Review

Can Tumor Necrosis Factor Inhibitors Be Safely Used in Pregnancy?

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ABSTRACT. ***Objective.*** We review available safety data for use of currently approved tumor necrosis factor (TNF) inhibitors during pregnancy and lactation and suggest guidelines for use of these agents among women of reproductive age.

Method. Although regulatory agencies encourage the inclusion of pregnant women and those of child-bearing age in randomized controlled trials, pregnant and lactating women have universally been excluded from studies because of unknown or potential risks to the fetus. Thus, strong evidence-based treatment recommendations during pregnancy are usually lacking and safety information is derived from voluntary reports of adverse events during postmarketing surveillance or via uncontrolled, observational studies, reviewed here.

Results. Uncommon adverse pregnancy outcomes observed with TNF inhibitor therapy appear to approximate those seen in women not receiving such therapy and may include premature birth, miscarriage, low birthweight, hypertension, and preeclampsia. There are rare reports of fetal malformations or congenital anomalies in patients exposed to TNF inhibitors during conception or pregnancy. However, the incidence of these events appears to be far below the 3% rate of congenital anomalies in the general population.

Conclusion. If the activity or disease severity precludes the cessation of a TNF inhibitor and/or DMARD, uncontrolled observations suggest that conception and early pregnancy are not adversely affected by use of TNF inhibitors. Nearly 70% of pregnant patients can discontinue their TNF inhibitor early in the pregnancy (or with determination of pregnancy) without augmenting maternal or fetal risks. (J Rheumatol First Release Dec 15 2009; doi:10.3899/jrheum.090536)

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Autoimmune disorders such as inflammatory arthritis (IA) and inflammatory bowel disease (IBD) disproportionately affect women of childbearing age. Despite treatment advances with disease-modifying antirheumatic drugs (DMARD), medical management of women with inflammatory conditions remains limited by the potential toxicities imposed upon the unborn child. Among the new class of biologic DMARD, tumor necrosis factor (TNF) inhibitors have proven to be highly effective in reducing disease activity and damage while maintaining function and quality of life in conditions like rheumatoid arthritis (RA) and Crohn's disease (CD). We review the available safety data of currently approved TNF inhibitors during pregnancy and lactation and suggest guidelines for the use of these agents among women of reproductive age.

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EFFECT OF PREGNANCY ON DISEASE ACTIVITY

Although RA is thought to improve during pregnancy, some women continue to have significant synovitis. Roughly 70% to 80% of women with RA experience an improvement in their arthritis symptoms during pregnancy[1,2]. The decrease in disease activity generally starts in the first trimester and lasts through the immediate postpartum period. Disease characteristics (duration, functional class, rheumatoid factor positivity) do not appear to predict whether a patient will remit or improve during pregnancy[3]. In a nationwide prospective study of 84 patients with RA in The Netherlands, Disease Activity Score in 28 joints (DAS28) and medication use were determined before conception, at

each trimester of pregnancy, and at 6, 12 and 26 weeks postpartum. Improvement and deterioration were determined by assessing changes in DAS28 and by applying the European League Against Rheumatism (EULAR) response criteria. Disease activity decreased with statistical significance ($p < 0.035$) during pregnancy and increased postpartum. In patients with at least moderate disease activity in the first trimester (n = 52), at least 48% had a moderate response during pregnancy according to EULAR-defined response criteria. In patients with low disease activity in the first trimester (n = 32), disease activity was stable during pregnancy. Thirty-nine percent of patients had at least a moderate flare postpartum according to revised EULAR response criteria. Less medication was used during pregnancy compared with before conception and compared with postpartum[4]. Not all studies, however, have found improvement in symptoms with pregnancy. As an example, one report that evaluated the clinical course of 140 pregnant women with RA noted only minimal improvement in Health Assessment Questionnaire (HAQ) scores and joint symptoms, and postpartum flares were also observed[5].

