Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register

Suzanne M M Verstappen, Yvonne King, Kath D Watson, Deborah P M Symmons, Kimme L Hyrich; BSRBR Control Centre Consortium, BSR Biologics Register

ABSTRACT

Objective  The British Society for Rheumatology Biologics Register (BSRBR) has collected data on adverse events including pregnancies in patients with rheumatoid arthritis treated with anti-tumour necrosis factor (anti-TNF) therapy. The purpose of this report is to summarise the pregnancy outcomes in women treated with anti-TNF in the BSRBR.

Methods  Patients were categorised according to anti-TNF exposure as follows: (1) exposure to anti-TNF and to methotrexate (MTX) and/or leflunomide (LEF) at conception (n=21 pregnancies); (2) exposure to anti-TNF at conception (n=50); (3) exposure to anti-TNF prior to conception (n=59); (4) no exposure to anti-TNF (control group; n=10).

Results  Eighty-eight live births in a total of 130 pregnancies were reported in patients who received anti-TNF before or during pregnancy. The rate of spontaneous abortion was highest among patients exposed to anti-TNF at the time of conception (with MTX/LEF 33% and without MTX/LEF 24%). This compared with 17% spontaneous abortions in those with prior exposure to anti-TNF and 10% spontaneous abortions in the control group. Ten terminations were performed.

Conclusion  Although the results to date have been promising, no firm conclusions can be drawn about the safety of anti-TNF during pregnancy and, without further evidence, guidelines which suggest these drugs should be avoided at the time of conception cannot yet be changed.

INTRODUCTION

Anti-tumour necrosis factor (anti-TNF) therapies have been available for the management of arthritis-related diseases for over a decade. The US FDA categorises anti-TNF agents as category ‘B’ drugs because animal reproduction studies have failed to demonstrate a risk to the fetus but adequate and well-controlled studies of pregnant women have not been conducted.1

To date, information on pregnancies in patients exposed to anti-TNF agents has been reassuring, with few reports of adverse pregnancy outcomes. One exception has been the report by Carter et al2 which listed 61 congenital anomalies reported to the FDA in 41 women exposed to anti-TNF agents including one child with the VACTERL syndrome (a syndrome seen in embryos and fuses characterised by abnormalities of the vertebrae (V), anus (A), cardiovascular tree (C), trachea (T), oesophagus (E), renal system (R) and limb buds (L)). However, this study lacked a denominator of exposure.

National registries such as the British Society for Rheumatology Biologics Register (BSRBR), which collects data on adverse events and pregnancy outcomes in patients treated with anti-TNF therapy, provide a more realistic representation of the effect of anti-TNF therapy on pregnancy outcome. Using data from the BSRBR, we previously reported on 32 pregnancies with known outcome in women exposed to anti-TNF agents.3 Since this publication, the number of pregnancies reported to the BSRBR has increased to 130 and the outcome of these pregnancies is reviewed in this paper.

METHODS

Study design and patient population

The patients for this study were participants registered in the BSRBR starting treatment with one of the three available anti-TNF therapies (adalimumab (ADA), etanercept (ETA) and infliximab (INF)). In addition to the anti-TNF cohort, a parallel cohort of patients with active rheumatoid arthritis (RA) receiving non-biological disease-modifying antirheumatic drugs (nb-DMARD) has been recruited (guide disease activity score in 28 joints (DAS28) >4.2).

Data collection

Follow-up information is collected from medical records every 6 months for the first 5 years and annually thereafter. Data at follow-up include any changes to anti-tumour necrosis factor, reasons for changes, and the onset of any adverse event including pregnancies. In addition, for the first 5 years of the study, patients are asked directly if they have received new treatments and about new referrals to (hospital) doctors. Data on pregnancies and pregnancy outcomes are also extracted from these patient reports.

All reports of pregnancies are followed up with an additional questionnaire which includes information on exposure to biological agents at the time of conception, details of pregnancy outcome including live births, spontaneous abortions and terminations. Details of pregnancy complications are collected as well as any details of congenital malformations. For the purpose of this analysis, pregnancies were divided into three groups: group I (exposure to anti-TNF at conception); group II (past exposure to anti-TNF); group III (never exposed to anti-TNF). Given the known risk of adverse pregnancy outcomes associated with the DMARDs methotrexate (MTX) and leflunomide (LEF), group I was further categorised into (a) those exposed to MTX and/or LEF at conception and (b) those not exposed.
exposed to MTX and/or LEF at conception. Women could have been included more than once in the analysis if more than one pregnancy had been recorded during the follow-up time and each pregnancy was allocated to the appropriate exposure group. For descriptive data, the denominator represents the number of pregnancies per group, and, therefore, the sum of the percentages presented within each group can be more than 100%.

