

The use of anti-TNF α medications for rheumatologic disease in pregnancy

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Abstract: Anti-TNF α medications have led to vast improvements in the treatment of inflammatory conditions, including rheumatoid arthritis and Crohn's disease. As these diseases often afflict women in their reproductive years, the safety of these drugs during pregnancy is an important issue. Prospectively collected data thus far appear to be reassuring; however an analysis of the FDA-reported anomalies has raised some questions. It appears that significant levels of these drugs cross the placenta as the pregnancy nears term, but little is passed through breast milk. Prior to using these medications during pregnancy, the risks and benefits of these drugs, other treatment options, and the ongoing inflammatory condition all must be carefully weighed by both doctor and patient.

Keywords: pregnancy, anti-TNF α medications, rheumatoid arthritis, Crohn's disease, teratogenesis

Introduction

Anti-tumor necrosis factor α (TNF α) medications have revolutionized the treatment of inflammatory arthritis. When the first biologic drugs for arthritis, infliximab and etanercept, were approved by the Food and Drug Administration (FDA) in 1999, they raised the hopes for a life without pain and disability for many patients. Our standards for acceptable joint inflammation increased dramatically, no longer expecting patients to have chronic inflammation and damage but now modifying treatment with the goal of eliminating active arthritis.

Many patients with inflammatory arthritis, especially rheumatoid arthritis, are women in their reproductive years. These women maintain fertility and often wish to build families of similar size to women without arthritis. With increasing use of anti-TNF α drugs to treat arthritis in young women, questions about the safety of these agents for the developing fetus and breastfed infant have arisen. Animal data regarding pregnancy are benign, earning these agents an FDA Pregnancy Classification of B, meaning no animal reproductive concerns but limited human data. Human data are slowly being accumulated and published, with largely reassuring results. It does appear, however, that significant amounts of anti-TNF α medication cross the placenta in the third trimester.

This review will detail the human clinical data for pregnancy outcomes and fetal health following anti-TNF α medication exposure. In addition, it will discuss lactation during anti-TNF α medication use.

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Clinical utility of anti-TNF α medications

Anti-TNF α medications have decreased pain, joint erosions, and disability in many people with inflammatory arthritis. In rheumatoid arthritis (RA), these drugs dramatically slow the accumulation of radiographic damage. Studies show that the most clinical benefit is derived from the combination of anti-TNF α medications and methotrexate; alone, anti-TNF α medications or methotrexate have similar degrees of benefit.¹ Of patients taking the combination of infliximab plus methotrexate, over 60% will get 20% better, about 50% will get 50% better, and over 30% will get 70% better. Between 10% and 15% will even get 90% better.¹ All of the anti-TNF α medications perform similarly with roughly equivalent improvement across studies.²

Anti-TNF α medications are typically indicated when inflammation from rheumatoid arthritis or psoriatic arthritis can not be controlled with oral agents, including methotrexate, hydroxychloroquine, or sulfasalazine. In clinical practice in the United States, an estimated 40% of patients with long-standing rheumatoid arthritis and 25% with early RA (<3 years duration) are taking anti-TNF α medications, 70% of the time with another disease-modifying antirheumatic drug (DMARD).³

During pregnancy, the options for arthritis therapy are limited. Both methotrexate and leflunomide are FDA Class X during pregnancy, indicating that the fetal risk outweighs any benefit to the mother. Methotrexate is a known teratogen and cessation of this drug is recommended 3 months prior to conception. The reported number of pregnancies exposed to the low weekly dose used in rheumatology is small, however. In a recent review of 6 reports including a total of 101 pregnancies, of those not electively terminated, 23% resulted in a miscarriage, and 66% in a live birth. Only 5 had a minor neonatal malformation.⁴ A report of prospectively collected pregnancies in women taking leflunomide at the time of conception shows a low rate of congenital anomalies (5%) that is comparable to prospectively collected rheumatoid arthritis and healthy control pregnancies.⁵ Despite these findings, it is still recommended that women discontinue these medications prior to conception.

The use of NSAIDs during pregnancy is typically restricted to occasional use in the first half of pregnancy. Use in the third trimester can cause premature closure of the ductus arteriosus. NSAIDs may also promote oligohydramnios (low amniotic fluid levels) by restricting fetal renal blood flow. For this reason, most women are encouraged to take acetaminophen for pain during pregnancy. This,

however, is often ineffective for the pain of inflammatory arthritis.

Medications considered relatively safe in pregnancy include corticosteroids, sulfasalazine, and hydroxychloroquine. Prednisone can promote maternal hypertension, diabetes, and excessive weight gain, all significant problems during pregnancy. It may also lead to a lower birth weight and preeclampsia.^{6,7} Sulfasalazine is considered relatively safe during pregnancy and can be continued.⁷ Hydroxychloroquine is also relatively safe, though less effective in treating inflammatory arthritis.⁷

With medications limited during pregnancy, the anti-TNF α medications take on a greater importance to women with inflammatory arthritis. Fortunately, up to 75% of women with RA will improve during pregnancy, with half of them having mild disease.^{8,9} However, half of women remain with moderate to severe RA activity throughout pregnancy. Women with psoriatic arthritis and ankylosing spondylitis do not generally improve during pregnancy. For these women, pregnancy can be a debilitating period marked by worsening joint pain, inflammation, and damage.