The effect of RA on pregnancy has not been thoroughly investigated. Kaplan and Diamond suggested that RA has no significant effect on the patient's ability to have a normal pregnancy, delivery, and infant[6]. Nelson, *et al* found no evidence of infertility in patients with RA, but there was diminished fecundability (the probability to achieve a pregnancy within one menstrual cycle)[7]. The same group reported a prospective case-control study that showed no adverse pregnancy outcomes in women who later developed RA[8].

In a nationwide project[9] that attempted to estimate the number of obstetric hospitalizations, deliveries, and cesarean deliveries in women with systemic lupus erythematosus (SLE), RA, pregestational diabetes mellitus, and the general obstetric population in the United States, it was found that women with RA had significantly increased rates of hypertensive disorders compared with the general obstetric population (11.1% vs 7.8%, respectively), longer hospital stays, and significantly higher risk of cesarean delivery. Women with RA were significantly older than women in the general obstetric population; however, disparities in the risk of adverse outcomes of pregnancy remained statistically significant after adjustment for maternal age[9]. Pregnancy outcomes included length of hospital stay, hypertensive disorders including preeclampsia, premature rupture of membranes, and intrauterine growth restriction[9]. While it seems that RA does impair pregnancy outcomes, no studies have examined if the inflammatory activity of RA influences fecundity.

SAFETY DESIGNATION OF DMARD DURING PREGNANCY

Clinical trials are frequently designed to measure drug safety for most of the general population. Although regulatory agencies encourage the inclusion of pregnant women and those of childbearing age in randomized controlled trials, pregnant and lactating women have universally been excluded from studies because of unknown or potential risks to the fetus[10]. Thus, strong evidence-based treatment recommendations during pregnancy are usually lacking and safety information is derived from voluntary reports of adverse events during postmarketing surveillance or via uncontrolled observational studies[11]. Problems with such reports include recall and publication bias, the lack of uniform data collection, or an inadequate comparator population. In addition, most clinicians are unfamiliar with interpreting maternal and fetal study outcomes or identifying limits of reproductive data[12]. Accordingly, many physicians rely on summary information, such as the US Food and Drug Administration (FDA) pregnancy safety categories to guide therapeutic decisions (Table 1). Despite the lack of human-derived data, product labels list all the TNF inhibitors as Class B, indicating that no well controlled studies have been conducted in pregnant women. Unlike methotrexate, guidelines about timing of discontinuation and reinitiation of these agents have not been published[13].

CLINICAL STUDIES OF TNF INHIBITOR USE IN PREGNANCY

TNF inhibitors have proven to be successful in the treatment

Table 1. Pregnancy safety categories and examples of immunosuppressive agents (adapted from FDA Consumer Magazine[17]).

Category	Definition	Drug
A	Well controlled studies of pregnant women have failed to demonstrate fetal risk	
B	Animal reproduction studies have failed to demonstrate fetal risk and there are no well controlled studies in pregnant women	Infliximab Etanercept Adalimumab Certolizumab
C	Animal reproductive studies have shown an adverse fetal effect but there are no well controlled studies in humans; potential benefits may warrant use of the drug in pregnant women	Prednisone Hydroxychloroquine
D	There is positive evidence of human fetal risk based on data from investigational or marketing experience in humans; potential benefits may warrant use of the drug in pregnant women despite potential risks	Azathioprine
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on investigational or marketing experience; the risks involved clearly outweigh potential benefits	Methotrexate Leflunomide

Table 2. Reports of pregnancy outcome among women treated with TNF inhibitors.

