

Review

Safety of Tumor Necrosis Factor Inhibitors during Pregnancy and Breastfeeding

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Received: 12 April 2012

Accepted: 6 August 2012

Published: 21 September 2012

Keywords: tumor necrosis factor (TNF) inhibitors; uveitis; pregnancy; breastfeeding

Citation: Raja H, Matteson EL, Michet CJ, Smith JR, Pulido JS. Safety of Tumor Necrosis Factor Inhibitors during Pregnancy and Breastfeeding. *Trans Vis Sci Tech.* 2012;1(2):6, <http://tvstjournal.org/doi/full/10.1167/tvst.1.2.6>, doi:10.1167/tvst.1.2.6

Purpose: Tumor necrosis factor (TNF) inhibitors are useful in the treatment of numerous inflammatory and immunologic disorders. Since many of these conditions occur in women of childbearing age, safety during pregnancy and breastfeeding is of considerable importance.

Methods: This paper is a review of the literature on the safety of TNF inhibitors during pregnancy and breastfeeding published between 2001 and 2011.

Conclusions: TNF inhibitors do not appear to be associated with a high risk of teratogenicity or intrauterine death. However, a small magnitude increase in risk cannot be ruled out given the paucity of data on the subject. Although TNF inhibitor use may be associated with a higher rate of preterm delivery, this may in fact be due to an active, underlying disease. Therefore, the decision to use these medications should be made on a case-by-case basis. If the disease cannot be managed with first line agents, TNF inhibitors may be helpful in reducing the number of disease exacerbations. Nevertheless, when using TNF inhibitors, it is prudent to discontinue treatment around the third trimester when transfer across the placenta is greatest and to restart postpartum.

Introduction

Commercially available tumor necrosis factor (TNF) inhibitors (e.g., adalimumab, certolizumab, etanercept, golimumab, and infliximab) have been found to be useful in the treatment of noninfectious inflammatory diseases, including inflammatory bowel disease (IBD),¹ rheumatoid arthritis (RA),^{2,3} and psoriatic arthritis (PsA).⁴ Their use is especially valuable in refractory disease, when first line agents have failed or caused intolerable side effects. In these cases, TNF inhibitors may be highly effective in reducing the number of disease exacerbations.^{1–4} For a few indications, including the management of moderate to severe RA, anti-TNF agents are also Food and Drug Administration (FDA) approved as initial therapy. Given the increasing use of these drugs in managing immunologic disorders, many of which occur in women of childbearing age, safety during

pregnancy is of concern. This is a review of the literature on the subject of safety of TNF inhibitors during pregnancy and breastfeeding published within the last 10 years. Particular attention is paid to adalimumab, infliximab, and etanercept, as these drugs have been the subject of the majority of published research in this area to date.

Methods

Literature Review

To accomplish as current a review of the literature as possible, we limited our search to articles published in peer-reviewed journals within the last 10 years (2001–2011). Articles were identified between September 1, 2011, and October 1, 2011, by performing a series of PubMed searches using the following Boolean search terms: “TNF inhibitors

AND pregnancy,” “adalimumab AND pregnancy,” “certolizumab AND pregnancy,” “etanercept AND pregnancy,” “golimumab AND pregnancy,” “infliximab AND pregnancy” “TNF inhibitors AND breastfeeding” and “TNF inhibitors AND placental transfer.” Original studies and case presentations, which reported the use of one or more TNF inhibitors in pregnancy or during breastfeeding, including outcomes, were included in our review.

Tumor Necrosis Factor-Alpha and Lymphotoxin

TNF- α is an inflammatory cytokine released by many cell types, including macrophages, in the setting of an immune response. As an endogenous pyrogen, TNF- α has multiple activities that contribute to the initiation and perpetuation of inflammation. Although its role in gestation has yet to be completely elucidated, TNF- α may serve two apparently competing roles.⁵ On one hand, it mediates a stress response within the embryo, triggering inflammatory loss of pregnancy if the embryo sustains structural damage. On the other hand, TNF- α is also believed to play a role in protecting the embryo against toxins during development.^{6,7} By disrupting the protective effects of TNF- α , TNF blockers could be associated with an increased risk of congenital anomalies.

