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Concise Report

Pregnancy and foetal outcomes following anti-tumor necrosis factor alpha therapy: A prospective multicentre study

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ABSTRACT

Objective: As many inflammatory rheumatic diseases affect patients in childbearing age, some concern has been expressed about the safety of biologic drugs during pregnancy. This study evaluated the effects of anti-tumor necrosis factor alpha (TNFα) agents on pregnancy/foetal outcomes.
Methods: Thirty-eight pregnancies were followed prospectively from November 2008 to February 2015. Information about the patients' exposure to anti-TNFα, disease activity, DMARD therapy, pregnancy/foetal outcomes were registered.
Results: Twenty-four/38 (71.1%) pregnancies were exposed to anti-TNFα at conception/I trimester, 11/38 (28.9%) prior to conception and 3 (11.1%) following paternal exposure. There were two congenital malformations: one infant (4.2%) was diagnosed with congenital diaphragmatic hernia and obstructive megaureter; the mother was exposed to adalimumab at conception/I trimester. While one foetus (9.1%) showed a trisomy 16, the mother 38 year-old had suspended etanercept 4 weeks before conception. There was no significant difference in pregnancy/foetal outcome between the two groups. Nor were there any significant differences in pregnancy/foetal outcomes in the various groups being treated with different anti-TNFα antagonists. No congenital malformations were found in connection to paternal exposure.
Conclusion: Study results suggest that anti-TNFα drugs could be safe when administered during conception/I trimester and following paternal exposure.

1. Introduction

The introduction of anti-tumor necrosis factor alpha (anti-TNFα) agents has significantly improved the outcome of inflammatory rheumatic diseases. As many of these diseases affect women and men in childbearing age, there is concern about the safety of biologic drugs during reproduction and pregnancy.

While the efficacy and safety of these agents have been investigated in clinical trials and, increasingly, in long-term observational studies, limited data about their use in pregnancy can be found in the literature. Data from more than 2000 pregnancies focusing for the most part in inflammatory bowel diseases (IBD) comes from case reports/small case series besides safety registries [1–6]. These data reported no increased risk of spontaneous abortion, low birth weight, prematurity, or congenital malformations. There was, also, no indication of excessive risk for infection in antenatally exposed children during the first year of life. Verstappen et al. [7] reported an increased risk of spontaneous abortions with anti-TNFα inhibitors, however, the authors could not exclude the role of disease severity and other antirheumatic treatments. Reassuring data came from gastroenterologists [8–12] using infliximab (IFX), adalimumab (ADA) and certolizumab pegol (CZP), even during the whole pregnancy. Recently reviewed data [2] on the use of anti-TNFα inhibitors in IBD reported rates of spontaneous abortions and stillbirth similar to that of general population. While, the rates of premature birth and small for gestational age were slightly higher than those of general population, probably due to the underlying diseases. In fact, have been reported that pregnancy outcomes after

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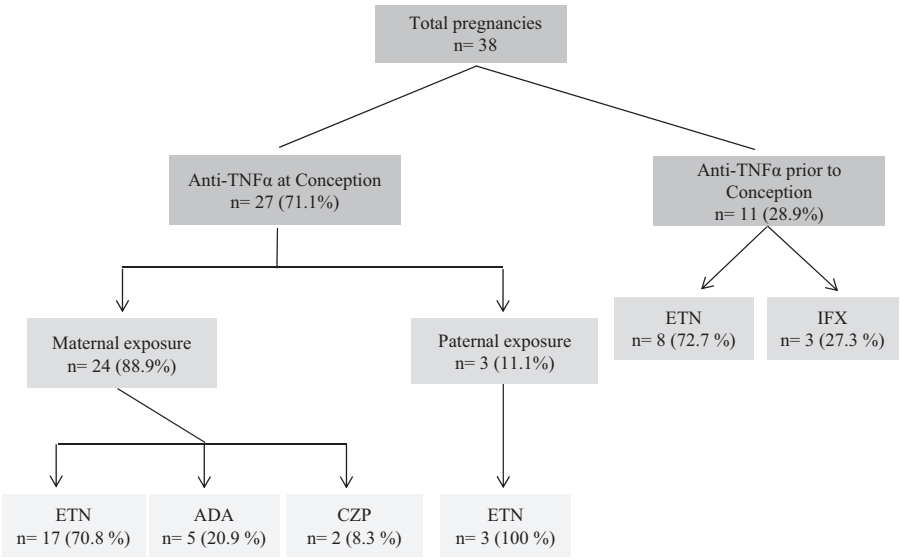

Fig. 1. Flow diagram illustrating the study cohort.

direct exposure to anti-TNFα agents were not different from those after indirect exposure to anti-TNFα, but they were worse than in pregnancies before IBD diagnosis [10,11].

