Maternal and Fetal Outcomes in a Cohort of Patients Exposed to Tumor Necrosis Factor Inhibitors throughout Pregnancy

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ABSTRACT. ***Objective.*** Tumor necrosis factor inhibitors (TNFi) are increasingly used in pregnancy but are frequently withheld in the second or third trimesters. We evaluated the maternal and fetal outcomes of women who continued their TNFi throughout pregnancy compared to women who interrupted TNFi during pregnancy.

Methods. We retrospectively analyzed the outcomes of women seen in clinic with rheumatoid arthritis (RA), psoriatic arthritis, juvenile idiopathic arthritis (JIA), or ankylosing spondylitis, who were exposed to TNFi during pregnancy. We separated pregnancies into 2 groups based on the level of TNFi exposure and compared outcomes.

Results. In Group 1 (TNFi exposure in first trimester only), 11 women had 14 pregnancies and 12 live births. There were 2 first-trimester losses (2/14, 14%), one in the setting of active RA. Five pregnancies (5/14, 35.7%) were complicated by a disease flare. Eight patients (8/12, 66%) flared postpartum. In Group 2 (TNFi exposure throughout pregnancy), 29 women had 32 pregnancies and 34 live births. Three (3/28, 10.7%) adverse pregnancy outcomes were reported in 2 patients. One patient had a twin pregnancy and delivered at 33 weeks after developing preterm premature rupture of membranes at 32 weeks in the setting of a JIA flare. Her second pregnancy was complicated by active JIA before and throughout gestation, and hemolysis, elevated liver enzyme levels, and low platelet levels (HELLP) syndrome at 39 weeks. Another patient with comorbid antiphospholipid syndrome underwent a cesarean birth at 36 weeks for suspicion of HELLP syndrome. Six (6/32, 18.7%) postpartum flares occurred.

Conclusion. Women who discontinued their TNFi during pregnancy had a higher risk of peri- or postpartum flare compared to those who continued their TNFi throughout pregnancy. (First Release July 1 2018; J Rheumatol 2018;45:1109–15; doi:10.3899/jrheum.171152)

Key Indexing Terms:
PREGNANCY RHEUMATOID ARTHRITIS PSORIATIC ARTHRITIS
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Inflammatory arthritides, which include rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA), are increasingly being recognized in women of childbearing age[1].

Studies indicate that fertility can be impaired in women with high disease activity or treated with cytotoxic medications, but fertility potential is comparable to the age-matched general population if the underlying disease is well controlled[2]. RA and PsA symptoms tend to improve or remit during pregnancy but have a high risk of flaring within the first postpartum year[3]. AS manifestations are less predictable, often running an independent course in pregnancy or postpartum[4,5]. In RA, pregnancy outcomes mirror disease activity; the risk of miscarriage, cesarean delivery, preeclampsia, preterm delivery, and low birth weight positively correlates with increased disease severity[6]. These outcomes are less established in AS and PsA but likely follow the same trend[4,5].

Acceptable maternal and fetal outcomes in patients with inflammatory arthritides rely heavily upon obtaining disease quiescence during a woman's reproductive years. There has been some debate concerning tumor necrosis factor inhibitor (TNFi) use for rheumatologic conditions during pregnancy, because safety data are mostly restricted to a handful of studies and 1 recent metaanalysis[7]. TNFi are frequently discontinued during the first trimester and there is a dearth of information regarding TNFi use during pregnancy. The ability to continue TNFi during pregnancy has obvious maternal benefits, and reducing maternal disease activity and flare risk may benefit pregnancy and fetal outcomes.

With the exception of certolizumab pegol (CZP)[8], all

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TNFi cross the placenta in the second and third trimesters and are detected in variable levels in the cord blood[9]. Whether transplacental transfer and neonatal serum TNFi levels affect fetal outcomes is a matter of debate. Although some case reports suggest an increased risk of adverse outcomes in such offspring, previous larger-scale studies in patients with inflammatory bowel disease (IBD) do not show an increase in congenital anomalies, infectious susceptibility, preterm birth, or small for gestational age infants, even when the TNFi is used during the second or third trimesters[10,11,12]. A Canadian consensus statement in gastroenterology recommends continuing TNFi throughout pregnancy in patients with IBD who had maintenance therapy before conception[13]. Owing to 1 case report of an infant with *in utero* infliximab (IFX) exposure who developed a fatal disseminated mycobacterial infection after receiving a bacillus Calmette-Guérin vaccine at 3 months, the recommendation is to postpone live virus vaccines for 6 months in infants exposed to TNFi in the third trimester[13,14].