Lymphotoxin, previously known as TNF- β , exerts a similar downstream effect by binding the same receptors as TNF- α . Lymphotoxin activates neutrophils and macrophages and alters expression of vascular endothelial adhesion molecules to help mobilize inflammatory cells. Although not a principal target of TNF blockers, lymphotoxin is targeted by etanercept, a soluble form of the TNF receptor that binds and inactivates both TNF- α and TNF- β .⁸

TNF Inhibitors

As a whole, TNF inhibitors are classified as Pregnancy Category B drugs by the FDA. According to this classification system, Category B comprises those drugs that reproductive studies in animals have failed to demonstrate risk to the fetus and that no well-controlled studies exist in pregnant women, or that reproductive studies in animals have demonstrated risk to the fetus, but that well-controlled studies in pregnant women have failed to substantiate this risk. Of note, infliximab has not been studied in animal reproductive models because this chimeric murine-human immunoglobulin G (IgG) 1 monoclonal antibody cross-reacts only with TNF- α in humans

and chimpanzees. However, no embryotoxicity, teratogenicity, or maternal toxicity was detected in developmental toxicology studies performed in mice using a functionally similar antibody directed at mouse TNF- α .⁹ Table 1 provides a summary of the various TNF inhibitors as adapted from Micromedex Healthcare Series.⁸

Given the obvious ethical limits to conducting a double-blind, controlled study to accurately assess the risks of the TNF blockers in pregnancy, there is a paucity of data on the safety of these drugs during pregnancy and breastfeeding. Since much of the data we have comes from case reports and case series with small sample sizes, the findings cannot be easily extrapolated. Some recent publications have presented data collected by voluntary reporting about adverse events associated with TNF inhibitors by patients and health care providers. Such methodology is confounded by recall and reporting bias, and often provides incomplete details about disease severity, comorbidities and/or concomitant medication use.

Transfer of TNF Inhibitors across the Placenta and into Breast Milk

The TNF inhibitors vary considerably in the degree that they cross the placental barrier from mother to fetus and enter breast milk during lactation. Infliximab, the most extensively studied TNF inhibitor in this regard, is a chimeric murine-human IgG1 monoclonal antibody against TNF- α . In studies designed to measure the degree of placental transfer of infliximab, drug levels in cord blood were between 2- and 3-fold higher than in maternal serum in three out of four infants from an IBD-complicated pregnancy.¹⁰

However, findings pertaining to postpartum levels of infliximab were less clear. One case report showed that infliximab levels are low, but detectable, up to 6 months postpartum in the blood of infants exposed to infliximab during pregnancy.¹¹ Yet, in apparent conflict with these findings, another case series reported undetectable levels of infliximab in infants born to mothers treated with the drug prior to conception through approximately 30 weeks gestation.¹²

The detection of infliximab in neonates and the observation that placental transfer of IgG is greatest during the third trimester have led to the general recommendation that treatment with infliximab should be concluded prior to the third trimester.¹³ On the other hand, studies consistently show no

Table 1. Summary of TNF Inhibitors as Adapted from Micromedex Healthcare Series (Internet Database), (Updated Periodically)