A high degree of inflammatory joint activity may promote an early delivery of a small infant.¹⁰ Up to a quarter of women with RA will deliver preterm and the average birth weight, even for full-term infants, is lower than in healthy controls.¹¹ In addition, continuing joint disease during pregnancy can lead to disability, pain, and further joint damage. For women with high levels of disease activity during pregnancy, anti-TNF α medications may be the best option for therapy.

Maternal risks from anti-TNF α medications

The risk for reactivation of tuberculosis is the primary infection concern for anti-TNF α medications. TNF α is an important cytokine for the maintenance of the granuloma that contains a prior tuberculosis (TB) infection. When TNF α is blocked effectively by these drugs, the granuloma may disintegrate, allowing the TB to reinfect the lungs or extra-pulmonary areas. A recent study of over 10,000 patients treated with anti-TNF α medications compared to over 3000 RA patients without anti-TNF α medications from the British Society for Rheumatology Biologics Register (BSRBR) demonstrated a significant risk for TB reinfection.¹² The risk of TB was 144 events/100,000 patient years for adalimumab, 136 events/100,000 patient years for infliximab, and 39 events/100,000 patient years for etanercept. Patients from areas with endemic TB are at highest risk. All patients

Table 1 The TNF inhibitor medications

Drug name and manufacturer	FDA indications	FDA pregnancy class	Estimated half-life	Type of antibody
Infliximab (Remicade [®] ; Centocor)	RA, AS, PsA, CD, US, PP	B	9–10 days	Chimeric monoclonal IgG1 antibody
Etanercept (Enbrel [®] ; Amgen)	AS, PsA, PP, JIA	B	3 days	TNF receptor linked to the Fc portion of human IgG1
Adalimumab (Humira [®] ; Abbott)	AS, PsA, CD, PP, JIA	B	10–13 days	Recombinant monoclonal IgG1 antibody
Certolizumab (Cimzia [®] ; UCB)	RA, CD	B	14 days	Pegylated humanized antibody Fab' fragment of TNF-alpha monoclonal antibody
Golimumab (Simponi [®] ; Centocor Ortho Biotech)	RA, AS, PsA	B	7–20 days	Human monoclonal IgG1 antibody

Abbreviations: RA, rheumatoid arthritis; AS, ankylosing spondylitis; PsA, psoriatic arthritis; CD, Crohn's disease; UC, ulcerative colitis; PP, plaque psoriasis; JIA, juvenile idiopathic arthritis.

should have tuberculosis screening prior to the initiation of any anti-TNF α medication.

Most experts cite a doubling of the risk of infection for patients on anti-TNF α medications. A review of the BSRBR, however, did not find an increase in serious infections for patients on anti-TNF α medications, though these patients did have a higher risk of skin and soft tissue infections.¹³ A meta-analysis of 5 studies infliximab for RA found no increase in serious infections (relative risk [RR] 0.96).¹⁴ A meta-analysis of all anti-TNF α medications for psoriatic arthritis also found no increase in serious side effects or infection.¹⁵ Despite these reassuring findings, it is essential to remain vigilant for infection in all patients on these medications. Pregnancy is a time of relative immunosuppression, so prompt evaluation and treatment of potential infection is important.

The injectable anti-TNF α medications may cause transient injection site reactions with swelling, erythema, and pruritis. These typically resolve within a week and rarely dose-limiting. Infliximab infusions can be accompanied by an infusion reaction, worsened by human-anti-chimeric antibodies (HACA). These antibodies are more prone to develop when a patient is not co-treated with methotrexate. HACA can also decrease the clinical benefit of infliximab. An infusion reaction is more likely if a patient has had a significant break between infusions. This poses a problem for infliximab use in pregnancy: methotrexate is contraindicated and many women will elect to stop use during pregnancy. When the drug is restarted post-partum, the risk for infusion reaction is high. This risk may be modified by skipping the loading dose and aggressive use of pre-medications.

The extent to which anti-TNF α medications increase the risk for malignancy remains under debate. All patients with rheumatoid arthritis are at increased risk, particularly for lymphoma. A recent meta-analysis of etanercept showed no increase risk in RA patients treated with the drug vs

placebo.¹⁶ A prospective cohort of over 10,000 RA patients also found no increase in lymphoma among patients treated with anti-TNF α medications compared to those on other disease modifying drugs.¹⁷ The absolute risk of malignancy in these patients remains very low.

There are several other, more rare, complications that may be associated with anti-TNF α medications. Demyelinating disorders was identified when a trial of an anti-TNF α medication for multiple sclerosis (MS) found an increase in new lesions on the drug compared to placebo. Fewer than 200 cases of new MS-like disease have been reported.¹⁸ Drug-induced lupus can occur rarely following anti-TNF α medications. Many patients will develop a positive ANA antibody and even positive anti-dsDNA antibody, but only an estimated 0.1%–0.3% will acquire symptoms of lupus.¹⁸ Pustular psoriasis may paradoxically develop during anti-TNF α medication therapy.