Although the literature on TNFi use in pregnant women with rheumatologic conditions is reassuring[15,16,17], it is less extensive than the IBD data. There are no clear guidelines regarding TNFi use during pregnancy in patients with inflammatory arthritis. A European League Against Rheumatism task force consensus recommended the use of IFX and adalimumab (ADA) up to 20 weeks and etanercept (ETN) up to 30–32 weeks but if indicated, these medications may be used throughout pregnancy. Golimumab (GOL) should be switched to an alternative agent after conception. The British Society for Rheumatology guidelines recommend discontinuing IFX at 16 weeks and ETN and ADA at the end of the second trimester. Both recommend continuing CZP throughout pregnancy[18,19].

In our clinic, we recommend continuing TNFi throughout pregnancy in patients with inflammatory arthritis or IBD who were taking maintenance TNFi before conception. The objective of our study was to compare maternal and fetal outcomes in patients who continued TNFi throughout pregnancy to those who stopped TNFi during the first trimester.

MATERIALS AND METHODS

This prospective observational single-center cohort study included women seen in our Connective Tissue Diseases in Pregnancy Clinic from September 2011 to August 2017 with inflammatory arthritides or IBD who had received at least 1 dose of TNFi after conception. Ethics approval was obtained from Veritas IRB (approval number 16164-13:31:134-07-2017). Informed consent was not sought for this study because information was extracted directly from medical charts and contact with the patient was not required. Further, patients were followed during pregnancy only and chart contact information was no longer valid for many subjects.

Patients were divided into 2 groups. Group 1 included patients who were taking TNFi at conception, who had been exposed to at least 1 dose of TNFi during the first trimester and elected to discontinue TNFi during pregnancy. Group 2 included patients who had TNFi treatment at conception and continued their TNFi throughout pregnancy. Study patients received 1 of the 5 approved TNFi (IFX, ETN, ADA, GOL, or CZP). We excluded patients with periconceptual exposure to known teratogens including methotrexate (MTX), mycophenolate, and leflunomide.

Patients were evaluated preconceptually and prospectively followed throughout pregnancy until 6 weeks postpartum. Data on exposure and outcomes were collected prospectively by the physician or retrospectively by phone contact. Maternal demographics collected at the initial visit included age, gravidity, parity, number of living children, and medications. Disease activity was assessed by the same physician throughout the followup period and included a joint count and assessment for extraarticular manifestations.

Pregnancy and fetal outcomes were assessed at the 6-week postpartum visit. Pregnancy-related complications included the following: spontaneous abortion (spontaneous loss of a fetus < 20 weeks gestation), preeclampsia/eclampsia, preterm delivery (live birth < 37 weeks gestation), and maternal infection. Fetal outcomes included birth weight [small for gestational age (SGA); birth weight below the 10th percentile for gestational age], congenital anomalies, infectious complications, and neonatal hospitalization. Gestational age was calculated using the first trimester viability ultrasound or if unavailable, the last menstrual period.

Continuous data are presented as mean ± SD; Student t test was used to calculate differences between groups. The chi-square statistic was used to calculate differences between categorical variables. P values were considered significant if < 0.05.

RESULTS

Study population. Forty women and 46 pregnancies were included in this cohort. Maternal characteristics and outcomes are summarized in Table 1. In Group 1, there were 11 women with 14 pregnancies and 12 live births. Mean maternal age was 31.9 years. All women in Group 1 stopped their TNFi at pregnancy diagnosis (between 4–8 weeks of gestation for 10 women; at 12 weeks for 1 patient). All patients who experienced a postpartum flare resumed TNFi; such data are not available for patients who did not flare postpartum.