Study Type	Disease	No. of Pregnancies	No. of Live Births (%)	No. of Miscarriages (%)	No. of Therapeutic Abortions (%)	Congenital Abnormalities (% of live births)
TNF inhibitors in general						
Registry[18]	RA	22	20 (91)	2 (9)	—	0
Registry[19,20]	IA	58	30 (52)	21 (36)	6 (10)	4 (7)
Registry[21,22]	IA	33	28 (85)	4 (12)	1 (3)	1 (3)
Survey[23]	IA	454	387 (85)	25 (6)	5 (1)	0
Infliximab						
Case reports[24]	CD	10	10 (100)	0	0	0
Registry[25]	CD	36	26 (72)	5 (14)	4 (11)	1 (4)
Registry[26]	CD	10	6 (60)	3 (30)	1 (10)	0
Registry[27,28]	RA, CD	627	452 (72)	100 (16)	72 (11)	14 (3)
Etanercept						
Registry[29,30]	RA	100	94 (94)	6 (6)	0	8 (9)
Survey[31]	RA	8	6 (75)	1 (13)	1 (13)	0
Case reports[32]	RA, IA	15	12 (80)	2 (17)	1 (7)	0
Case reports[33]	RA, IA	5	3 (60)	2 (40)	0	0
Adalimumab						
Registry[29,30]	CD, IA	30	27 (90)	3 (10)	0	2 (7)
Case report[35]	CD	1	1 (100)	0	0	0
Case report[36]	CD	1	1 (100)	0	0	0
Case report[37]	CD	1	1 (100)	0	0	0

RA: rheumatoid arthritis; IA: inflammatory arthritis; CD: Crohn's disease.

of several autoimmune disorders. To date, they have received regulatory approval for CD, ulcerative colitis, RA, ankylosing spondylitis (AS), psoriasis and psoriatic arthritis (PsA), and juvenile idiopathic arthritis (JIA). Treatment of these conditions often requires prolonged therapy to achieve and maintain disease control or remission. Hence, since their introduction in 1998, TNF inhibitors have been prescribed to nearly 2 million people worldwide and have led to over $9 billion US in sales annually[14]. With growing use, an increasing number of fecund candidates will receive these drugs and confront the issue of pregnancy during the course of treatment.

Preclinical studies of TNF inhibitors have been performed as a requirement prior to human exposure. Safety assessments of infliximab have been limited due to its restricted cross-reactivity with only monkey and human TNF. Despite this, mouse models using an analogous TNF antibody have shown no adverse reproductive effects[15]. Similarly, no increased embryotoxicity or teratogenicity has been demonstrated in rats or rabbits given higher than approved doses of etanercept[16]. Few studies of adalimumab and certolizumab have been performed because of the lack of relevant animal models. However, available data do not suggest any impairment to fertility or reproduction[17]. Based on animal exposure data, all available TNF inhibitors have been designated as FDA category B concerning fetal risk.

Most reported outcomes of pregnancy in humans have come from patients with CD and RA. Small case reports and safety databases of infliximab were the earliest to report reproductive outcomes. Since then, newer prospective drug registries and surveys of physician practice have provided additional data on the safety of all TNF inhibitors (Table 2).

1. Infliximab

Although the outcomes of pregnancies with TNF inhibitors (predominantly infliximab) have been published, most are case reports (Table 2). The largest study of the outcome of pregnancy in patients receiving a TNF inhibitor involved infliximab for treatment of CD and RA[27]. In that study the infliximab safety database (maintained by Centocor Inc.) was queried for the outcome of pregnancy in women receiving infliximab. The results were compared to those of healthy pregnant women in the US population and pregnant patients with CD not exposed to infliximab.

The database identified 131 women with direct infliximab exposure and outcome data were available for 96 women, including 15 women in whom infliximab exposure occurred indirectly through exposure of male partners to the drug. The population comprised 82 patients with CD, 8 with RA, 1 with ulcerative colitis, and 3 unknown. The timing of exposure to infliximab could be calculated in 90 of 96 (94%) patients with available outcome information. Of patients in whom timing of exposure could be calculated, 29% were exposed only 3 months prior to conception and during the first trimester. The number of infliximab infusions ranged from 1 to 9. The outcome of 96 pregnancies revealed 67% live birth, 15% miscarriages, and 19% therapeutic abortions. Of the 68 live births, 5 infants were born

with complications. Fetal complications occurred either at the rate expected or may have been related to exposure to medications other than TNF inhibitors prescribed for the management of underlying disease. These results are similar to those expected for the general US population of pregnant women[38] or pregnant women with CD not exposed to infliximab[39]. There were several limitations in this study: the database relied upon voluntary reports to the manufacturer of infliximab, data were incomplete on the date of conception for some patients, and information regarding congenital abnormalities and birth defects was not reported consistently.