Transplacental passage of immunoglobulins

Infants are protected from infectious diseases in the first months of life by the maternal antibodies that cross the placenta in the latter half of pregnancy.¹⁹ Antibody transfer across the placenta does not begin until the second trimester, but then increases in a linear fashion until delivery. At term, the amount of maternal IgG antibody is higher in the neonate than in the mother. This pattern holds when the IgG antibody is an anti-TNF α medication. A specific Fc receptor neonate (FcRn) facilitates transfer of the IgG antibodies across the syncytiotrophoblast into fetal circulation.¹⁹

Transplacental transfer of anti-TNF α medications

A small study of pregnant rats found that a murinized TNF α inhibitor on a PEGylated Fab fragment (similar to

certolizumab) had less placental and milk transfer than a murinized TNF α -inhibitor in the form of IgG1.²⁰ All 5 rats treated during pregnancy with the PEGylated form had no or minimal (<0.5% of maternal levels) transfer into the fetal circulation 7 days later. The half-life of the drug, however, was noted to be very short and TNF levels were not reported. In contrast, the IgG1 form was found in all rats at a mean 15.6% of maternal concentration. There appeared to be higher levels of the IgG1 than the PEGylated form in the breastmilk of rats treated during pregnancy. These rats were not, however, treated post-partum with either medication. This report is limited in several ways: most importantly, TNF levels were not measured. The PEGylated form has a shorter half-life so the fetus may have a shorter window of exposure but may have an extended period of drug effect. In addition, these are murine data using drugs that are modified for use in rats, making it difficult to extrapolate to humans.

Infants exposed to infliximab in the weeks prior to delivery will likely be born with serum infliximab levels similar to their mother. Maternal and fetal infliximab serum levels have been monitored in several small studies. One case report of a 35-year-old woman who received infliximab 10 mg/kg every 6 to 8 weeks throughout pregnancy (including 2 days prior to delivery) for severe Crohn's disease reported high levels of infliximab in the infants' serum 6 weeks after delivery.²¹ At 6 weeks, the mother and infant had the same amount of infliximab in the serum, despite the mother having received another 10 mg/kg dose after delivery. From that point on, the mother's levels fluctuated with infliximab therapy but the infant's levels fell slowly over the next 6 months, despite breastfeeding.

Pregnancy outcomes with exposure to anti-TNF α medications

For the purposes of this report, pregnancies will be grouped according to the anti-TNF α medications utilized in pregnancy. The largest report of pregnancies exposed to anti-TNF α medications, however, does not include data about which anti-TNF α medication was used. From a survey completed by rheumatologists, 454 pregnancies in women with RA were identified. The anti-TNF α medication was continued throughout pregnancy in 31% of these.²² Pregnancy results were available for 417 pregnancies, of which 378 (90%) were normal deliveries, 9 were premature, 5 electively terminated, and 25 (6%) ended in a miscarriage. Though none were reported to have congenital anomalies,

3 were born with 'medical problem(s) due to' the anti-TNF α medications.²²

Infliximab

A large collection of TNF-inhibitor exposed pregnancies from the Centocor safety database was reported in 2004.²³ Pregnancies were collected in two ways: 1. self-reported to the company by a physician or patient and 2. pregnancies that occurred within clinical trials (21 pregnancies). This report includes 96 pregnancies with direct exposure and known pregnancy outcomes. Exposure was remote (none within 3 months of pregnancy) in 7% of pregnancies, but the remaining pregnancies were exposed either within 3 months of conception (26%) and/or during the first trimester (60%). None of these pregnancies appear to have been exposed in the second or third trimesters, though timing of exposure is unknown in 6. Of the 96 pregnancies, 19% were electively terminated, 15% ended with a pregnancy loss, most in the 1st trimester, and 66% resulted in a live birth. Of these, 2 infants had congenital anomalies: 1 tetralogy of Fallot and 1 with intestinal malrotation, both after the first trimester infliximab exposure.

Four case reports of women with Crohn's disease with infliximab use during pregnancy have been reported. One reported a woman receiving infliximab at the time of conception for colonic Crohn's with a rectovaginal fistula who did not continue the drug during pregnancy, though she did take mesalamine, metronidazole, and azathioprine. Unfortunately, her baby was delivered at 23 weeks gestation and died 3 days later with cerebral and pulmonary hemorrhage.²⁴ Three other cases have happier outcomes: 1 continued infliximab throughout pregnancy and delivered without complications at 36 weeks gestation.²⁵ Another received 2 doses of 5 mg/kg infliximab 1 and 3 weeks after conception and delivered a healthy baby at term.²⁶ Another woman with fistulizing peri-anal disease received 500 mg infliximab 3 days after conception. Her pregnancy was complicated by a small bowel obstruction at week 17, but she delivered a healthy baby at 36 weeks gestation.²⁷ One case of a pregnancy in a woman with rheumatoid arthritis on infliximab resulted in a full term birth.²⁸