RESULTS

Study population

A total of 130 pregnancies in 118 women ever exposed to anti-TNF agents and 10 pregnancies in 10 women never exposed to anti-TNF agents were reported. At registration, baseline DAS28 and Health Assessment Questionnaire (HAQ) scores were significantly higher in the anti-TNF therapy groups than in the nb-DMARD group (table 1). For both baseline DAS28 and HAQ score, a significant difference was observed between groups Ia and Ib. Patients in group Ia also had a higher HAQ score compared with patients in group II.

Pregnancy outcomes

Eighty-eight live births in a total of 130 pregnancies (including three pregnancies with twin gestation) in patients exposed to anti-TNF therapy were reported: 42/71 (59%) in group I and

Table 1 Overview of pregnancy outcomes in the BSRBR

<table>
<thead>
<tr>
<th></th>
<th>Group la: anti-TNF therapy + MTX or LEF at time of conception</th>
<th>Group lb: anti-TNF therapy but no MTX or LEF at time of conception</th>
<th>Group I: anti-TNF therapy prior to conception</th>
<th>Group III: never exposed to anti-TNF therapy</th>
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<tbody>
<tr>
<td>Number of women with pregnancy</td>
<td>20</td>
<td>44</td>
<td>54</td>
<td>10</td>
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<tr>
<td>Number of pregnancies</td>
<td>21</td>
<td>50</td>
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<td>10</td>
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<td>Single births</td>
<td>21</td>
<td>49</td>
<td>58</td>
<td>9</td>
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<tr>
<td>Twins</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Age, mean (SD)</td>
<td>29.7 (8.1)</td>
<td>34.4 (5.2)</td>
<td>32.6 (4.9)</td>
<td>32.5 (5.2)</td>
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<tr>
<td>Baseline DAS28 score, n/N*</td>
<td>20/20</td>
<td>40/44</td>
<td>52/54</td>
<td>10/10</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>6.5 (0.6)</td>
<td>6.1 (1.2)</td>
<td>6.0 (1.0)</td>
<td>5.1 (1.2)</td>
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<td>Baseline HAQ score, n/N†</td>
<td>20/20</td>
<td>41/44</td>
<td>49/54</td>
<td>8/10</td>
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<tr>
<td>Mean (SD)</td>
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<td>1.9 (0.5)</td>
<td>1.8 (0.6)</td>
<td>1.0 (0.4)</td>
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<td>RA</td>
<td>16</td>
<td>36</td>
<td>46</td>
<td>10</td>
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<td>PsA</td>
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<tr>
<td>AS</td>
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<td>SLE</td>
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<td>Anti-TNF therapy at conception</td>
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<td>Infliximab</td>
<td>5</td>
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<td>Etanercept</td>
<td>12</td>
<td>36</td>
<td>–</td>
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<tr>
<td>Adalimumab</td>
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<td>10</td>
<td>–</td>
<td>–</td>
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<td>Anti-TNF therapy prior to conception</td>
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<td>Infliximab (INF)</td>
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<td>Adalimumab (ADA)</td>
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<td>&gt;1 anti-TNF agent</td>
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<td>Conventional DMARD use at conception</td>
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<td>Methotrexate (MTX)</td>
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<td>Leflunomide (LEF)</td>
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<td>Sulfasalazine (SSZ)</td>
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<td>Hydroxychloroquine (HCQ)</td>
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<td>IM-gold (iAU)</td>
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<td>0</td>
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<td>Combination of DMARDs</td>
<td>13</td>
<td>2</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Steroid use at conception</td>
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<tr>
<td>Live birth</td>
<td>10 (48%)</td>
<td>32 (64%)</td>
<td>46 (78%)†</td>
<td>10 (100%)§</td>
</tr>
<tr>
<td>Termination</td>
<td>4 (19%)</td>
<td>4 (8%)†</td>
<td>2 (3%)</td>
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<tr>
<td>Spontaneous abortion</td>
<td>7 (33%)</td>
<td>12 (24%)</td>
<td>10 (17%)</td>
<td>1 (10%)</td>
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<tr>
<td>Neonatal death</td>
<td>0</td>
<td>1 (2%)</td>
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<td>0</td>
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<tr>
<td>Intrauterine death</td>
<td>0</td>
<td>2 (4%)†</td>
<td>2 (3%)†</td>
<td>0</td>
</tr>
<tr>
<td>Premature delivery (≤36 weeks)</td>
<td>3</td>
<td>8</td>
<td>2</td>
<td>2</td>
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</table>

