table 3 displays the results of the first and second sensitivity analyses. When considering only women without treatment with sulfasalazine or leflunomide, we deleted 52 women (33 in RA women treated with MTX and 19 in RA women without MTX). Findings were consistent with those performed on the entire sample. Also excluding women with oral contraceptive treatments during follow-up (34 in RA women treated with MTX, 35 in RA women without MTX treatment and 191 in women without RA) the main results did not change significantly.

The percentage of days covered by MTX treatment was calculated on the RA cohort treated with MTX. On average, one woman in this cohort was exposed to MTX for 32% (SD=31) of the days between her entry date and 3 months before conception. Greater coverage was associated with an increased risk of pregnancy loss. By increasing the percentage of days covered by treatment by 10%, the probability of having pregnancy losses increased by 4% (OR (95% CI) 1.04 (0.95 to 1.14), p=0.391).

The fourth sensitivity analysis (performed on RA women treated with MTX) showed that the exposure to MTX treatment in the period close to the conception date was associated with a four-fold increased risk of elective TOP (OR (95% CI) 4.77 (1.08 to 19.40) (table 4). The analysis included only 17 patients treated with MTX in the trimester before conception.

DISCUSSION

Our study based on AHD data observed a significant reduction in the probability of becoming pregnant among women affected by RA, compared with the

Table 2 Demographic and clinical characteristics of pregnant women of the three cohorts at baseline and during follow-up

Baseline variables	RA with MTX (N=223)	RA without MTX (N=323)	No RA (N=1690)
Age, mean (SD)	30.5 (4.5)	31.9 (5.0)	32.2 (5.1)
Age, median (IQR)	31 (27–34)	32 (28–36)	32 (29–36)
Diabetes, n (%)	1 (0.4)	4 (1.2)	6 (0.4)
Hypertension, n (%)	0 (0.0)	2 (0.6)	2 (0.1)
Thyroid diseases, n (%)	0 (0.0)	4 (1.3)	9 (0.5)
Chronic kidney failure, n (%)	1 (0.4)	0 (0.0)	0 (0.0)
Glucocorticoids, n (%)	111 (49.8)	32 (9.9)	0 (0.0)
During follow-up			
Abortion, n (%)	70 (31.4)	81 (25.1)	392 (23.2)
Pregnancy losses, n (%)	49 (22.0)	48 (14.9)	237 (14.0)
Of which after the 28th week, n (%)	0 (0)	0 (0)	1 (0.4)
Elective termination of pregnancy, n (%)	21 (9.4)	33 (10.2)	155 (9.2)
Live born children, n (%)	153 (68.6)	242 (74.9)	1298 (76.8)
Of which with congenital abnormalities, n (%)	1 (0.7)	0 (0.0)	4 (0.3)

MTX, methotrexate; RA, rheumatoid arthritis.

general population. These data are even more significant comparing patients with RA treated with MTX to RA women not treated with MTX. Reasons for reduced fertility in RA are complex and multifactorial. Prolonged time to pregnancy, concerns about the well-being of pregnancy and disability contributed to a decrease in the number of pregnancies conceived in women with RA.[18] Regarding the potential effect of exposure to immunosuppressants, recently a systematic literature review evaluated the impact of conventional synthetic DMARDs, including MTX, on fertility in RA.[4] The authors concluded, based on retrieved evidence, that MTX use did not negatively affect fertility, contrary to what is traditionally believed.[4 18–21] An explanation for the lower pregnancy rate observed in our cohort of patients with RA treated with MTX could be sought by additional risk factors such as higher disease activity. This is evidenced not only by exposure to MTX, which by itself may express