A woman with rheumatoid arthritis with a complicated pregnancy history had a miscarriage on infliximab. Her first 4 pregnancies resulted in a stillbirth due to an acute hypoxic event at 36 weeks, a miscarriage at 15 weeks, and 2 healthy infants born preterm at 34 weeks and 35 weeks. Her final pregnancy resulted in a miscarriage at 6 weeks. She was taking methotrexate 20 mg per week, folic acid 5 mg per week,

diclofenac and infliximab 3 mg/kg every 8 weeks at the time of conception of this final pregnancy.²⁹

Etanercept

The OTIS registry is a prospective cohort study of pregnant women with inflammatory arthritis including rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. This registry reported 100 pregnancies exposed to etanercept, compared to 54 disease controls, in an abstract in 2008.³⁰ The timing and duration of etanercept exposure was not reported. The etanercept and control pregnancies had similar live birth rates: 94% with etanercept vs 87% for controls. The rate of major congenital anomalies was also similar, with 8% after etanercept exposure and 5.7% without it. The 8 anomalies after etanercept included one each of congenital hypothyroidism, microcephaly, pyloric stenosis, cystic adenomatoid malformation, and hypospadias. In addition, one child had esotropia, an inguinal hernia, and an atrial septal defect. One child had displacement of the stomach, epispadias, and retinal abnormalities. One child had a ventricular septal defect and mild peripheral pulmonic stenosis. In the control group, 2 infants had Down's syndrome and 1 had a duplex kidney. The authors concluded that these data did not raise a significant concern about the safety of etanercept in pregnancy.

Eight pregnancies exposed to etanercept for rheumatoid arthritis, collected by survey from rheumatologists across the United States, resulted in 6 full-term deliveries, one spontaneous abortion (also exposed to methotrexate), and one elective termination.²⁸

A 40-year-old woman with RA and 2 prior 1st trimester miscarriages conceived while taking etanercept and continued the drug through pregnancy and lactation. Maternal serum levels of the drug remained stable throughout, ranging from 2239 ng/mL at the time of delivery to 3849 ng/mL in the first trimester. The cord blood contained 81 ng/mL of etanercept, a level almost 30-fold lower than in the maternal serum at the time.³¹ By 1 week post-partum, the baby's etanercept level had fallen to 21 ng/mL, by week 3 to 2 ng/mL, and it was undetectable by week 12, despite breastfeeding exclusively.

Adalimumab

In 2008, OTIS presented data on adalimumab at the American College of Rheumatology national scientific meeting.³² This report included 30 adalimumab-exposed RA pregnancies, compared with 53 RA patients without medications and 40 healthy pregnancies. All adalimumab exposure was limited to the first trimester. Each group has similar rates

of live birth (90%–91%). Preterm birth was most common in the RA control group (19%), second most common in the adalimumab group (11%), and there were no preterm births in the healthy control group. Congenital anomalies were noted in 2 adalimumab exposed babies (1 with undescended testicle and 1 with microcephaly), compared to 1 chromosome abnormality in the RA control group and 2 major defects identified in the healthy controls. A larger case-series of pregnancies exposed to adalimumab either for reasons other than RA or that were reported retrospectively included 58 pregnancies, of which 10% had major malformations: 3 chromosome abnormalities, 1 spina bifida with hydrocephalus, 1 ventricular septal defect, and 1 congenital hip dysplasia with inguinal hernia.

Four case reports of adalimumab in pregnancy have been reported, all with good maternal and fetal outcomes. Two reports include 34- and 35-year-old women with ileocolonic Crohn's diseases on adalimumab prior to conception and continuing throughout the pregnancy and lactation. On this medication, one woman's Crohn's disease became well controlled and she was able to taper her prednisone. The other had a flare at 20 weeks gestation that was treated with additional steroids. Both pregnancies were uncomplicated, with babies born at term, with normal growth at 6 months of age.^{33,34} A third woman with Crohn's disease was started on adalimumab and azathioprine at 19 weeks pregnancy for a severe flare. Within 2 weeks she was feeling better and after 3 months she was able to taper off prednisone. The baby was born at term and was doing well 1 year later.³⁵ A young woman with Takayasu's arteritis complicated by multiple arterial stenoses in major vessels was on adalimumab 40 mg every 4 weeks and leflunomide 10 mg a day at conception. On discovery of the pregnancy at 8 weeks the leflunomide was stopped but the adalimumab was continued with low dose prednisone and dalteparin. The baby was delivered at term via cesarian section without complication.³⁶

Certolizumab

Certolizumab was FDA approved for Crohn's disease and inflammatory arthritis in 2008, leaving little time for the collection of pregnancies at this point. However, 2 cases have been reported. A 22-year-old woman with Crohn's disease received 9 injections of certolizumab prior to pregnancy and one injection in the first trimester. She felt well and discontinued the drug until she had a flare at 31 weeks gestation. At that time she received 1 injection of the drug to treat a flare and felt better. She delivered her baby at term without complication.³⁷