* DAS28 score significantly higher in the anti-TNF groups compared with the nb-DMARD group. DAS28 significantly higher in group Ia compared with group II (p=0.0213, unpaired t test).
**Since the number of outcomes is divided by the number of pregnancies, the total sum of percentages can be more than 100%.
†HAQ score significantly higher in the anti-TNF groups compared with the nb-DMARD group. HAQ score significantly higher in group Ia compared with group II (p<0.001).
¶Including one of twins.
§Including twins.
††One because of Down’s syndrome.

DAS28, disease activity score in 28 joints; HAQ, Health Assessment Questionnaire; n/N, number of patients with available data/number of women with pregnancy; RA = rheumatoid arthritis; PsA = psoriatic arthritis; JIA = juvenile idiopathic arthritis; AS = ankylosing spondylitis; SLE = Systemic Lupus Erythematosus.
46/59 (78%) in group II; 10/10 (100%) live births were reported in the nb-DMARD group. In two of the three twin pregnancies (one in group I and one in group II), one of the fetuses died in utero and one was delivered at/near term (table 1). The rate of spontaneous abortion was highest among patients exposed to anti-TNF at the time of conception (group I): overall 19/71 (27%); with MTX/LEF 7/21 (33%); without MTX/LEF 12/50 (24%). This compared with 10/59 spontaneous abortions (17% of pregnancies) in those with prior exposure to anti-TNF agents (group II) and 1/10 spontaneous abortion (10% of pregnancies) of those never exposed to anti-TNF (group III). In total there were 10 terminations (4 in group Ia, 4 in group Ib and 2 in group II). Of the 42 live births or 22 spontaneous abortions/intrauterine or neonatal deaths in women who were receiving anti-TNF therapy at the time of conception (group I), 33/42 (79%) and 18/22 (82%), respectively, discontinued anti-TNF therapy during the first trimester, 5/42 (12%) and 0 (0%) during the second trimester and 4/42 (9%) and 1/22 (5%) received anti-TNF therapy throughout their pregnancy. No data on anti-TNF exposure during pregnancy was available for 0 and 3 pregnancies, respectively. In those patients with prior exposure to anti-TNF, the length of time since the last dose of anti-TNF therapy did not differ between those with a live birth and those who miscarried (median 7.1 months (IQR 4.4–13.2) vs median 5.7 months (IQR 0.1–10.4); p=0.275).

Pregnancy complications

Of 88 live births in the anti-TNF groups, 19 babies (22%) were born prematurely (11/42 (26%) in group I and 8/46 (17%) in group II) compared with 2/10 (20%) in the nb-DMARD group. One full-term baby had a low birth weight. Four fetuses died in utero (two in group Ib and two in group II), including two single fetuses in two twin pregnancies. One neonatal death 24 h after delivery was reported in a patient who received ETA during the first trimester. The cause of death was perinatal hypoxia. There were four reports of congenital malformations, two in group Ib (congenital dislocation of the hip and pyloric stenosis) and two in group II (winking jaw syndrome and strawberry birth mark).

DISCUSSION

Our study presents the results of the largest detailed prospective collection of pregnancy outcomes in women with arthritis-related diseases exposed to anti-TNF therapy. In our study population a potential signal of an increased spontaneous abortion rate was observed in women exposed to anti-TNF therapies at conception, although this was most evident in those also receiving MTX or LEF (53%). Two general population-based studies found a clinical spontaneous abortion rate of around 12%, although the actual rate may be higher (~25%) if clinically undetectable pregnancies are also included.8

To put these results into context with the evidence currently available, it is important to compare our findings with those published in previous reports (see table in online supplement).7–15 Of the known outcomes in pregnancies in cohort studies including any patients exposed to anti-TNF agents before or during pregnancy, the spontaneous abortion rate ranged from 0% to 14%. In one study, including data from a survey of US rheumatologists,8 one spontaneous abortion occurred in a patient using ETA in combination with MTX at the time of conception. Across all studies, 31 terminations were reported.7–9 12 14 15 One pregnancy was terminated because of concomitant MTX use at the time of conception.7 Eleven babies were born with complications or neonatal illnesses.9 10 14 15 Data from OTIS, published only in abstract form, show that the spontaneous abortion rate was 7.4% in patients exposed to ADA during the first trimester and 6.1% in the RA comparison group. These percentages are lower than we found in our study population, but no information regarding DMARD intake at conception and general disease activity was provided for the OTIS population.16