A large study was reported by Lichtenstein, *et al*[25] from the TREAT prospective registry of patients with CD, who may or may not have been treated with infliximab. Of the 5807 patients enrolled, 36 pregnancies were reported with prior infliximab exposure. The rates of miscarriage (11% vs 7.1%; p = 0.53) and neonatal complications (8.3% vs 7.1%; p = 0.78) were not significantly different between those receiving and not receiving infliximab.

Another smaller study involved a retrospective chart review of 10 women with CD[40]. The primary outcome measure was the occurrence of congenital malformations. Secondary outcome measures were the rate of premature birth, low birthweight and small for gestational age infants, intrauterine growth retardation, and cesarean section. Eight women received maintenance infliximab infusions throughout their pregnancy and 2 received their initial infusions during pregnancy. All 10 pregnancies resulted in live births. No infant had congenital malformation or growth retardation. Three infants were premature and one had low birthweight.

There are also multiple single case reports of infliximab use in pregnancy. There are 4 reports in CD, 3 of which resulted in live births, and 2 reports in RA, one of which ended in a live birth and one in miscarriage[26,40,41].

2. Etanercept

Several reports of the use of etanercept in pregnancy have been published. A large cohort of pregnant women exposed to TNF inhibitors was reported by Chambers, *et al* from the Organization of Teratology Information Services project (OTIS) RA in pregnancy study[29]. The OTIS RA in pregnancy project prospectively followed 33 pregnant women with first-trimester exposure to etanercept (n = 29) or infliximab (n = 4) between 1999 and 2004. The pregnancy outcome in the group treated with TNF inhibitors was compared with the outcome in 77 women with RA not receiving TNF inhibitors (RA control) and 50 women without RA (non-disease controls). In 29 pregnancies, spontaneous abortion occurred in 10.7% of the etanercept-exposed women and 25% of the infliximab-exposed women, 6.8% of RA controls, and 4.1% of non-disease controls. The overall rate of malformations in the TNF inhibitors group (3%) was similar to those in the 2 control groups (4.0% and 4.1%, respectively). Preterm delivery was significantly more common in the TNF inhibitors group and RA controls relative to the non-disease controls: etanercept 7/25 (28%), infliximab 2/3 (66.7%), RA controls 16/68 (23.5%), non-disease controls 2/47 (4.3%) ($p < 0.01$). Mean birthweight in fullterm infants was also significantly lower in the TNF inhibitor and RA control groups relative to non-disease controls ($p < 0.001$). Abnormalities in preterm delivery and growth remained statistically significant after adjustment for potential confounders. These data suggested that the increased risks for preterm delivery and poor growth in the offspring of women with RA may be attributable to the underlying disease.

Etanercept was also evaluated in a small study of 4 pregnant women[31]. The patients (2 with juvenile arthritis, 2 with adult-onset RA) had 5 pregnancies, and were exposed to etanercept in early pregnancy. All patients stopped etanercept by the third week of pregnancy. Medication during pregnancy included prednisolone and sulfasalazine. The 5 pregnancies resulted in 2 early spontaneous abortions and 3 fullterm deliveries with healthy babies. No birth defects, preeclampsia, growth retardation, or preterm births were observed. The babies showed normal development 12 months postpartum.