A second case of a 22-year-old women with Crohn's disease who started certolizumab 400 mg subcutaneously in the second trimester and continued it every 4 weeks through the end of pregnancy. Her last dose was 2 weeks prior to delivery. She delivered a healthy baby at 37 weeks gestation. The certolizumab level at delivery was 18.83 µg/mL and in the cord blood was 1.65 µg/mL. This appears to demonstrate that the level of certolizumab that crosses to fetal circulation may be more limited than with some other TNF α -inhibitors.³⁸

Golimumab

There are no reports of human pregnancies exposed to golimumab in the literature at this time. A study of the drug in macaque monkeys, however, provides interesting data. Pregnant monkeys were studied over two separate time periods: first trimester with exposure to 25 mg/kg, 50 mg/kg, or placebo twice a week from gestational day (GD) 20 to 50; and later in pregnancy with the same dosing given from GD50 through lactation day (LD) 33.³⁹ The typical human dose is 100 mg every 4 weeks, making the doses in this study at least 40-fold higher than would be used clinically.

After first trimester exposure, the pregnancies were terminated at GD100 for anatomic and immune analysis. At this time point, there were no differences in the number or distribution of B and T cells in lymphoid tissue or between percentages of lymphocyte subsets in any of the treatment groups. The fetal serum level of golimumab was, on average, half that of the mother.

For the second group with exposure later in pregnancy, each monkey delivered naturally and all infants were breastfed. Pregnancy loss occurred in 3 control pregnancies and in 3 with 50 mg/kg dosing. Neonatal death occurred within 2 weeks of delivery for 2 preterm infants, one in the 25mg/kg group and one in the 50 mg/kg group. At birth, there was no difference in weight or anatomy in the treatment groups. Humeral immunity and delayed type hypersensitivity in response to tetanus toxoid was the same in each group. Finally serum levels in the mother, infant, and milk were all measured and showed a dose response (see Table 2).

Possible association between anti-TNF α medications and VACTERL association

Some concern has been raised that the use of TNF during pregnancy may increase the incidence of VACTERL association.^{40,41} VATER or VACTERL association (as it is labeled in 2 articles by the same team) is a non-random

Table 2 Golimumab concentrations in the maternal serum and milk and infant serum³⁹

	Maternal serum		Milk		Infant serum
	After 1st dose	After last dose	LD14	LD28	LD15 ^a
25 mg/kg twice per week	176 µg/mL	851 µg/mL	0.75 µg/mL	0.79 µg/mL	219 µg/mL
50 mg/kg twice per week	321 µg/mL	1482 µg/mL	3.65 µg/mL	3.62 µg/mL	534 µg/mL

^aSome infants had detectable golimumab up to 6 months following birth.

collection of congenital anomalies that include a wide range of systems (VATER association: Vertebral, Anal, Tracheal, Esophageal, and Radius or Renal; VACTERL association: Vertebral, Anal, Cardiac, Tracheoesophageal, Renal, and Limb). There may be a genetic defect causing a small number of cases, but most appear to be sporadic and without known cause.⁴² This concern was triggered by a baby born with VATER association after exposure to 50 mg twice a week of etanercept throughout pregnancy for psoriatic arthritis in the mother. This baby was born with multiple anomalies, including tracheal atresia and trachoesophageal fistula, esophageal atresia, imperforate anus, a T12 vertebral anomaly, a patent foramen ovale, hypospadias, and spina bifida occulta. In a 2006 report of this pregnancy and offspring, the authors postulate a connection between anti-TNF α medications, and etanercept in particular, in triggering these anomalies based on similar anomalies found in a knock-out TRAF4 mouse.⁴⁰ This mouse lacks TNF receptor associated factor 4 (TRAF4) and some of the offspring have tracheal atresia, pulmonary inflammation, vertebral anomalies, and spina bifida.

To determine whether this case was isolated or not, the same authors requested the list of adverse events reported to the FDA for anti-TNF α medications and identified 61 congenital anomalies out of over 120,000 events. This database included all reports between when anti-TNF α medications were first commercially available to December of 2005. The majority of this time, only infliximab and etanercept were available, with adalimumab approved December 31, 2002. Of these 61 anomalies, 7 were from the index case reported above, leaving 54 other anomalies in 40 babies.⁴¹

The authors then took a somewhat unorthodox leap to determine the number of anomalies out of the 54 that could be included in the VACTERL association. In this calculation, they included all heart defects (n = 9), kidney (n = 3), limb

(n = 3), and tracheal (n = 2) abnormalities. They also included 2 cases of hypospadias, 2 cases with lung malformations, a case with intestinal malrotation, and an infant with trisomy 18 as infants with components with the VACTERL association. They determined that 56% of the reported anomalies were consistent with those found in VACTERL association.