In Group 2, there were 29 women with 32 pregnancies and 34 live births. Mean maternal age was 34 years. All women continued their TNFi throughout pregnancy except 1 patient who elected to discontinue at 36 weeks. Maternal age was similar in both groups ($p = 0.188$).

Maternal outcomes. In Group 1, five pregnancies (5/14, 35.7%) were complicated by a disease flare. Two patients (1 with AS, 1 with RA) had mild flares and declined further treatment. One patient with a moderate RA flare resumed ETN at 24 weeks with complete remission; another with PsA had a severe cutaneous and moderate arthritic flare at 18 weeks and partially responded to resuming ETN. One patient with AS, ulcerative colitis, and scleritis developed diarrhea and inflammatory lumbar/costochondral pain 1 month after discontinuing her TNFi. She failed to respond to ADA and required a switch to GOL at 18 weeks, with complete remission at 20 weeks. She elected to discontinue the GOL at 36 weeks and developed inflammatory polyarthritis 4 weeks postpartum; she responded to resumption of GOL. Seven other patients (5 RA, 1 AS, 1 PsA) had postpartum flares manifesting as inflammatory arthritis (8/12, 66%). All patients went into remission after resuming their TNFi, except 1 patient with AS who failed to respond to CZP and

Table 1. Cohort pregnancy outcomes. Values are n (%) or mean ± SD unless otherwise specified.

Variables	Group 1, TNFi Therapy at Conception	Group 2, TNFi Therapy throughout Pregnancy
No. women with pregnancy	11	29
No. pregnancies	14	32
Singleton, live born	12	30
Twins, live born, sets	0	2
Age, yrs	31.9 ± 5.35	34 ± 4.75, p = 0.188
Diagnosis		
RA	6	15
PsA	2	6
AS	2	2
JIA	1	2
IBD/psoriasis	0	4
Baseline disease control		
Quiescent	11/14 (78.6)	22/32 (68.7)
Mild	2/14 (14.3)	7/32 (21.8)
Moderate	1/14 (7.14)	3/32 (9.37)
Severe	0	0
TNFi agent		
Infliximab	0	3/29 (10.3)
Adalimumab	0	6/29 (20.6)
Etanercept	6/11 (54.5)	12/29 (41.4)
Golimumab	2/11 (18.2)	1/29 (3.4)
Certolizumab	3/11 (27.3)	7/29 (24.1)
Conventional DMARD use		
Hydroxychloroquine	0	5/29 (17.2)
Sulfasalazine	0	3/29 (10.3)
Azathioprine	0	2/29 (6.9)
Steroids	0	2/29 (6.9)
Mode of delivery		
Vaginal	8/12 (66)	21/32 (65.6)
Cesarean	4/12 (33)	11/32 (34.3)
Pregnancy outcome		
Live birth	12/14 (85.7)	34 (100)
Spontaneous abortion	2/14 (14.3)	0
Maternal outcomes		
Peripartum flare	5/14 (35.7)	3/32 (9.4), p = 0.030
Postpartum flare	8/12 (66)	6/32 (18.7), p = 0.002
Preeclampsia	0	2/32 (6.25)
Preterm delivery	0	2/32 (6.25)
Fetal outcomes		
Birth weight, g	3366 ± 370	3199 ± 715, p = 0.445
Premature, < 37 weeks	0	3 (9.37)
Congenital anomalies	1 (7.14)	0

RA: rheumatoid arthritis; PsA: psoariatic arthritis; AS: ankylosing spondylitis; JIA: juvenile idiopathic arthritis; IBD: inflammatory bowel disease; TNFi: tumor necrosis factor inhibitor; DMARD: disease-modifying antirheumatic drug.

responded partially to ETN. In total, 11 patients (11/14, 78.6%) had a peripartum and/or a postpartum flare.

