The Use of Biologic Therapy in the Pregnant Patient

**INTRODUCTION**

Inflammatory bowel disease (IBD) affects women during their childbearing years, with the peak age of onset between 15 to 30 years of age. The use of more effective therapy for IBD allows more women to be healthy enough to consider conception. However, along with the benefit of therapy comes concern about the safety of these medications during conception, pregnancy and lactation. Given the limited data and potential adverse outcomes, pregnant women with IBD require an interdisciplinary approach to therapy with close monitoring and counseling to optimize their clinical disease course and neonatal outcomes. This review will present the best evidence to date on the use of anti-tumor necrosis factor (TNF) therapy on fertility and pregnancy in women with IBD.

**FERTILITY**

There is no data that anti-TNF therapy negatively impacts fertility. Hypothetically, if it is effective in inducing remission, it will likely increase the chances of the mother conceiving. Women with IBD may have an elevated ratio of Th1/Th2 cytokines contributing to difficulties in conception and pregnancy loss. Protection of the fetus from maternal attack has been correlated with a shift toward a Th2 cytokine profile in the general population. This may explain why some women feel their IBD disease activity is the lowest during pregnancy. It also raises the possibility that anti-tumor necrosis factor (TNF)-α agents can improve fertility. Winger, et al, significantly improved IVF outcomes and implantation rates by the use of adalimumab and IVIG in a study enrolling 75 subfertile women without IBD from an assisted reproductive facility in London, who all had elevated Th1/Th2 cytokine ratios. Implantation rates were 59% using adalimumab and IVIG, vs. 47% using IVIG alone, vs. 0% with neither. The role of anti-TNF agents in improving fertility in women with IBD may be related to both improving disease activity and shifting the Th1/Th2 balance.

**INFliximAB**

Infliximab (INF) is a pregnancy category B drug. It is a chimeric anti-TNF monoclonal IgG1 antibody used for the induction and maintenance of CD5 and UC6. It
likely does not cross the placenta in significant amounts during the first trimester, protecting the infant from exposure during the critical period of organogenesis. INF does, however, cross very efficiently in the second and third trimester7 and is detectable in the infant several months after birth.8,9

There is cumulative evidence for INF as a low risk drug during pregnancy. The 2 largest studies are the TREAT Registry10 and the INF Safety Database11 maintained by Centocor (Malvern, PA). The TREAT Registry is a prospective registry of patients with CD.10 Of the >6200 patients enrolled, 117 of 168 reported pregnancies were exposed to INF. There was no difference in the rates of miscarriage (10% vs. 6.7%) and neonatal complications (6.9% vs. 10%) between those treated with INF and those who were not, respectively.

The INF Safety Database is a retrospective data collection instrument. 96 women (82 CD, 1 UC, 10 RA, 3 unknown) with direct exposure to INF gave birth to 100 infants.11 Exposure was primarily during conception and the first trimester. Treatment was often stopped when women became aware they were pregnant. Pregnancy outcomes among women exposed to INF were similar to that of the general population.

There are two case series reporting on the use of INF during pregnancy. The first describes 10 women maintained on INF throughout pregnancy. All 10 ended in live births with no reported congenital malformations.12 Another series13 of 22 patients with exposure to INF within 3 months of conception, continued until 20 weeks of gestation at which time the drug was stopped to minimize placental transfer. Several of the patients did flare in the third trimester. There were 3 spontaneous abortions, 1 missed abortion, 1 stillbirth at 36 weeks (umbilical strangulation), 2 preterm births, 3 low birth weight infants, and no congenital anomalies.

A review of the US Food and Drug Administration (FDA) database reports of congenital anomalies in infants exposed to anti-TNF therapy was published by Carter et al.14 A total of 61 congenital anomalies in 41 children born to mothers taking a TNF antagonist were reported. Etanercept was taken in 22 mothers (not used in IBD), and infliximab in 19. The most common reported congenital anomaly was some form of heart defect. However, the authors also note that 24/41 (59%) children had one or more congenital anomalies that are part of vertebral abnormalities, anal atresia, cardiac defect, tracheoesophageal, renal, and limb abnormalities (VACTERL) association. There were 34 specific types of congenital anomalies in total, and 19 (56%) of those are part of the VACTERL spectrum. However, only 1 child was actually diagnosed with VACTERL. In 24/41 cases (59%) the mother was taking no other concomitant medications. While the authors felt this may suggest an association with anti-TNF use and VACTERL, as the majority of the defects were cardiac, a common anomaly, it is unclear if this association is true. Results of the ongoing PIANO (Pregnancy in IBD And Neonatal Outcomes) registry should provide more information.15

Placental transfer of INF in the second and third trimesters results in drug levels detectable in the infant up to 6 months after birth. A case report8 noted higher than detectable INF levels in an infant born to a mother on INF therapy every 4 weeks. The mother breast-fed and continued to receive INF but the infant’s INF level dropped over 6 months, suggesting placental rather than breast milk transfer. In a case series9 of 8 patients receiving INF during pregnancy, all 8 patients delivered a healthy infant. Mean time between delivery and the last infusion was 66 days (range 2–120 days). The INF level at birth was always higher in the infant and cord blood than in the mother and remained detectable from 2–7 months after birth. This may be because the infant reticuloendothelial system is too immature to clear the antibody as efficiently as the adult mother. INF has not been detected in breast milk.16–17