Drug	Structure	Active Against TNF-?	Active Against Lympho-toxin?	Mechanism(s) of Action	FDA Approved Indications
Adalimumab	Human mono-clonal TNF- α antibody	Yes (blocks TNF- α from interact-ing with TNF cell surface re-ceptors p55 and p75)	No	Lyses cells expressing surface TNF- α in vi-tro. Modulates TNF regula-tion of vascular en-dothelial adhesion molecules. Increases CRP, ESR, IL6, and MMP-1 and MMP-3	AS CD (moderate to severe) if conventional thera-py is insufficient. JIA CPP (moderate to severe) PA RA (moderate to severe)
Certolizumab Pegol	PEGylated Fab fragment of humanized TNF- α monoclonal antibody	Yes	No	Interferes with prosta-glandin, inflammato-ry mediators, IL1, PAF, and NO	CD RA (moderate to severe)
Etanercept	Dimeric solu-ble form of TNF receptor	Yes	Yes	Modulates TNF regula-tion of serum cyto-kine levels, serum MMP levels, and vascular endothelial adhesion molecule expression	AS JIA (moderate to severe) CPP (moderate to severe) in patients who may warrant systemic thera-py or phototherapy PsA RA (moderate to severe)
Golimumab	Human mono-clonal TNF- α monoclonal antibody	Yes (soluble and transmembrane forms)	No		AS PsA +/-MTX RA (moderate to severe) in combination with MTX
Infliximab	Chimeric hu-man-mouse immuno-globulin IgG1-kappa	Yes (soluble and trans-membrane forms)	No		AS CD Fistulizing CD (moderate to severe) if conventional thera-py is insufficient CPP PsA RA (moderate to severe) in combination with MTX UC (moderate to severe) if conventional thera-py is insufficient

Table 1. Continued.

AS, Ankylosing Spondylitis; CPP, Chronic Plaque Psoriasis; CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate; IL, Interleukin; JIA, Juvenile Idiopathic Arthritis; MMP, Matrix Metalloproteinase; NO, Nitric Oxide; PAF, Platelet Activating Factor; UC, Ulcerative Colitis.

passage of infliximab to the infant during breastfeeding as evidenced by stable serum levels in the breastfeeding infant and undetectable levels of infliximab in breast milk.^{11,12,14}

Like infliximab, adalimumab is a monoclonal IgG1 antibody against TNF- α . However, unlike infliximab, it is a fully humanized antibody. Because of similarities in their structure, adalimumab is presumed to have a comparable degree of transfer across the placental barrier as infliximab.¹⁵ However, at this time, serum levels of adalimumab cannot be measured commercially, so data on adalimumab levels in maternal and infant serum are lacking.¹⁶ According to an assessment of the safety and efficacy of various biologic therapies used in pregnant women with Crohn's disease (CD) by the World Congress of Gastroenterology, use of adalimumab in pregnancy is challenging due to its frequent dosing schedule. Discontinuing treatment with adalimumab early in the third trimester before immunoglobulin transfer across the placenta is at its greatest is also particularly difficult without potentiating a flare. For that reason, it was recommended that adalimumab be stopped approximately 8 to 10 weeks prior to the delivery date. No safety information is available on the subject of adalimumab and lactation.¹⁶

In contrast to infliximab and adalimumab, certolizumab is a PEGylated Fab fragment of the anti-TNF- α antibody. As a result of this structural difference, certolizumab crosses the placenta slowly, through the process of diffusion rather than by active transport across a membrane receptor as occurs with whole antibodies.¹⁷ In a study performed in rats, levels of anti-TNF agent in breast milk and pup serum were lower if mothers received the Fab antibody fragment rather than whole antibody.¹⁸ These findings were supported by a report of a 22-year-old woman with IBD initiated on subcutaneous certolizumab in the second trimester, in whom maternal serum levels of certolizumab far exceeded the concentration in cord blood, suggesting minimal in utero transfer of certolizumab.¹⁹

Similarly, cord blood levels of etanercept have been shown to be lower than maternal serum levels in women exposed to the drug during pregnancy.²⁰

Although etanercept may be detected in breast milk at a low concentration, serum levels in the nursing infant were reported to decline rapidly (i.e., undetectable at 12 weeks) despite regular breastfeeding in the case of a 40-year-old woman with RA treated with etanercept, indicating that little, if any, drug passes to the infant during lactation.²¹ Slightly higher, but still minimal, levels of etanercept were noted in breast milk in another patient after pulsed treatment with the drug postpartum.²² See [Table 2](#) for a summary of original papers describing the use of TNF inhibitors during breastfeeding.