3. Adalimumab

Forty first-trimester exposures in women with IA or IBD have resulted in 36 live births, one elective termination, and 3 miscarriages[18,19,34,42,43]. In the OTIS adalimumab registry, 3 spontaneous abortions and 3 preterm births were observed[34]. However, the proportion of pregnancies in the exposed group that ended in spontaneous abortion or prematurity was still comparable to the disease-matched and healthy controls. Additionally, there are 4 reports of successful live births after intentional adalimumab use throughout pregnancy in women with active CD[35-37].

ANTI-TNF REGISTRIES

A total of 14 pregnancies in 13 women were identified in the BIOBADASER Spanish registry for adverse events among 3550 women exposed to biological therapies in rheumatic diseases[22]. Eight pregnancies occurred during treatment with etanercept, 4 with infliximab, and 2 with adalimumab. The time of exposure ranged between Weeks 4 and 14 of conception. There were 7 births without complications (3 with infliximab, 4 with etanercept), 3 therapeutic terminations (2 with etanercept and one with adalimumab), and one miscarriage with infliximab. Three patients had maternal diabetes (one of them taking corticosteroids), without fetal complications.

The British Society for Rheumatology Biologics Registry identified 35 pregnancies among its 11,473 registrants treated with TNF inhibitors[19]. Twenty-nine pregnancies had known outcomes. Twenty-two patients were directly exposed to anti-TNF inhibitors and concomitant treat-

Table 3. Outcomes of pregnancies from study patients compared to healthy population (Orozco, et al, 2005 unpublished data). Data are percentages.

Outcomes	Taking TNF Inhibitors	Controls (taking DMARD)	Healthy
Live births	93	73	67
Miscarriages	5	0	17
Fetal malformation	2	0	4

TNF: tumor necrosis factor; DMARD: disease-modifying antirheumatic drugs.

ment with methotrexate or leflunomide at the time of conception (16 etanercept, 3 infliximab, and 3 adalimumab) and 7 patients discontinued treatment a mean of 4 months (range 1–10 mo) prior to conceiving (4 etanercept and 3 infliximab). In patients directly exposed to TNF inhibitors, there were 6 first-trimester miscarriages (3 with concomitant methotrexate and one leflunomide), 3 elective first-trimester terminations, and 13 live births (one premature and one low birthweight). In patients not directly exposed at conception, there were 6 live births, one stillbirth (in a twin pregnancy), and one first-trimester miscarriage. There were no reports of congenital malformations.

SURVEY DATA FROM CURRENT PRACTICE

In 2003, Chakravarty, *et al*[31] described the practices of rheumatologists who prescribed TNF inhibitors to women with RA of childbearing age and the pregnancy outcomes of patients who become pregnant while taking these medications. A questionnaire was mailed to 600 members of the American College of Rheumatology inquiring about their perception of fetal risk, their recommendation regarding the use of birth control in women taking DMARD, and the outcomes of women with exposure to TNF inhibitors. One hundred seventy-five rheumatologists (29%) returned completed surveys. Respondents were more likely to agree that pregnancy is contraindicated in women taking methotrexate (95%) or leflunomide (92.7%) than for women taking etanercept (38.6%) or infliximab (46.5%). Accordingly, most required birth control for women taking methotrexate (95.7%) and leflunomide (97.3%), and fewer for women taking etanercept (75.4%) or infliximab (73.4%). An almost equal number (49.7% etanercept and 45.4% infliximab) indicated that they were uncertain about the safety of these medications. Indeed, respondents generally required effective methods of birth control when prescribing these medications to their female patients. The opinions of respondents reflect the paucity of human data available to date. One of the limitations of this study was that the response rate was lower than the average physician response rate reported for mailed surveys of 52%–61%[44]. A second limitation of the study was that respondents might exhibit bias when self-reporting their prescribing practices. For example, respondents may overestimate the actual frequency of which they discuss birth control with patients to approximate an ideal practice style rather than their actual performance.