In Group 2, three pregnancies (3/32, 9.4%) were complicated by a disease flare. One patient with active JIA and partial response to ADA prior to conception had 2 pregnancies, which were complicated by moderate peripartum disease flares requiring oral steroids and nonsteroidal antiinflammatory drugs. Another patient with quiescent RA taking ETN developed a moderate flare requiring oral and intramuscular corticosteroids. Six (6/32, 18.7%) postpartum flares were reported. One patient with quiescent AS and Crohn disease treated with IFX during pregnancy developed an IBD flare 3 months postpartum, requiring an iliocolectomy. She responded to MTX and ADA. Another patient with quiescent RA taking CZP developed secondary CZP failure 4 months postpartum and required a switch to tocilizumab. Two flares were mild and did not require any adjustment in therapy: 1 occurred in a patient with quiescent RA and the other occurred in the previously described JIA patient's first pregnancy. Two other mild flares may have been caused by medication noncompliance: 1 occurred in a patient who discontinued her TNFi at 36 weeks, and another occurred in a patient who discontinued hydroxychloroquine at conception. In total, 8 patients (8/32, 25%) experienced a peripartum and/or a postpartum flare. Group 1 experienced significantly more peri- and postpartum flares (p = 0.03 and p = 0.002, respectively). No maternal infections were reported.

Pregnancy outcomes. In Group 1, obstetrical complications included 1 first-trimester miscarriage in a 24-year-old woman with quiescent RA and 1 late first trimester loss (13 weeks) in a 38-year-old woman who developed a moderate RA flare at 10 weeks.

In Group 2, three adverse obstetrical outcomes were reported in 2 patients. The first patient was 33 years old at the time of her first pregnancy and had underlying JIA with partial response to ADA (as previously described). She had a moderate JIA flare during her third trimester and required an intramuscular steroid injection at 32 weeks. She developed preterm premature rupture of membranes (PPROM) 24 h later and delivered her twins vaginally at 33 weeks. She was 38 years old during her second pregnancy, which was complicated by moderately active JIA before and throughout gestation as well as a flare at 10 weeks, requiring a moderate dose of oral steroids. She developed hemolysis, elevated liver enzyme levels, and low platelet levels (HELLP) syndrome at 39 weeks and required a cesarean delivery. The second patient was a 39-year-old with RA who was diagnosed with obstetric antiphospholipid syndrome (APS) after 4 second-trimester pregnancy losses. She was treated with CZP, aspirin, and low molecular weight heparin throughout her fifth pregnancy. At 36 weeks, she developed thrombocytopenia and hypertension and underwent a cesarean delivery because of suspicion of HELLP syndrome.

Fetal outcomes. In Group 1, one congenital anomaly was reported in the offspring of a 38-year-old patient with RA who received ETN until 4 weeks of gestation. Her genetically normal son was born with a small omphalocele and developed 1 episode of generalized seizures at 18 months of age. Both conditions were managed conservatively without evidence of neurocognitive delay at 2 years of age. No neonatal intensive care unit (NICU) hospitalizations, neonatal infections, or SGA infants were reported.

In Group 2, there were no congenital anomalies or SGA infants reported. Mean birth weight was similar in both groups ($p = 0.445$). One term male developed a urinary tract infection at 2 weeks of age (cultures were positive for *Escherichia coli*). There were 6 neonatal hospitalizations, including both sets of twins. The first set of twins was born vaginally at 37 weeks to a mother with quiescent RA taking ETN. They remained in the NICU for 5 days because of low birth weight (2010 g and 2211 g). The second set of twins was born vaginally at 33 weeks of gestation because of maternal PPROM and was hospitalized in the NICU for 4 weeks because of prematurity and low birth weight (1410 g and 1470 g). One term neonate (2800 g) received prophylactic antibiotics because of a suspected meconium aspiration. Another term neonate (3710 g) was observed for 48 h with nonspecific respiratory issues.

We do not have data on offspring infectious outcomes or vaccination responses after the study period.

DISCUSSION

This is a single-center cohort of 40 patients treated with TNFi during 46 pregnancies, most of whom had TNFi exposure for the entire pregnancy (32/46, 69.5%). Mean maternal age was higher in Group 2 but not enough to affect obstetric and fetal outcomes.

TNFi continuation throughout pregnancy was recommended for each patient who was taking TNFi prior to conception, but the final decision to continue or discontinue was patient-driven. Because baseline disease activity differed in both groups, patient decision to discontinue TNFi in Group 1 therapy might have been biased by lower disease activity.