Table 3 Adjusted ORs and relative 95% CIs of cohort effect on pregnancy outcomes

	Abortion	Pregnancy losses	Elective termination of pregnancy
Cohort	OR (95% CI)	OR (95% CI)	OR (95% CI)
Main analysis			
Women without RA (reference)—N=1690	1	1	1
RA women treated with MTX—N=223	1.76 (1.17 to 2.60) **	2.22 (1.40 to 3.45) ***	0.97 (0.50 to 1.76)
RA women not treated with MTX— N=323	1.13 (0.84 to 1.49)	1.11 (0.78 to 1.56)	1.10 (0.72 to 1.63)
First sensitivity analysis			
Women without RA (reference)—N=1690	1	1	1
RA women treated with MTX—N=190	1.56 (1.01 to 2.38) *	1.98 (1.20 to 3.18) **	0.91 (0.44 to 1.72)
RA women not treated with MTX—N=304	1.17 (0.87 to 1.56)	1.13 (0.78 to 1.59)	1.17 (0.77 to 1.74)
Second sensitivity analysis			
Women without RA (reference)—N=1499	1	1	1
RA women treated with MTX—N=189	1.97 (1.27 to 3.01) **	2.37 (1.45 to 3.82) ***	1.08 (0.52 to 2.07)
RA women not treated with MTX—N=288	1.08 (0.79 to 1.47)	0.89 (0.59 to 1.30)	1.36 (0.88 to 2.04)

Adjustment for age, diabetes, hypertension, thyroid diseases, chronic kidney failure and glucocorticoids use.
Main analysis, first sensitivity analysis (excluding patients with cotreatment with sulfasalazine or leflunomide) and second sensitivity analysis (excluding patients treated with oral contraceptive).
*p<0.05, **p<0.01, ***p<0.001.
MTX, methotrexate; RA, rheumatoid arthritis.

Table 4 Fourth sensitivity analysis: adjusted ORs and relative 95% CI of the proportion of days covered by MTX treatment and the presence of MTX treatment in the 3 months window before conception

	Abortion	Pregnancy losses	Elective termination of pregnancy
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Proportion of days covered (increase of 10%)	1.02 (0.92 to 1.13)	1.06 (0.95 to 1.19)	0.92 (0.76 to 1.08)
Taking MTX at conception	2.12 (0.72 to 6.31)	0.99 (0.24 to 2.83)	4.77 (1.08 to 19.40)*

Adjustment for age, diabetes, hypertension, thyroid diseases, chronic kidney failure and glucocorticoids prescription.
*p<0.05.
MTX, methotrexate.

a more severe disease, but also by the higher percentage of glucocorticoid prescription in this cohort (51.8% in RA with MTX vs 13.5% in RA without MTX). In addition, in our cohort of RA women treated with MTX, we recorded a greater prevalence of comorbidity that could further affect fertility. Certainly, the influence of the guidelines and recommendations, that properly discourage pregnancy when starting MTX, deserves consideration since it could further drive fertility rates down. It is indisputable that reproductive sphere is a complex area that involves the patients' concerns about the health of offspring and parenting capability.[22] In this perspective, an analysis based on the AHDs, cannot adequately answer this question since valuable information, such as the adoption of safe contraceptive measures or knowing how many women had a desire to have children, is lacking.

In terms of pregnancy outcome, we found a positive association between MTX exposure at any time before conception and the risk of pregnancy losses (two times higher risk). It should be emphasised that only pregnancy losses requiring hospitalisation were included in our analyses. After excluding women treated with other conventional synthetic DMARDs to limit distortions related to the use of different or combinations of immunosuppressants, our findings were still consistent with the main analysis. In addition, because RA women receiving MTX could be more likely to use oral contraceptives than unexposed women, we performed a second sensitivity analysis excluding women exposed to oral contraceptive treatments during follow-up, the results confirmed again the positive association between MTX exposure and pregnancy losses of the primary analysis. In addition, looking at the third sensitivity analysis performed only on RA women treated with MTX, we observed that increasing the percentage of days covered by treatment by 10%, slightly increased the probability of having pregnancy losses, even if not statistically significant. Our unusual observation is not entirely new in the literature. In 2015, a nationwide prospective cohort study analysed the association between spontaneous abortion (before gestational week 16) and serologic findings, disease activity and periconceptional use of antirheumatic drugs. At univariate analysis, among other variables of interest, spontaneous abortion tended to be more often observed in women that received MTX therapy in the past. Nevertheless, due to the low frequency of spontaneous abortion in this study (28 events observed), the association with past MTX use did not reach statistical significance at multivariate analysis (OR 2.52, 95% CI 0.86 to 7.36).[23] In contrast, in a prospective multicentre cohort study that evaluated the risk of spontaneous abortion and elective TOP in women treated with MTX during pregnancy or within 12 weeks before conception (preconception cohort), the HR for preconception exposure was 0.8 (95% CI 0.4 to 1.4) relative to the disease-matched cohort and 1.3 (95% CI 0.6 to 3.0) relative to the cohort of women without autoimmune diseases.[11] There are different potential reasons for our finding; the most likely explanation is that the woman with more severe arthritis is treated and therefore longer exposed to MTX, meaning that the relative increased risk of pregnancy losses observed in our work expresses a more active disease. Furthermore, we were unable to correct all clinical variables or all possible confounding factors, and some residual potential confounding intrinsic to observational studies may still modify the risk of pregnancy loss estimation in our cohort.