In a more recent survey[45], American and Canadian rheumatologists were asked about TNF safety during pregnancy. The 1212 respondents (40% response rate) identified 463 pregnancies conceived while taking TNF inhibitors, and 31% of patients took the TNF inhibitors throughout gestation. Pregnancy outcomes included 93% live births, 9% cesarean section, 5% miscarriages, 2% low birthweight, and no termination or premature or fetal deaths. There was 1 fetal malformation; a meromelia. Matched controls showed similar outcomes, with 77% live births, 18% cesarean section, and 1 premature and jaundice at birth (11%). These results compare well with expected rates for healthy women (Table 3). No subsequent infant abnormalities were described with up to 5 years of followup.

TNF INHIBITOR USE AND LACTATION

The safety of breastfeeding while receiving TNF inhibitor therapy remains unclear. A case report of a woman with a postpartum flare of RA found moderate levels of infliximab in breast milk[46]. In contrast, levels were undetectable in a woman with CD[47]. The immunoglobulin structure of infliximab may theoretically allow transfer into breast milk but the antibody is likely to be digested by a normally functioning gastrointestinal system. Since the overall risk of toxicity to a nursing infant from such exposure is unknown, all current product monographs advise against lactation in women receiving active therapy. However, in a recent study by Kane, *et al*[48], 3 patients diagnosed with CD who had a history of infliximab use during and after pregnancy were followed prospectively. Patients received 5 mg/kg infliximab at regular intervals until about gestational week 30, and resumed infliximab treatment 3 to 14 days after giving birth. Serum samples from patients and children and breast milk samples were collected postpartum. Infliximab was detected in the mothers' sera, but not in breast milk of nursing mothers or in sera of the breastfed newborns.

Additionally, studies of etanercept have demonstrated its passage into breast milk. Serial levels in breast milk were measured from an RA patient who began treatment 4 weeks after delivery. The maximal etanercept level occurred the day after administration and declined steadily thereafter[49]. Once again, the oral bioavailability in the infant and its clinical implications remain uncertain. Nevertheless, an infant's gastrointestinal tract is likely to digest the large protein structure so that little is systemically absorbed.

Adalimumab, like infliximab, may enter breast milk but no studies in animals or humans are available. One study of certolizumab showed favorable results in animals[50]. Pregnant rats were treated with anti-TNF IgG1 antibody and PEGylated Fab' fragment. The PEGylated Fab' fragment was undetectable compared to IgG1 in milk at 8 days post-

Table 4. Reported congenital anomalies with use of tumor necrosis factor (TNF) inhibitor.

Study	No. of Congenital Anomalies	Anomaly	TNF Inhibitor (timing of exposure)	Fetal Outcome
Katz[31]	2	Tetralogy of Fallot, Intestinal malrotation	Infliximab (T1) Infliximab (pre, T1)	Live birth, successful repair of defect. Live birth, longterm unknown
Snoeckx[32]	15	Cardiac (3), musculoskeletal (4), reproductive system (3), eye (2), nervous system (1), digestive system (1), teratoma (1)	Infliximab (unknown)	Unknown
Chambers[33]	1	Trisomy 18	Etanercept (T1)	Spontaneous abortion (37 wks gestational age)
Carter[51]	1	VACTERL	Etanercept (pre, T1, T2, T3)	Live birth, longterm unknown
Johnson[34]	8	Undescended testicle (1), microcephaly (1) Congenital hip dysplasia (1), spina bifida with hydrocephalus (1), chromosomal (3), ventricular septal defect (1)	Adalimumab (T1) Adalimumab (unknown)	All live births, longterm unknown
Carter	41	Cardiac defect (12), cystic kidney (3), hypospadias (3), teratoma (3), tracheal stenosis (2), trisomy 21 (2), hydrocele (1), VACTERL (1), unknown (13)	Unknown	Unknown
King[24]	4	Congenial hip dysplasia Pyloric stenosis Strawberry nevus "Winking jaw syndrome"	Unknown (T1) Unknown (T1) Unknown (pre) Unknown (pre)	Live birth, longterm unknown Live birth, longterm unknown Live birth, longterm unknown Live birth, longterm unknown

Pre: preconception; T1: first trimester; VACTERL: vertebral, anal, cardiac, tracheal, esophageal, renal or limb anomalies.

partum. Larger human studies are needed to confirm these findings and to analyze the potential systemic or developmental effects in the nursing infant.