Both MTX and LEF are ‘X’ category drugs. There is a recognised association between high-dose MTX and spontaneous abortion. A recent systematic review found that 25% of pregnancies exposed to high-dose MTX and spontaneous abortion. A recent systematic review found that 25% of pregnancies exposed to high-dose MTX and spontaneous abortion was associated with an increased risk of spontaneous abortion, but the role of disease severity is not known whether they were informed about the detrimental effects of these drugs, although we do know that a few patients became pregnant while using oral contraceptives which suggests that these were unplanned pregnancies. However, it cannot be concluded that the concurrent use of MTX and/or LEF is the only explanation for this increased rate of spontaneous abortion, as the rate of spontaneous abortion in women exposed to anti-TNF therapy at conception were also higher than in those previously or never exposed to anti-TNF agents. There are data to suggest that women with severe RA may have an unfavourable pregnancy outcome, and those patients unable to discontinue anti-TNF therapies may be those with the most severe disease.18 19 We did not collect data on disease activity at time of conception. It is thus important to weigh the impact of disease severity on pregnancy outcome and the results found in our study with regard to the somewhat increased risk of spontaneous abortions in patients receiving anti-TNF agents at conception. Despite the exposure of anti-TNF therapy at conception, few patients opted for termination. Compared with the termination rate of 12.9% in women aged 30–34 years in the general population of England and Wales (ie, the percentage of pregnancies resulting in one or more live births or a stillbirth or legal abortion that were terminated by abortion),20 the termination rate was higher in those exposed to clinical anti-TNF therapy plus MTX or LEF at conception (19%) but lower in those exposed to anti-TNF agents alone (8%).

Data on drug safety during pregnancy are largely restricted to the cumulative experience of patients and physicians and often limited to case reports. One of the biggest challenges in obtaining safety data is ensuring that outcomes in all exposed patients are recorded, not just those with particularly good or bad outcomes. The BSRBR, through the systematic follow-up of patients, has captured all pregnancy outcomes as they have occurred since the study started in 2001, including information on terminations, spontaneous abortions as well as pregnancy complications. This may also in part explain the higher rate of spontaneous abortion observed in this study compared with previous reports. We were also able to compare the pregnancy outcomes of patients exposed to anti-TNF therapy before or at conception with a control group of patients with RA who were never exposed to anti-TNF therapy. However, the number of recorded pregnancies in this control group was small.

CONCLUSION

The results of this current study, one of the largest detailed prospective studies to date, suggest that treatment with anti-TNF therapy at the time of conception may be associated with an increased risk of spontaneous abortion, but the role of disease severity is not known whether they were informed about the detrimental effects of these drugs, although we do know that a few patients became pregnant while using oral contraceptives which suggests that these were unplanned pregnancies. However, it cannot be concluded that the concurrent use of MTX and/or LEF is the only explanation for this increased rate of spontaneous abortion, as the rate of spontaneous abortion in women exposed to anti-TNF therapy at conception were also higher than in those previously or never exposed to anti-TNF agents. There are data to suggest that women with severe RA may have an unfavourable pregnancy outcome, and those patients unable to discontinue anti-TNF therapies may be those with the most severe disease.18 19 We did not collect data on disease activity at time of conception. It is thus important to weigh the impact of disease severity on pregnancy outcome and the results found in our study with regard to the somewhat increased risk of spontaneous abortions in patients receiving anti-TNF agents at conception. Despite the exposure of anti-TNF therapy at conception, few patients opted for termination. Compared with the termination rate of 12.9% in women aged 30–34 years in the general population of England and Wales (ie, the percentage of pregnancies resulting in one or more live births or a stillbirth or legal abortion that were terminated by abortion),20 the termination rate was higher in those exposed to clinical anti-TNF therapy plus MTX or LEF at conception (19%) but lower in those exposed to anti-TNF agents alone (8%).

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A safety assessment of tumor necrosis factor antagonists during pregnancy and, without further evidence, guidelines which suggest these drugs should be avoided at the time of conception must remain.

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Competing interests Members of the Manchester team, BSR trustees, committee members and staff complete an annual declaration in relation to conflicts of interest. The authors declare no other conflict of interest.

Patient consent Obtained.

Ethics approval The study received ethical approval from the UK North West Research Ethics Committee (MREC 00/8/53).

Provenance and peer review Not commissioned; externally peer reviewed.

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