Adverse Effects of TNF Inhibitors during Pregnancy

A number of studies have suggested that the use of TNF inhibitors during pregnancy is not associated with teratogenic effects. A registry study reported on pregnancy outcomes of 33 women with RA who were treated with TNF antagonists and followed prospectively during pregnancy in comparison to non exposed disease matched women and otherwise healthy women, and found no clear difference in the rate of major malformations between the three groups.²³ However, neonates born to mothers in the group exposed to TNF antagonists and in the disease matched control group were significantly more likely to be born preterm. These findings have been recapitulated by an ongoing registry study by the same group, which prospectively followed pregnant women with RA treated with adalimumab adding comparison groups.²⁴

In a second study of pregnancy outcomes in 10 women treated with infliximab, all pregnancies resulted in live births without congenital malformations, intrauterine growth retardation (IUGR), or infants small for gestational age (SGA).²⁵ While there were three preterm deliveries and two cases of neonatal illness, no association with infliximab use could be made due to concomitant use of other biologic agents in several of the women. Numerous case reports and other small case series have documented the use of anti-TNF agents during pregnancy without complication ([Table 3](#)).

Table 2. Original Articles on TNF Inhibitors and Breastfeeding and Transfer across the Placenta

Reference	Drug	Study Size	Timing of Drug Administration	Main Findings
19	Certolizumab	22-year-old with IBD	T2–postpartum	Healthy delivery with low cord blood levels.
20	Etanercept	34-year-old with AS	4 years before conception–postpartum	Healthy delivery with low cord blood levels and undetectable infant serum levels despite breastfeeding.
22		34-year-old with RA	Postpartum	Low breast milk levels after treatment with etanercept.
21		40-year-old with RA	Shortly before conception–postpartum	Healthy delivery with low cord blood levels and decline in infant serum levels despite breastfeeding.
12	Infliximab	3 patients, ages 24–32 years with CD	Maintenance therapy through 25–30 weeks gestation and restarted postpartum	3 healthy pregnancies (1 preterm) with undetectable levels in breast milk and infant serum.
14		1 patient: 22-year-old with CD	12 weeks gestation–postpartum	Healthy delivery with undetectable levels in breast milk.
11		32-year-old with CD	5 doses throughout pregnancy	Healthy delivery with undetectable levels in breast milk and steady decline in infant serum levels during the first 6 months postpartum despite breastfeeding.
10		4 patients, ages 19–31 years, with IBD	Before pregnancy–30 weeks gestation	Healthy deliveries with variable cord blood levels in 3 of 4 infants and undetectable levels in 1 infant. 1 infant with detectable levels of infliximab in the cord blood was born with polydactyly. At 3–6 month follow up postpartum, there was no increased risk of infection and an appropriate antibody response to nonliving vaccines.

ELISA, Enzyme-Linked Immunosorbent Assay; T2, second trimester.

With regard to the potential abortifacient effects of TNF inhibitors, two studies suggest no significant difference in the rates of miscarriage between infliximab-exposed and infliximab-naïve women.^{28,29} Additionally, a recent observational study including 212 subjects implied that overall abortion rates in women treated for IBD did not differ significantly regardless of exposure history to TNF inhibitors.²⁶

Furthermore, regardless of whether the women received anti-TNF therapy, abortion rates did not differ from rates amongst healthy controls. There was, however, an increased risk of preterm delivery in women treated with anti-TNF agents compared with healthy controls due either to the underlying disease, the use of TNF blockers, or a combination thereof.

In contrast to these reports, a recent study

Table 3. Original Articles and Case Presentations on the Safety of TNF Inhibitors during Pregnancy

