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 fetuses 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.
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>Diagnosis</th>
<th>Group Ia: anti-TNF therapy + MTX or LEF at time of conception</th>
<th>Group Ib: anti-TNF therapy but no MTX or LEF at time of conception</th>
<th>Group II: anti-TNF therapy prior to conception</th>
<th>Group III: never exposed to anti-TNF therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of women with pregnancy</td>
<td>20</td>
<td>44</td>
<td>54</td>
<td>10</td>
</tr>
<tr>
<td>Number of pregnancies</td>
<td>21</td>
<td>50</td>
<td>59</td>
<td>10</td>
</tr>
<tr>
<td>Single births</td>
<td>21</td>
<td>49</td>
<td>58</td>
<td>9</td>
</tr>
<tr>
<td>Twins</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>Baseline HAQ score, n/N†</td>
<td>20/20</td>
<td>41/44</td>
<td>49/54</td>
<td>8/10</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.2 (0.4)</td>
<td>1.9 (0.5)</td>
<td>1.8 (0.6)</td>
<td>1.0 (0.4)</td>
</tr>
<tr>
<td>Anti-TNF therapy at conception</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>5</td>
<td>4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Etanercept</td>
<td>12</td>
<td>36</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>4</td>
<td>10</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Anti-TNF therapy prior to conception</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab (INF)</td>
<td>4</td>
<td>2</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Etanercept (ETA)</td>
<td>1</td>
<td>1</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Adalimumab (ADA)</td>
<td>1</td>
<td>0</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>&gt;1 anti-TNF agent</td>
<td>1</td>
<td>2</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Conventional DMARD use at conception</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate (MTX)</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leflunomide (LEF)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sulfasalazine (SSZ)</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Hydroxychloroquine (HCQ)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Azathioprine (AZA)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>IM-gold (iAU)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Combination of DMARDs</td>
<td>3 (MTX/HCQ) and 2 (MTX/SSZ)</td>
<td>2 (SSZ/HCQ)</td>
<td>(AZA/SSZ)</td>
<td></td>
</tr>
<tr>
<td>Steroid use at conception</td>
<td>6 (29%)</td>
<td>17 (34%)</td>
<td>24 (41%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Pregnancy outcome**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
<td>0</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>7 (33%)</td>
<td>12 (24%)</td>
<td>10 (17%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>0</td>
<td>1 (2%)</td>
<td>0</td>
<td>0</td>
</tr>
<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>0</td>
</tr>
</tbody>
</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 Ib (p = 0.0353) and 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.
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. In two of the three twin pregnancies, one neonatal death 27 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).

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 27 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 therapy at conception without 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), the termination rate was higher in those exposed to 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 and other antirheumatic treatment cannot be excluded. Although the collected results to date have been promising with few reports of congenital malformations, no firm conclusions can be drawn about the safety of anti-TNF therapy 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.

REFERENCES


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