Based on their molecular structure, a different transplacental passage of biologics has been observed [8,9,13]. Higher concentrations of IFX and ADA have been reported in infants and their cord than in their mothers depending on the timing the last dose had been administered, while, CZP and etanercept (ETN) showed lowest concentration in infant blood.

Overall, reassuring data came up, however, Carter et al. [14] reported a VATER association (vertebrae anomalies; anal anomalies; tracheal problems; oesophageal problems; radius or renal defects) in an infant exposed to high dose ETN in utero. One report on an infant exposed in utero to IFX who died at 4.5 months of age due to disseminated tuberculosis after being vaccinated at 3 months for bacillus Calmette-Guèrin [15] has raised concerns about the safety of vaccinations in these infants.

Given the paucity of large population-based studies and prospective data concerning pregnant women, there are as yet no guidelines concerning the use of anti-TNFα at conception and during pregnancy in patients with inflammatory arthritis.

This prospective study was designed to evaluate the effects of anti-TNFα agents on pregnancy and foetal outcomes in patients with inflammatory rheumatic diseases. The study's primary outcome was the prevalence of congenital malformations in infants exposed to biologic agents. Secondary outcomes were the rate of premature births (defined as < 37 weeks of gestation), small for gestational age (defined as < 10th percentile) newborns, and the prevalence of vaccine complications.

2. Methods

2.1. Study population

Thirty-eight pregnancies of 32 patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis attending four Rheumatology Units (Belluno, Padua, Trento and Udine) were consecutively enrolled and monitored between November 2008 and February 2015. In agreement with the patients' attending physicians, they were treated with IFX, ETN, ADA, or CZP.

The study was carried out in accordance with the principles outlined in the Declaration of Helsinki and all the participants gave informed consent.

2.2. Data collection

A 28-item form including information on biological agents exposure, disease activity, the concomitant use of disease modifying antirheumatic drugs, information about the pregnancy and foetal outcomes was filled out by the treating rheumatologist. Details concerning pregnancy complications and information about congenital malformation and vaccine adverse events were also collected. Children's follow-up was performed through maternal reports during their outpatient follow-up.

Once this data were collected, the pregnancies were divided in two groups: group I composite of 27 pregnancies of 23 patients which were treated with anti-TNFα agents at conception/I trimester [anti-TNFα therapy was discontinued between 7th-11th weeks of gestations (WG); one woman restarted ETN at 29th WG until delivery at 38th WG] and group II composite of 11 pregnancies of 9 women withdrawn anti-TNFα prior to conception [anti-TNFα therapy was discontinued between one to six months prior to conception, following the leaflet recommendations]. Given the known differences in [8,9,13,16,17] placental transfer due to the different structure of these agents, group I was further categorized into those exposed to ETN, ADA or CZP (Fig. 1).

2.3. Statistical analysis

Fisher's exact tests were used to compare the categorical variables for group I and group II and for the groups treated with different anti-TNFα agents. The Mann–Whitney or Kruskal–Wallis tests were employed to analyze variables measured along a continuous scale. *P*-values less than 0.05 were considered statistically significant.

3. Results

An overview of all pregnancies is illustrated in Fig. 1. Thirty-eight pregnancies, including one twin pregnancy, were enrolled; 6 women have had multiple pregnancies, three in group I, one in group II, and two have had pregnancies in both group I and II. Thirty-five pregnancies following anti-TNFα maternal exposure at conception/I trimester (group I) or prior to conception (group II) are outlined in Table 1; the women's demographic and clinical features and the results of the statistical comparison between the two groups are also outlined.