Reference	Study Type	Study Size	Drug
23	OTIS Registry Study prospectively following pregnant RA patients, adding controls	33 patients with RA receiving anti-TNF therapy compared with disease matched controls ($n = 77$) and healthy controls ($n = 50$)	Etanercept ($n = 29$) Infliximab ($n = 4$)
26	Observational study with IBD patients	42 pregnancies with IBD exposed to TNF antagonist compared with 23 nonexposed pregnancies prior to IBD diagnosis, 78 pregnancies after diagnosis of IBD but before starting a TNF antagonist, 53 pregnancies with indirect exposure to a TNF antagonist, and 56 healthy controls.	Adalimumab Infliximab
27	Review of pregnancy outcomes from the BSRBR	140 pregnancies, 130 of which were exposed to anti-TNF therapy at or before conception	Not specified
5	Retrospective review of reported adverse events with anti-TNF agents from the FDA database	Review of > 120,000 reported adverse events with anti-TNF agents	Adalimumab Etanercept Infliximab
28	Retrospective review of BSRBR data	32 total pregnancies. 23 pregnancies in patients mostly with RA, directly exposed to an anti-TNF agent at time of conception. The other 9 patients discontinued anti-TNF therapy at a mean length of 5 months before conception	Adalimumab ($n = 3$) Etanercept ($n = 17$) Infliximab ($n = 3$)
29	Retrospective chart review of infliximab safety database (US and Europe)	96 pregnancies complicated by CD, UC, or RA, exposed to infliximab with known outcomes compared with historic healthy controls and disease matched controls not receiving infliximab	Infliximab
25	Retrospective chart review	10 patients with CD	Infliximab

Table 3. Extended

Reference	Timing of Drug Administration	Main Findings
23	T1	Significant increase in the rate of preterm delivery in the anti-TNF and non exposed disease matched groups relative to healthy controls. No clear difference in the rate of malformations between all 3 groups.
26	Direct exposure = within 3 months of conception and/or during pregnancy until T2. Indirect exposure = before, but not during, pregnancy	Increased risk of preterm delivery in the direct exposure group compared with healthy controls. No significant difference in spontaneous abortion rates between IBD pregnancies regardless of TNF exposure and healthy controls.
27	At conception (+/-methotrexate or leflunomide), before conception, or not at all	Rate of spontaneous abortion was highest in the group exposed at conception followed by exposure prior to conception, and no exposure. Cases of premature delivery, neonatal death, and intrauterine death were also reported.
5	Unclear	61 reported congenital anomalies in 41 children born to women taking a TNF inhibitor. 24 of 41 infants had 1 or more VACTERL-associated malformations. Miscarriages were also reported in women exposed to etanercept.
28	All but 2 patients stopped taking medications during T1.	6 of 23 pregnancies resulted in miscarriage in women directly exposed to a TNF inhibitor at conception. No major malformations, 1 premature delivery, 1 low birth weight infant, and 1 C-section for fetal distress were reported. In the group of women who discontinued anti-TNF therapy before conception, 1 case of fetal demise in utero was reported in a patient who discontinued MTX 4 months before conception.
29	Variable	Rates of live births, miscarriages, and therapeutic terminations were similar between all 3 groups. Cardiac malformation, preterm delivery, complicated neonatal course, intestinal malrotation, and an infant with hypothyroidism and developmental delay, were reported. Some of these cases occurred in pregnancies complicated by known teratogenic medication use, maternal infection, etc.
25	8 patients treated throughout pregnancy, 1 treated in T3, and 1 treated in T1.	No malformations, IUGR, or SGA neonates. Preterm delivery, low birth weight infancy, and neonatal illness were reported.

Table 3. Continued Extended

Reference	Study Type	Study Size	Drug
30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41	Multiple case reports and 1 case series, compiled	15 total patients, ages 22–36 years, with CD, PsA, RA, or TA	Adalimumab, Certolizumab, Etanercept and/or Infliximab
42	Case Report	29-year-old with CD	Infliximab
43	Case Series	4 patients, ages 27–40 years, with seronegative erosive JIA, RA, or polyarthritis consistent with lupus	Etanercept (<i>n</i> = 1) Infliximab (<i>n</i> = 3)
44	Case Report	26-year-old with CD	Infliximab
45	Case Report	30-year-old with CD	Infliximab
46	Case Report	36-years-old with UC	Infliximab
47	Case Report	28-year-old with psoriasis	Etanercept
48	Case Report	28-years-old with CD	Infliximab
49	Case Report	2 patients, ages 23- and 31-year-old, with CD	Infliximab
50	Prospective case series	3 patients, ages 21, 37, and unspecified years	Adalimumab (<i>n</i> = 1) Etanercept (<i>n</i> = 2)
51	Case report	26-year-old with CD	Infliximab
52	Case report	24-year-old with SLE	Etanercept
53	Case series	15 pregnancies in patients 22- to 42-years-old, with JIA, PsA, RA, or SpA	Adalimumab (<i>n</i> = 2) Etanercept (<i>n</i> = 10) Infliximab (<i>n</i> = 3)
54	Case report	29-years-old with RA	Infliximab