ADALIMUMAB
Adalimumab (ADA) is a pregnancy category B drug and FDA approved for induction and maintenance of remission in CD.18 Three case reports19–21 document the successful use of ADA to treat CD during pregnancy, including one in which the patient received weekly dosing throughout pregnancy for a total of 38 doses.21 OTIS (Organization for Teratology Information Specialists) reports 27 women enrolled in a prospective study of ADA in pregnancy and an additional 47 ADA exposed pregnant women in a registry.22 There was no difference in the rate of

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spontaneous abortion and stillbirth for those with CD compared with the general population and the rates of congenital malformation and preterm delivery are also within the expected range.

ADA, an IgG1 antibody, would be expected to cross the placenta in the third trimester as INF does. However, as ADA levels cannot be checked commercially, this has not been confirmed. ADA is considered compatible with breastfeeding though there is no human data.

CERTOLIZUMAB PEGOL
Certolizumab pegol (CZP) is a PEGylated Fab’ fragment of a humanized anti-TNFα monoclonal antibody efficacious in the treatment of CD.23 It does not have an Fc portion and so is not expected to be actively transported across the placenta as INF and ADA are. In a study of pregnant rats24 much lower levels of drug were found in the infant and in breast milk when given the PEGylated Fab’ fragment of this antibody vs. the murinized IgG1 antibody of TNFα. Similarly, in humans, a series of 10 patients with CD receiving CZP during pregnancy up to 2 weeks prior to delivery describes high levels of drug in the mother’s serum but low levels in the infants and their cord blood on day of birth.25 It is hypothesized that the Fab’ fragment may cross the placenta passively in low levels in the first trimester during the period of organogenesis. Yet, this may be true for all anti-TNF agents, and further data are clearly needed to establish safety. CZP was not detected in breast milk in 1 patient tested.

INFANT VACCINATIONS
The effect of exposure to anti-TNF therapy on the infant’s developing immune system is unknown. Thus far there has been no reported adverse event associated with elevated INF levels in the newborns, although there is no long-term follow up. In our experience, infants exposed to INF in utero have appropriate response to standard early vaccinations.26 In adults receiving ADA, pneumococcal and influenza vaccinations were given safely and effectively.27 However, in adults maintained on combination immunomodulator (6MP/ AZA) and biologic (INF/ADA) therapy, there is a recent report of a lower response to pneumococcal vaccine (PSV-23) by measured antibody titers.28 Live vaccinations such as varicella, small pox, etc. are contraindicated in immunosuppressed patients on anti-tumor necrosis factor therapy.29 Traditionally the first live virus encountered by an infant was at one year of age (varicella, measles-mumps-rubella) when INF levels would be undetectable. However, now, rotavirus live vaccine is given at 2 months of age. Though it is given orally and is significantly attenuated, its safety in this setting is not known and the mother and pediatrician should be cautioned against its use if INF or ADA levels may be present. Rotavirus vaccine can be given to the infant if there is no detectable infliximab in their blood at the time of vaccination or if they were exposed to certolizumab, as it does not cross the placenta in significant levels. As testing for adalimumab levels is not commercially available, we advise mothers not to have their child vaccinated against rotavirus. Of note, some areas still use oral polio vaccine (live) rather than the attenuated injection. This should also be avoided in the first 6 months of life in the infant exposed to INF/ADA in utero.

TIMING OF ANTI-TNF THERAPY IN PREGNANCY
All three anti-TNF’s should be continued through conception and the first and second trimester on schedule. In our practice, if the patient is in remission, we give the last dose of infliximab around week 30 gestation and then immediately after delivery. We give the last dose of adalimumab at approximately week 32 of gestation and then immediately after delivery. If the mother flares during this time period, the options include restarting anti-TNF or using steroids to manage the patient until delivery. This decision is driven by how far the mother is from delivery. While we would refrain from giving infliximab at week 39 of gestation, a mother who is flaring at week 34 on adalimumab would likely benefit from continuing dosing on schedule. Certolizumab, given its minimal transfer across the placenta, is continued on schedule until delivery.

SUMMARY
Women with IBD on anti-TNF therapy with infliximab, adalimumab or certolizumab can continue its...
use during conception, pregnancy and lactation as it is considered compatible with use in pregnancy and lactation. There is no negative impact on fertility reported and there actually is a theoretical benefit with respect to reduction in inflammation leading to higher conception rates. If the mother remains in remission, infliximab and adalimumab should be discontinued in the early third trimester (weeks 30–32) and restarted immediately after delivery to minimize exposure to the infant. Certolizumab has minimal passive transfer and immediately after delivery to minimize exposure to the early third trimester (weeks 30–32) and restarted immediately after delivery to minimize exposure to the infant. Certolizumab has minimal passive transfer and may be restarted immediately after delivery.

References