TNF INHIBITOR USE AND CONGENITAL ANOMALIES

While the great majority of TNF inhibitor-associated pregnancies have resulted in successful outcomes, a small fraction has yielded congenital anomalies. Table 4 lists the 72 anomalies reported to date.

The Infliximab Safety Database, which analyzed pregnancy outcomes from the product launch in 1998 until 2003, reported 2 congenital problems in women receiving infliximab preceding or coincident with pregnancy[27]. One child was diagnosed with tetralogy of Fallot, which occurs in the general population at a rate of 4:10,000 live births and represents the most common cyanotic congenital heart defect. The other infant was born with intestinal malrotation but had *in utero* exposure to leflunomide, which is a known teratogen. The same database recently evaluated outcomes until 2007 and identified 15 unique cases with more than 1 congenital anomaly among infants born to mothers exposed to infliximab. These included a variety of organ system anomalies. A cytogenetic abnormality was reported for 3 cases, including one case of trisomy 21[28]. However, the timing of exposure to infliximab and the total number of women exposed were not provided, preventing accurate calculation of absolute risk compared to the general population.

The British Society of Rheumatology Biologics Register documented 4 congenital abnormalities among 106 pregnancies. One case of congenital hip dysplasia and one pyloric stenosis occurred among women with direct exposure to TNF inhibitors at time of conception, whereas one strawberry nevus and one "winking jaw syndrome" (unilateral ptosis and elevation of the lid on opening of the jaw) were observed in infants whose mothers had been exposed to an anti-TNF inhibitor prior to confirmation of pregnancy[20].

Regarding etanercept, one case of trisomy 18 was identified in a first-trimester exposed pregnancy, which ended in miscarriage[29]. In addition, a major congenital malformation known as VACTERL (vertebral anomalies, anal atresia, cardiac defects, tracheo-esophageal fistula, esophageal atresia, renal anomalies, and limb dysplasia) was described in a woman with PsA who was treated with high-dose etanercept (50 mg biweekly) throughout her pregnancy[51].

The possible association between congenital anomalies

and adalimumab was reported by the OTIS Collaborative Research Group[42] and Johnson, *et al*[52]. The type and proportion of anomalies did not differ significantly between disease-matched women treated with DMARD and healthy controls. Although timing of exposure was not uniformly available, all resulted in live births.

To determine possible associations of TNF inhibitors and congenital abnormalities, Carter, *et al* searched the FDA Adverse Event Reporting System of infliximab, etanercept, and adalimumab for congenital anomalies[53,54]. A total of 41 children with congenital anomalies were born to mothers exposed to TNF inhibitors. Most cases involved congenital heart defects, but the anomaly type was not listed in 13 cases. While 24 of these demonstrated one or more features of the VACTERL spectrum, only one case met the full criteria for the syndrome and this represented the index case that prompted this investigation. Among the cases, 22 were exposed to etanercept, 19 to infliximab, and none to adalimumab. However, the dose and timing of gestational exposure was not specified. Further, details were not provided on concomitant medication use, which occurred in 41% of women. Although the number of reported anomalies is noteworthy, this type of study may be misinformative for a number of reasons. First, no denominator of women exposed was provided, making it very difficult to estimate the true magnitude of risk. Second, the anomalies described are the most common in the population, and single components, such as heart defects, do not necessarily represent a complex syndrome or VACTERL association. Third, reporting of events was voluntary and may not have reflected the true number of events.