CAH, congenital adrenal hyperplasia; c/b, complicated by; ICU, Intensive Care Unit; PFO, Patent Foramen Ovale; SLE, Systemic Lupus Erythematosus; SpA, Spondyloarthritis; T1, first trimester; T3, third trimester; TA, Takayasu's Arteritis; UTI, urinary tract infection.

Table 3. Continued Extended

Reference	Timing of Drug Administration	Main Findings
30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41	Variable	Healthy term deliveries
42	3 months before pregnancy	Healthy preterm delivery
43	Before conception– birth	2 preterm and 2 full term healthy pregnancies
44	Before pregnancy– postpartum	Healthy preterm delivery
45	Before conception– birth	Premature delivery c/b low birth weight
46	T2	Pregnancy c/b growth retardation, depressed fetal heart rate and SGA diagnosis in patient with active disease
47	Years before conception– birth. Pregnancy followed dosage increase.	Preterm delivery c/b tracheal atresia and tracheoesophageal fistula, esophageal atresia, imperforate anus, PFO, hypospadias, and thoracic vertebral anomaly.
48	Before conception– birth	Healthy preterm delivery. Vaccinated with BCG vaccine at 3 months and died from complications at 4.5 months.
49	Before conception– birth	1 premature delivery c/b low birth weight, acute respiratory distress, and prolonged ICU stay. Normal development at 8 months.
50	Before conception	Preterm delivery in 1 pregnancy exposed to adalimumab, and neonatal jaundice, UTI and CAH (also in father) in 1 pregnancy exposed to etanercept.
51	At conception	Preterm delivery c/b intracerebral and intrapulmonary bleeding and neonatal death
52	Before conception and T2–birth	Healthy delivery at 36 weeks; pregnancy complicated by pre-eclampsia at 26 weeks.
53	Variable	12 full term deliveries and 2 miscarriages
54	Before conception–5 weeks	T1 miscarriage. Concomitant MTX, folic acid, and diclofenac before pregnancy.

following outcomes of 130 pregnancies in 118 women with RA concluded that the rate of spontaneous abortion was higher in women exposed to anti-TNF therapy at conception than those exposed before conception or not at all.²⁷ It is unclear if these findings were statistically significant.

Finally, in a recent paper observing patterns of medication use in 393 pregnancies complicated with RA, 281 pregnancies ended in live births versus 75

that ended in spontaneous abortions.⁵⁵ Of these 281 live births, 35 of 281 (12.5%) were exposed to biologic disease-modifying antirheumatic drugs (DMARDs) during pregnancy, and of the 75 spontaneous abortions, a similar proportion (9/75 [12%]) was exposed to biologic DMARDs. The disparity in exposure rate was considerably different with regard to the use of category D and X nonbiologic DMARDs in the group resulting in live delivery

Table 4. Comparison of the Difference in Exposure Rate between Nonbiologic DMARDs (Category D or X) and Biologic DMARDs in Pregnancies Resulting in Live Delivery and Spontaneous Abortion^a

	Pregnancies Resulting in Live Delivery (281)	Pregnancies Resulting in Spontaneous Abortion (75)
No. exposed to nonbiologic DMARDs (category D or X)	11 (3.9%)	6 (8%)
No. exposed to biologic DMARDs	35 (12.5)	9 (12%)

^aBased on a Study by Kuriya, et al.⁵⁵

(3.9%) compared with the group resulting in spontaneous abortion (8%) (Table 4). Furthermore, the authors showed that use of biologic DMARDs tend to decrease over the course of the pregnancy because of a lack of data on the safety of TNF inhibitors.³⁰

One of the largest studies reviewed more than 120,000 adverse events reported to the US FDA between 1999 and 2005 in relation to the use of etanercept, infliximab, and adalimumab.⁵ Conducting a search of the database for adverse outcomes associated with pregnancy, the authors identified reports of 61 congenital anomalies in 41 children born to mothers taking a TNF inhibitor. The most common anomalies were referring to the non random grouping of congenital malformations including vertebral, anal, cardiac, tracheo-esophageal, renal, and limb defects (VACTERL). However, 41% of women were also taking concomitant medications, including methotrexate (MTX), a Pregnancy Category X drug with known teratogenic potential.

