Low Risk of Birth Defects for Infants Whose Mothers Are Treated With Anti–Tumor Necrosis Factor Agents During Pregnancy

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BACKGROUND & AIMS: **Safety data on anti-tumor necrosis factor (anti-TNF) treatment during pregnancy are limited. We studied the risk of birth defects after anti-TNF treatment in early pregnancy.**

METHODS: **We collected data on 1,272,424 live-born infants identified from the Danish (2004–2012) and Swedish (2006–2012) population-based health registers. We determined the prevalence of birth defects among infants born to women with chronic inflammatory disease (inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, or psoriasis), with (n = 683) and without (n = 21,549) anti-TNF treatment during early pregnancy, and in the general population. We compared the risk of any major birth defect and birth defect by organ system for infants born to women with chronic inflammatory disease, with and without anti-TNF treatment. Risks were presented as odds ratios (ORs) with 95% confidence intervals (CIs). We adjusted for maternal age, parity, smoking, body mass index, multiple gestation, country, and chronic inflammatory diagnosis.**

RESULTS: **Birth defects were more prevalent among infants born to women with chronic inflammatory disease, regardless of anti-TNF treatment status, than in the general population (4.8% vs 4.2%). Birth defects occurred in 43 of the infants born to the 683 women who received anti-TNF treatment (6.3%), and 1019 of the infants born to women with chronic inflammatory disease (4.7%). The OR for any defect in women receiving anti-TNF therapy was 1.32 (95% CI, 0.93–1.82); the OR for a cardiovascular defect was 1.60 (95% CI, 0.93–2.58), and the OR for a urinary defect was 2.22 (95% CI, 0.86–4.71).**

CONCLUSIONS: **Based on an analysis of data from the health registries in Denmark and Sweden, women who received anti-TNF agents during pregnancy had a slightly (but not significantly) higher risk of having children with birth defects. Although larger studies are needed, the heterogeneity of the observed birth defects did not indicate a common etiology.**

Keywords: TNF; Pregnancy; Inflammatory Bowel Disease; Rheumatoid Arthritis.

The anti–tumor necrosis factor (anti-TNF) drugs etanercept, infliximab, adalimumab, certolizumab-pegol, and golimumab have become important treatment options for chronic inflammatory diseases, including Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, psoriasis, and ankylosing spondylitis. Studies have shown that curbing disease activity during pregnancy is vital for successful pregnancies in women with chronic inflammatory disease, particularly ulcerative colitis, Crohn's disease, and rheumatoid arthritis.[1,2]

Given the beneficial effects of anti-TNF treatment on chronic inflammatory disease, it is important to ascertain their safety during pregnancy. Current data on risks of birth defects are available mainly from case reports or case series, and the few studies that included comparison groups were hampered by limited numbers of exposed women.[3] Although the majority of studies found no evidence of increased teratogenic effects, 1 study reported a possible link with the vertebral anomalies, anal atresia, cardiac effect, trachea-esophageal defects, renal defects,

Abbreviations used in this paper: anti-TNF, anti–tumor necrosis factor; ASD, atrial septal defect; BMI, body mass index; CI, confidence interval; OR, odds ratio; VACTER-L, vertebral anomalies, anal atresia, cardiac effect, trachea-esophageal defects, renal defects, and limb defects; VSD, ventricular septal defect.