A majority of patients were receiving ETN (46%), followed by CZP (23%), ADA (15.4%), IFX (7.7%), and GOL (7.7%). This distribution is likely because ETN was the first approved TNFi for treatment of RA, CZP has the least transplacental transfer, and GOL is a relatively new available TNFi agent.

In maternal outcomes, there were significantly more peri- and postpartum disease flares in Group 1 compared to Group 2, despite Group 2 having higher disease activity preconceptually, with fewer patients achieving disease quiescence before pregnancy (Table 1). Of note, the flare rate in Group 2 may have been overestimated; 2 postpartum flares could have been due to medication noncompliance, and a third may have been caused by the development of anti-IFX antibodies. Most patients in Group 1 responded to resuming their TNFi, but 2 patients developed secondary TNFi failure and required an alternate TNFi; 1 patient had partial remission with the alternate agent. These results support maternal benefits of continuing TNFi therapy throughout gestation and illustrate the potential risk of secondary TNFi failure after discontinuation[20]. Risk factors for a peri- or postpartum disease flare included first trimester TNFi discontinuation and active disease at conception. The physician assessing the disease activity was not blinded to the treatment group; this will be addressed in future larger studies.

Regarding pregnancy outcomes, all pregnancies in Group 2 resulted in live births. In Group 1, there were 2 miscarriages (2/14, 14.3%), one of which occurred in the setting of an active RA flare. The miscarriage rate in Group 1 is below that of the general population (15–25%, depending on maternal age)[21]. According to the current literature, if preconceptual teratogenic medication use is excluded, patients with RA do not have an increased risk of miscarriage[22,23,24]. However, in 2 large retrospective studies, women with RA who miscarried were more likely to have had a higher disease activity[22,23]. We are not excluding the possibility of active RA having contributed to the 13-week miscarriage, but we cannot determine its exact cause from the information available to us. One could hypothesize that TNFi treatment during the first trimester should prevent miscarriages associated with active disease, but our study was not designed to verify this possibility. Regardless, in our cohort and in accordance with previously published reports[19,25,26], TNFi treatment during pregnancy does not increase the risk of miscarriage.

Regarding obstetric outcomes, there were more adverse events in Group 2 than in Group 1. However, these outcomes occurred in 2 patients who were at increased obstetric risk; 1 had underlying APS and the other had moderately severe JIA

with partial response to TNFi and active disease before conception. Both these patients had pregnancies complicated by HELLP syndrome, although it was suspected and never confirmed in the patients with APS. APS is a prothrombotic, microangiopathic disease associated with placental ischemia and dysfunction, which are both hallmarks of preeclampsia[27,28]. So it is not surprising that women with APS have a higher risk of developing preeclampsia[27], including severe forms of the disease[28]. In the patient with APS, however, we cannot determine whether the continued use of TNFi contributed to the development of the suspected HELLP syndrome or if it was due to underlying APS or other unknown co-factors.

Similarly, in the patient with JIA, we cannot determine whether continued use of TNFi, underlying active JIA, or use of oral corticosteroids contributed to her developing HELLP syndrome. However, cytokine and hormonal signaling produced by the uterine immune system at conception directs trophoblast invasion, spiral artery remodeling, and decidualization. Preeclampsia is associated with maternal immune dysregulation whereby the normal tolerogenic immune environment is offset by an increased production of proinflammatory cytokines [TNF-α, interleukin (IL) 6, and IL-17]. These abnormal cytokines impede trophoblastic invasion in early placentation, which leads to insufficient uteroplacental perfusion and placental hypoxia[29,30]. Resulting oxidative stress stimulates trophoblastic release of TNF-α, which further promotes hypoxia and endothelial injury, possibly by inducing the release of anti-angiogenic factors[31]. If maternal immune dysregulation truly contributes to defective placentation, women with active rheumatic disease should be at increased risk for preeclampsia[32]. Only 1 population-based health care registry reported a statistically significant increased risk of preeclampsia in patients with RA compared to age-matched healthy controls (5.0 vs 3.4%), but this was not correlated with disease severity or flare[24]. This trend is not uniform in the literature. Some studies show an increased risk of hypertensive disorders in pregnancy in patients with inflammatory arthritis[33,34] while others do not[23,35,36].