The authors acknowledged several limitations of their study. Foremost, since this database cataloged only adverse events in patients treated with a TNF blocker and was reliant on patient or provider reporting, it is unknown how many women were ultimately treated to generate this number of adverse events. Additionally, since the data relied on voluntary reporting, there was potential for reporting bias. The lack of information concerning the patients' other comorbidities was an additional limitation. Findings consistent with an increased rate of vertebral, anal, tracheo-esophageal, and renal anomalies (VATER) and VACTERL-associated defects in women treated with TNF blockers was previously reported by the same authors in a patient with psoriasis treated with etanercept.⁴⁷

Complications have also been reported in the postnatal period following the use of TNF inhibitors during pregnancy. One case report describes a 28-year-old woman with IBD treated with infliximab whose infant was born without complication and, at 3 months of age, was immunized with the bacille

Calmette-Guerin (BCG) vaccine. The infant died from clinically diagnosed disseminated BCG, a rare complication of the live, attenuated vaccine thought to relate to maternal use of infliximab during pregnancy, which has an unknown effect on immune system development and function in infants.⁴⁸

Another publication reported on an infant born prematurely at 24 weeks gestation to a 26-year-old woman with IBD treated with infliximab, as well as azathioprine, metronidazole, and mesalamine, during pregnancy.³³ The neonate developed intracerebral and intrapulmonary bleeding and died 3 days after birth. This case illustrates the difficulty in identifying potential drug side effects in the presence of concomitant medication use. Additional cases affirm the difficulty in identifying potential drug side effects when patients are taking multiple medications, some of which are known to have teratogenic effects⁵⁴ or when pregnancy is complicated by an active underlying disease.^{46,49} Table 3 provides a summary of the key studies summarized in our review.

Conclusion

In conclusion, TNF inhibitors are risk category B drugs in pregnancy that, based on our evaluation of the available literature, do not pose high risk of teratogenicity or intrauterine death. A small magnitude increase in risk cannot be ruled out given the paucity of data on the subject. Although TNF inhibitor use may be associated with a higher rate of preterm delivery, this may in fact be due to the active underlying disease. The decision to use these drugs should, therefore, be made on a case-by-case basis, taking into account severity of disease and the potential benefits and harms of using immunomodulators versus contending with the inherent risks to the pregnancy caused by the inflammatory disease. Questions regarding activity of the disease, the potential for organ- or life-threatening complications, and available alternative medications must be ad-

dressed when a patient desires to become pregnant or has become pregnant while taking a TNF inhibitor. If the disease is quiescent or can be managed with low dose prednisone and a medication such as azathioprine or sulfasalazine, the treating physician may recommend against continuation of the anti-TNF agent. On the other hand, if the disease is active and an anti-TNF agent is the best therapeutic alternative for the patient, continuing the medication may be the best option. If TNF inhibitors are used during pregnancy, discontinuing use at the beginning of the third trimester is prudent, as transplacental transfer of IgG is greatest after this time. If treatment with TNF inhibitors must be continued in the long term, it appears safe to do so after delivery. It is important to emphasize that an assessment of the risks and benefits of these medications during pregnancy should be carefully discussed with the patient

Acknowledgments

The authors would like to thank Douglas Jabs, Department of Ophthalmology, Mount Sinai School of Medicine, and Russell Van Gelder, Department of Ophthalmology, University of Washington, for their insights during the preparation of this manuscript.

Disclosure: **H. Raja**, None; **E.L. Matteson**, None; **C.J. Michet**, None; **J.R. Smith**, None; **J.S. Pulido**, None

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