In addition, the authors compared the relative frequency in the reported anomalies from the FDA database to the relative frequency of congenital anomalies in the general population. Using this method, they concluded that several anomalies were found more commonly than anticipated, including pulmonary malformation (n = 3), cystic kidney (n = 3), teratoma (n = 3), atrial septal defect (n = 2), tracheal stenosis (n = 2), Duane's syndrome (n = 1), ventricular hypokinesia (n = 1), and optic neuropathy (n = 1).

This reported connection between VACTERL association and anti-TNF α medications is tenuous, at best. A very critical editorial was written by the directors of the MotherRisk Program in Canada and published in the same edition of the *Journal of Rheumatology* in which this paper appeared.⁴³ These editorialists point out numerous problems with the methodology including the assumption that the spontaneous reports to the FDA could be extrapolated to the general population, the bias towards reporting for babies with anomalies following a drug exposure compared to an anomaly following a more normal pregnancy, and skepticism of the validity of VACTERL as an association related to drugs. These authors also cite several reports of other medications initially thought to be associated with anomalies from studies of similar method to this VACTERL study that were later proved to be incorrect by prospective studies.

Other problems with this study include the lack of a denominator, the number of pregnancies exposed to anti-TNF α medications, making it impossible to determine whether the overall or specific rate of anomalies is greater than would be expected. In addition, the data available about each anomaly vary widely, making the classification of each anomaly difficult. Having one anomaly that could be a part of VACTERL association does not provide a diagnosis of this association. We expect that the etiology of the many different cardiac anomalies, for example, may vary widely. This report, however, ventures to lump them all together into one cause. Finally, drawing conclusions about the relative frequency of anomalies, when many have only been reported one time, is problematic. The laws of probability demand that some anomalies occur and that some be rare in any large group of pregnancies. Having one reported case of a rare anomaly does not lead to causation.

In summary, the report of VATER association in one infant after high dose etanercept exposure is interesting. The data that suggest this is a systemic problem with anti-TNF α medications are weak and not supported by prospective studies.

Use of anti-TNF medications in fertility therapy

In some reproductive immunology clinical practices anti-TNF α medications have been used to promote fertility. The theory behind this is controversial, but hinges on the overproduction of TNF α in the uterine lining by NK cells, thought to impair implantation. Two retrospective, non-randomized studies have shown improvements in live birth rates when including an anti-TNF α medication in therapy around conception. The first study included 75 women with recurrent miscarriage.⁴⁴ The live birth rate for women treated at the time of conception with an anti-TNF α medications (etanercept or adalimumab from 30 days prior to conception until fetal cardiac activity was identified by ultrasound) plus IVIg and low-molecular weight heparin had a higher live birth rate (71%) than women treated only with anticoagulation (19% live birth rate) or women treated with anticoagulation plus IVIg (54% live birth rate). The average gestational age of live births was similar between all groups (ranging from 37.2 to 38.8 weeks). One baby exposed to anticoagulation and IVIg was born with Down's syndrome; the remaining babies were born without congenital anomalies.

A second study by the same authors included another 75 women with Th1/Th2 cytokine elevation treated with various therapies, including adalimumab 40 mg 2 to 4 times prior to conception with IVIg (intravenous immunoglobulin), IVIg alone, adalimumab alone, or no therapy.⁴⁵ Therapy was not randomized, but based on clinical decision. IVIg was administered at 400 mg/kg once during the IVF cycle and during the first trimester of pregnancy. The results of the study were dramatic, with no untreated cycle resulting in a pregnancy or live birth compared to 73% of cycles resulting in a live birth after adalimumab and IVIg (see Table 3). A separate abstract by the same authors found no increase in congenital anomalies in pregnancies exposed to adalimumab pre-conception (2% – 1 report of Di George Syndrome, a chromosome 22 deletion), compared to IVIG (3%) or no immunotherapy (2%).⁴⁶

There are several problems with these studies and the use of anti-TNF α medications is not widely accepted in the reproductive endocrinology field. For the second study, the immunologic and clinical benefit of adalimumab given 2 months prior to embryo transfer is unclear. While the authors report that this treatment significantly altered

Table 3 Results of a non-randomized trial of adalimumab with or without IVIg with in vitro fertilization in women with an elevated Th1:Th2 cytokine ratio⁴⁵

	Group 1	Group 2	Group 3	Group 4	P value
Treatment	Adalim- umab plus IVIg	IVIg	Adalim- umab	No treatment	
Number of cycles	41	23	6	5	
Number of prior failed IVF cycles	1.7 ± 1.8	0.8 ± 1.2	1.2 ± 1.6	1.6 ± 1.7	0.20
Number of embryos transferred	2.1 ± 0.3	2.0 ± 0.2	2.2 ± 0.4	1.8 ± 0.4	0.07
Live birth rate	73%	52%	50%	0	0.003

ratios of TNF α :IL-10 and IFN γ :IL-10 2 months prior to transfer, this is not documented at the time of embryo transfer. Measuring NK cells and these cytokine levels is not standardized and only performed in specific labs. These studies were not randomized and it is not clear how therapy was determined or how patients were selected for this retrospective review. In particular, the abstract with birth defect information contains many more pregnancies with IVIG alone and no therapy than are included in the other published reports. A randomized trial will be required to confirm these findings.