One twin pregnancy resulted in a 33-week preterm birth because of PPROM in the setting of a disease flare. Again, we cannot determine whether continued TNFi use, underlying disease activity, twin gestation, or use of corticosteroids were contributory. However, active inflammation during pregnancy could theoretically impede a woman's ability to carry her pregnancy to term. Indeed, parturition is an inflammatory event partly initiated by cell-free fetal DNA binding to Toll-like receptor 9 on immune cells and triggering the release of proinflammatory cytokines (interferon-α, IL-6, IL-12, TNF-α), which induce the expression of uterine activation protein on the myometrium, decidua, and cervix[37,38]. The same cytokines are also released during an arthritis flare and could presumably initiate the same cascade of events leading to preterm labor. This mechanism could potentially explain the increased rate of preterm births found in patients with JIA[39,40] and other inflammatory arthritides[7]. In this case, many different proinflammatory cytokines are produced and TNF-α blockade may not be sufficient to block uterine activation protein expression, which in turn may explain why the rate of preterm births in patients with inflammatory arthritis is independent of TNFi treatment during pregnancy and more closely correlated with disease activity[7].

Regarding neonatal outcomes, one child was born with a small omphalocele that was treated conservatively and did not occur in the setting of other congenital anomalies. His mother had underlying RA and stopped her ETN at 4 weeks of gestation. It is unlikely that the TNFi contributed to this outcome because ETN has a short half-life (70 h) and would have been cleared from the maternal circulation before intestinal organogenesis began at 6 weeks. We cannot exclude that TNF inhibition may have interrupted earlier pathways of development and indirectly caused this anomaly. Considering that major congenital anomalies occur in 3–5% of Canadian newborns, our study is underpowered to evaluate the effect of TNFi use on the risk of birth defects[41].

Although there is still some debate regarding the risk of congenital anomalies with first trimester exposure to TNFi, the available literature is reassuring. One multicenter prospective cohort study reported a 2-fold increased risk of congenital anomalies in TNFi-exposed pregnancies, but their control population was healthy and had a low prevalence of birth defects, likely overestimating the effect of TNFi exposure[42]. In a previously published large Scandinavian health registry[11], congenital anomalies were more common in offspring born to mothers with chronic inflammatory disease (4.7%) compared to healthy controls (4.3%), with a nonsignificant increase in birth defects in TNFi-exposed pregnancies (6.3%; OR 1.32, 95% CI 0.93–1.82). The frequency of birth defects was highest in offspring with *in utero* ETN exposure (7%), but ETN was the most frequently used TNFi in this cohort[11]. Carman, *et al* recently published a large retrospective cohort comparing birth outcomes in women with chronic inflammatory arthritis with and without ETN exposure during pregnancy[43]. They found no difference in major congenital anomalies between exposed and unexposed women (6.1% and 5.5%, respectively; OR 1.03, 95% CI 0.51–2.10). The prevalence of birth defects in their control population was 5.7%. Other studies, most recently with ADA[25] and CZP[26], do not report an increased risk of birth defects with first trimester TNFi exposure.

Although our cohort is too small to comment on the relationship between *in utero* TNFi exposure and congenital anomalies, our data are reassuring, with 2.17% of offspring presenting with a birth defect. Interestingly, we had no reports of SGA infants. Although offspring from mothers with RA tend to be of lower birth weight[44], we do not have a control

population to evaluate this. Six newborns in Group 2 underwent routine NICU observation; 1 postnatal infection was reported.

We did not find that TNFi use throughout pregnancy posed any specific obstetric or fetal risk in this small cohort. We observed a significantly higher peri- and postpartum flare rate in mothers who discontinued their TNFi during the first trimester. In a patient with chronic inflammatory disease with pre- or periconceptual indications for TNF inhibition, we believe that the maternal benefits of continuing TNFi throughout pregnancy outweigh the remote possibility of adverse pregnancy or fetal outcomes.

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