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and limb defects (VACTER-L) association, and 1 study reported a doubled risk of major birth defects.[4–8]

Anti-TNF treatment counteracts the biologic effect of tumor necrosis factor, a cytokine implicated in both the inflammatory pathophysiology of the underlying disease and in the delicate course of conception and pregnancy.[9–11] Infliximab, adalimumab, and golimumab are IgG antibodies, whereas etancercept is created from the fusion of a TNF receptor and the fragment crystallizable region (Fc) of IgG. Certolizumab-pegol consists of a recombinant humanized anti-TNF antigen-binding fragment (Fab'). IgG antibodies are not capable of independent transport cross the placental barrier, but their transport is increasingly facilitated from the second trimester and therafter.[12] Consequently, infliximab and adalimumab have been detected in cord blood.[13,14] Certolizumab-pegol, lacking the Fc region required for placental transport, is theoretically prevented from placental transport in late pregnancy. However, reports of IgG transfer into embryonic tissue at 4 weeks and separate reports of low levels of certolizumab-pegol detected in cord blood suggest yet unidentified mechanisms for placental transport.[13,15] Thus, fetal exposure to each of the anti-TNF substances cannot be ruled out when a pregnant woman is treated during organogenesis.

We investigated a possible association between anti-TNF treatment in early pregnancy and the risk of birth defects in the Danish and Swedish populations.

Methods

Study Population

We conducted a register-based study including information on women and their infants up to 1 year of age. Data were obtained from national medical birth registers, patient registers, and registers on prescribed drugs in Denmark and Sweden. We also accessed information on drug treatment from the Swedish disease-specific registers; Antirheumatic therapies in Sweden (ARTIS) and the Swedish Registry for Systematic Psoriasis treatment (PsoReg). Data in these registers can be linked using the unique personal identification number assigned at birth or upon immigration to all 15 million residents of Denmark and Sweden.

We used the national medical birth registers to identify all women who gave birth between January 2004 and December 2012 in Denmark, and between July 2006 and December 2012 in Sweden. The registers have collected nationwide information on births for several decades with almost complete coverage.[16,17] Midwives and physicians record information about the pregnancy, the delivery, and the neonatal period using structured forms. We obtained data on maternal age, parity, smoking, body mass index (BMI), multiple gestation, and gestational age at delivery. Determination of start of pregnancy and gestational age was based primarily on the routine early pregnancy ultrasound, offered to all pregnant women in Denmark and Sweden.

Anti–Tumor Necrosis Factor Treatment

Women who had filled prescriptions for etanercept, infliximab, adalimumab, certolizumab-pegol, or golimumab within 90 days before and 90 days after their last menstrual period were identified from the national registers on prescribed drugs.[18] Prescriptions are typically specified to last for 90 days. The first anti-TNF substances were introduced in 1998 and the start of the study period for Denmark was set to January 2004. We assumed that after 5 years of availability, anti-TNF treatment would be used in pregnancy not only in extraordinary conditions. For Sweden, the start was in July 2006 to obtain complete information for all pregnancies 12 months before delivery. Individual data in the Swedish register on prescribed drugs were made available in July 2005.

In Denmark, anti-TNF treatment also was identified from visits recorded in the patient register covering all Danish hospitals using a specific treatment code.[19] In Sweden, additional information on anti-TNF treatment was obtained from the ARTIS and PsoReg registers.[20,21] ARTIS contains information on patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis who are treated with anti-TNF. Similarly, PsoReg contains information on patients with psoriasis and psoriatic arthritis who are treated with anti-TNF.

Chronic Inflammatory Disease

To determine which diagnosis led to initiation of anti-TNF treatment, we obtained information on chronic inflammatory diseases as International Classification of Diseases, 10th revision, codes recorded at any time before or during pregnancy, from 1998 and onward (Supplementary Table 1). The information was obtained from the patient registers, ARTIS, PsoReg, and the medical birth registers. For patients diagnosed with more than 1 chronic inflammatory disease, the latest diagnosis was used. In the few patients in whom more than 1 disease was recorded during pregnancy, we used the following hierarchy: Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and, finally, psoriasis.

Birth Defects

Occurrence of birth defects, in general and by organ system–specific subgroups, and hospital visits in infants up to 1 year of age were ascertained from International Classification of Diseases, 10th revision, codes in the medical birth registers and in the patient registers (Supplementary Table 2). Minor birth defects were not studied and persistent ductus arteriosus was considered