While these data raise caution, other reports and safety databases have failed to demonstrate a higher than expected incidence of congenital anomalies compared to the general population risk of 3%. As an example, let us estimate that roughly 2,000,000 patients worldwide have been exposed to TNF inhibitors and that 65% are female. If half receive therapy during potential childbearing years (N = 650,000) and roughly one-third become pregnant (N = 220,000), we would expect close to 4600 congenital malformations among live births (70% of all pregnancies) to occur by chance alone. Such numbers are not currently in evidence from the literature and are too extreme to be attributable to underreporting of adverse events to regulatory agencies. Nonetheless, large prospective studies are needed to measure reproductive outcomes and to determine if a causal link between TNF inhibitor exposure and adverse fetal outcomes truly exists.

CONCLUSIONS

Overall, these data suggest that many patients with RA and CD have experienced successful pregnancies following TNF exposure. Patients with unplanned pregnancies or inadvertent exposure to TNF inhibitors either before or after conception do not require termination of pregnancy unless additional maternal-fetal assessments suggest untoward or dangerous effects. While most of the existing data on TNF inhibitor use in pregnancy have been generated during conception and the first trimester of pregnancy, there is limited and inadequate information regarding their use throughout pregnancy or during breastfeeding. Although the available studies provide some insight into this important safety issue, many unanswered questions remain, including the safety of the TNF inhibitors during breastfeeding, and their relationship with specific malformations such as the VACTERL syndrome. Large, prospective, observational, systematic studies of TNF inhibitor use in pregnant women are needed to more definitively determine if drug therapy imparts greater fetal risk than that imposed by chronic uncontrolled inflammation.

RECOMMENDATIONS ON PREGNANCY AND TNF INHIBITOR USE

Per Observational Studies

1. Fecund women with RA or CD who aspire to become pregnant should ideally plan to conceive when their disease is well controlled while taking no drugs, or if necessary while using agents posing the least possible risk to the growing fetus (category B).
2. While RA or CD disease activity will often abate during pregnancy, in a significant number of patients it may not. There is no profile, biomarker, or clinical variable to predict the effect of pregnancy on disease activity. A strategy to manage maternal disease activity during pregnancy is necessary for the health of the mother and to limit potential toxicity to the fetus.
3. If the activity or disease severity precludes cessation of a TNF inhibitor and/or DMARD, uncontrolled observations suggest that conception and early pregnancy are not adversely affected by use of TNF inhibitor. Nearly 70% of pregnant patients can discontinue their TNF inhibitor early in the pregnancy (or with determination of pregnancy) without augmenting maternal or fetal risks.
4. Uncommon adverse pregnancy outcomes observed with TNF inhibitor therapy appear to approximate those seen in women not receiving such therapy and may include premature birth, miscarriage, low birthweight, hypertension, and preeclampsia.
5. There are rare reports of fetal malformations or congenital anomalies in patients exposed to TNF inhibitors during conception or pregnancy. However, the incidence of these events appears to be far below the 3% rate of congenital anomalies in the general population. Thus it appears that the frequency of fetal malformations in those receiving TNF inhibitors is no greater than that seen in the general population.
6. Depending on the patient's preference and disease severity, continued use of TNF inhibitors throughout the pregnancy may pose more benefit than harm.

Unanswered Questions and the Need for Future Research

1. Are maternal-fetal risks modified by uncontrolled (and untreated) inflammatory disease or by TNF inhibitor therapy?
2. Regarding TNF inhibitor use, is there an optimal (or hazardous) period of exposure during the pregnancy? Is it safe to use TNF inhibitors throughout pregnancy?
3. Are any longterm or developmental consequences seen in children born following maternal exposure to a TNF inhibitor?
4. Does TNF inhibitor therapy add to the risks incurred by women with a history of problematic pregnancy (e.g., premature births, recurrent fetal wastage, congenital anomalies, etc.)?
5. Does the TNF inhibitor cross the placenta and can any be found in breast milk; or more important, can such therapy alter the infant's immune status or development?
6. What are the short and longterm effects of breastfeeding the newborn while receiving TNF inhibitor therapy?

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