Anti-TNF α medications and male fertility

TNF α may be important both in promoting and impairing sperm production and motility. TNF α may inhibit germ cell apoptosis in seminiferous tubules, a function that may be lost in rats by infliximab.⁴⁷ In addition, the extrusion of the cytoplasm that must take place in the development of the spermatozoa may be regulated by TNF α .⁴⁷ On the other hand, elevated levels of TNF α have been found in the semen of men with genital tract infections.⁴⁸ Also high levels of TNF α may interfere with sperm binding to the zona pellucida.⁴⁸

Several studies have sought to determine the impact of anti-TNF α medications on sperm viability. One study exposed human sperm samples to increasing levels of TNF α with or without infliximab. They found that sperm motility and sperm DNA damage both worsened with TNF α , but this was largely prevented by co-incubation with infliximab.⁴⁸ Another study compared semen samples in men with inflammatory bowel disease before and after infliximab therapy.⁴⁷ Seven of these men were taking ongoing therapy,

so it is unclear how unaffected the initial sperm collection might be from prior infliximab treatments. This study found that infliximab may modestly diminish sperm motility and morphology; however given the small number of subjects and the inherent variability in sperm analysis, this finding is not conclusive. The authors do not recommend discontinuing infliximab therapy unless male-factor infertility is identified.

A total of 17 pregnancies conceived by men taking infliximab have been reported.^{23,49,50} Fifteen of the men received infliximab within 3 months of conception; for the remaining 2 the relationship between timing for conception and infliximab was unknown. One pregnancy resulted in a first trimester miscarriage in a woman with Addison's disease and a prior miscarriage. The remaining 14 pregnancies resulted in healthy babies. One of these reports, as well as a report of a pregnancy conceived by a father on etanercept, suggest that the anti-TNF α medications promoted male fertility.^{50,51} In both of these reports the men were taking sulfasalazine, a drug well documented to diminish sperm number and motility, when prior sperm samples were analyzed. Both pregnancies, however, were conceived within several weeks of anti-TNF α medication initiation, suggesting either an improvement of sperm function or increased sexual activity following therapy.

Anti-TNF α medications in breastmilk

Absorption of maternal antibodies through the breastmilk is limited in humans.¹⁹ The predominant immunoglobulin in human breastmilk is IgA, which provides mucosal immunity in the gut of the infant. Little IgG or other large immunoglobulins cross into breastmilk and these do not enter infant circulation in significant amounts. For this reason, we would expect that the transfer of the IgG anti-TNF α medications would be minimal, as well. There are limited clinical data that support this theory (see Table 4). Half a dozen case reports of women receiving IV infliximab for the treatment of Crohn's disease have not shown any transfer of this drug into the milk in women breastfeeding their infants. The timing of milk and serum assessment varies, but whether measured within 24 hours or 30 days of dosing, each sample has been negative. One report of a woman with RA breastfeeding an infant while taking etanercept found a minimal level of etanercept in the breastmilk (3.5 ng/mL) at a time when the maternal serum level was 2872 ng/mL, a transfer rate of about 0.1%.³¹ After exposure *in utero*, the infant had falling levels of etanercept from week 1 to week 3, probably reaching an undetectable level by week 4 or 6 post-partum, though a repeat measure was not performed until week 12. Two cases have been reported of women treated with anti-TNF α

Table 4 TNF use during lactation: level of TNF in maternal serum and milk, and infant serum

	Maternal disease	TNF-therapy	Maternal serum levels	Milk levels	Infant serum levels
Kane ⁵²	Crohn's Disease 29 y/o	Infliximab D/C dose at 31 weeks. Restart ppd#3	74.27 μ g/mL	Undetectable	Not collected
	Crohn's disease 32 y/o	Infliximab D/C week 32. Restart ppd#10	62.62 μ g/mL	Undetectable	Undetectable
	Crohn's disease 24 y/o	Infliximab dosed week 19, 21, 25. Restart ppd#14	59.97 μ g/mL	Undetectable	Undetectable
Peltier ⁵³	Crohn's disease	Infliximab 5 mg/kg	Not collected	None detected at 24 h and 1 week after infusion	Not collected
Stengel ⁵⁴	Crohn's disease	Infliximab 10 mg/kg q 4 weeks	Not collected	None detected in daily collections x30	Not collected
Vasiliauskas ²¹	Crohn's disease 32 y/o	Infliximab 10 mg/kg – dose 2 wk predelivery, also with lactation	Not reported in abstract	Undetectable	39.5 μ g/mL 6 wk post-partum, slowly declined over 6 months
Murashima ³¹	Rheumatoid arthritis 40 y/o	Etanercept 25 mg sq twice per week	2239 ng/mL at delivery 2872 ng/mL at time of breastmilk collection	3.5 ng/mL	81 ng/mL cord blood. 21 ng/mL 1 week postpartum 2 ng/mL 3 weeks postpartum; undetectable 12 weeks postpartum

Abbreviations: D/C, discontinued; y/o, year old; ppd, post-partum day.

medications post-partum who were not actively breastfeeding for over 1 month, but had residual lactation.^{55,56} In each of these cases, the anti-TNF α medication (etanercept in one, infliximab in the other) was measurable in the excreted milk 3 to 4 months post-partum. It is likely that the milk ducts were more porous in these two women who were not actively breastfeeding, allowing these large molecules to pass.⁵⁷ It is reassuring that the women breastfeeding their children had no or minimal anti-TNF α medication excreted into milk.