In our study, the exposure to MTX in the trimester before conception significantly increased the risk of elective TOP. Our result confirmed a previous observation by Weber-Schoendorfer *et al*, that estimated increased rates of elective TOP both in the MTX exposed postconception cohort (adjusted HR 7.4, 95% CI 4.5 to 12.2) and in the preconception cohort (adjusted HR 2.4, 95% CI 1.1 to 5.6) compared with the non-autoimmune disease cohort suggesting an inappropriately high rate of unplanned pregnancies in women exposed to MTX.[11]

Regarding congenital malformations, we have registered only five cases combining all three cohorts. Although there was not a single pregnancy with MTX exposure during the first trimester or after the presumed day of conception, the rate observed was far below the background rate. It should be noted that, in the RECORD AHD used for our analysis, congenital malformations were only assessed in live births, and this is a relevant limitation that could affect our results because we do not have these data for stillbirths and electively TOP. Concerning this, a recent work based on three AHDs (Population Data BC, PharmaNet and BC Perinatal Database Registry) indicated that MTX exposure during the first trimester was associated with elevated odds for

congenital anomalies (adjusted OR 6.58, 95% CI 1.15 to 37.75).[9]

A strength of our study consisted of the generalisability of results linked to our use of an AHD which guaranteed us to analyse (1) an unselected population; (2) of adequate size and with complete data and (3) three distinct cohorts (exposed RA women, matched non-exposed RA women, women without RA) to disentangle the effect of the disease from the treatment.

We acknowledge that our study has several limitations that are intrinsic to the administrative data. In general, most of the spontaneous abortions occur early in pregnancy and uncomplicated pregnancy losses that occurred before 15 weeks did not require hospitalisation and may not even be recognised in AHDs.[24 25] In this respect, almost 57% of the pregnancy losses of this study occurred after the first trimester. As previously mentioned, the lack of data related to disease activity state could inflict the interpretation of the results. In fact, analysing the treatments dispensed in the two cohorts, an imbalance in glucocorticoid use was observed in the MTX cohort compared with RA not treated with MTX, in which the percentage of exposure was equal to 28% and 12%, respectively. Apparently, our data suggested that the disease was less active and/or that pregnancy planning was adopted in RA not treated with MTX, both conditions that can favourably influence the outcome and, in part, the differences observed in our study between the two RA cohorts. Strikingly, most patients with RA were not taking DMARDs or glucocorticoids during pregnancy, a result partially confirmed by a retrospective cohort study using healthcare utilisation data in which approximately 24% of women with RA received a synthetic DMARD and one third were exposed to steroids in the 180 days before conception.[26]

Our approach based on AHD did not provide additional variables including lifestyle (maternal socioeconomic status, smoking, alcohol, weight or body mass index), results of laboratory examinations as well as data about the newborn (birth weight, length and head circumference, neonatal adverse events). We did not include non-steroidal anti-inflammatory drugs (NSAIDs) as a predictor of pregnancy losses in our multivariate models. As previously observed, NSAIDs exposure could be difficult to estimate because may be used without prescription and, usually, as needed.[12] A study using AHD did not find any difference in concomitant NSAID use between MTX users and non-users.[12 27] Finally, the first pregnancy during the period of data captured is not necessarily the first-ever pregnancy because enrolment periods in health insurance do not cover the entire individual woman's reproductive history. In summary, women with RA exposed to MTX at any time before conception appeared to have a higher risk of pregnancy losses than non-RA women. Exposure to MTX in the 3 months window before conception was significantly associated with elective TOP.

These aspects confirm and reinforce the need for adequate preconception counselling to avoid unplanned pregnancies. The preliminary data on the role of cumulative dose of MTX on the risk of pregnancy losses warrant further research.

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Patient consent for publication Not applicable.

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