A study of pregnant and lactating rats compared TN3 PEGylated Fab' (comparable to certolizumab) and TN3 IgG1 antibody (comparable to the classic anti-TNF α medication IgG1 molecules).²⁰ In the rats treated with the PEGylated molecule, milk levels contained about 5% of the maternal serum level and the infant's serum level was undetectable. Following TN3 IgG1 treatment, the milk contained 24% of the maternal plasma level and the infant serum level was actually higher than the maternal level. The drug was only given prior to delivery, so it is likely that much of this high IgG1 level in the offspring was from transplacental transfer.

While more reports of anti-TNF α medication levels in human breastmilk would be helpful, particularly for drugs other than infliximab, the data thus far are reassuring.

Treatment recommendations

The data presented in this review are, at times, conflicting and always limited in power. It is necessary, however, to draw some

clinical conclusions for our patients. The overriding principle in determining medication use during pregnancy is balancing the risks of no therapy to the mother and fetus vs the risks of therapy. For some diseases, in particular active Crohn's disease, the risk of very active disease far outweighs the risk of anti-TNF α medications. For other diseases, such as rheumatoid arthritis which often improves during pregnancy and activity has little impact on pregnancy outcomes, the balance may be different.

Pre-conception

It is hypothesized that the anti-TNF α medications do not cross to the fetus in the first trimester. For this reason, it may not be unreasonable to allow women to continue to use these medications until the time of conception. Pregnancy termination after a first trimester anti-TNF α medication exposure without evidence of a congenital anomaly is not recommended.

During pregnancy

For women with rheumatoid arthritis, holding the anti-TNF α medication when pregnancy is discovered is often well tolerated. Many women improve during pregnancy and are able to bear this drug holiday. Others are able to live with moderate inflammatory arthritis with low dose prednisone and/or sulfasalazine or hydroxychloroquine. For women with a history of severe erosive disease or who flare during pregnancy, consideration can be made for continuing (or restarting) the anti-TNF α medication during the pregnancy.

For women with ankylosing spondylitis or psoriatic arthritis, pregnancy is rarely accompanied by remission. For these women, continuation of the anti-TNF α medication, perhaps with less frequent dosing, through pregnancy may make this period less painful. Prior to continuing the anti-TNF α medication, however, the risks and benefits, including the uncertainty about these medications, must be discussed.

The recommendations of the European Crohn's and Colitis Organization state that "the greatest risk to mother and fetus during pregnancy is active disease, and not the medication used to treat it".⁵⁸ They recommend continuing anti-TNF α therapy for women with Crohn's disease due to the high risk of relapse and ensuing pregnancy complications. They recommend discontinuing the anti-TNF α medication in the middle of the third trimester, however, to diminish the exposure to the fetus prior to delivery. Due to the high rate of IgG transfer near term, babies have been found to have similar blood levels of infliximab to the mother. By discontinuing this drug 8 to 10 weeks prior to delivery, the baby will likely be born with no or minimal serum levels, thus avoiding immunosuppression in a young infant.

Though there are some suggestive data that certolizumab does not cross the placenta as easily as the IgG derived drugs, this is still a preliminary finding that has not been well confirmed.

Breastfeeding

Data from actively breastfeeding patients confirms that low levels of IgG anti-TNF α medication transfer into human milk. The number of patient reports, however, is limited. After discussion of the risks and benefits, some patients decide to restart anti-TNF α medication following delivery. This can be particularly beneficial in women with rheumatoid arthritis who will often flare in the weeks following delivery. By restarting an anti-TNF α medication soon after delivery, this flare may be avoided.

Summary

Though the human clinical data on the use of anti-TNF α medications during pregnancy and lactation are limited, what is available is reassuring. Despite the collection of congenital anomalies reported to the FDA, prospective cohorts of exposed pregnancies have not found an increased rate of anomalies. *In utero* exposure, particularly close to delivery, may result in an infant born with anti-TNF α medications detectable in the serum. For this reason, it may be prudent to discontinue the drug several half-lives prior to expected delivery. In addition, these infants should be monitored closely for infection. It is important that all women who take anti-TNF α medications during or following pregnancy understand the potential risks

as well as the absence of confirmatory data demonstrating the safety of these drugs. In women with severe inflammatory disease that cannot be managed with better documented medications, however, anti-TNF α medications may improve the health of the mother, and thus the fetus.

Disclosure

The author declares no conflicts of interest.

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