Management of Biologic Agents During Pregnancy in Patients with Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) affects women in their peak reproductive years. Since disease activity has been shown to increase the risk of pregnancy and neonatal complications, it is generally advised that women continue appropriate medical therapy throughout pregnancy. There is growing evidence that the use of biologics is safe during pregnancy and does not increase the incidence of congenital malformations. However, recent studies confirming the placental transfer of anti-tumor necrosis factor (TNF)-α antibodies and the potential impact of these agents on the development of the neonatal immune system are concerning. Results from prospective trials with long-term follow-up will provide further insight into the impact of these drugs on neonatal health and help clarify the proper use of these agents during pregnancy.

INTRODUCTION

Inflammatory Bowel Disease (IBD) is common in women of childbearing age with a peak incidence in the third decade of life. Compared to age-matched controls, pregnant women with IBD are more likely to have pregnancy complications, such as preterm delivery and small for gestational age (SGA) births. Disease activity has been shown to increase the rates of adverse events further. Therefore, most guidelines recommend that women continue their medications during the majority of their pregnancy with a goal of maintaining disease remission. For some patients, this requires the continued use of biologic agents.

Safety of Anti-TNFα Use in Pregnancy

Infliximab (IFX), Certolizumab (CZP) and Adalimumab (ADA) are Food and Drug Administration (FDA) category B in pregnancy. Case reports and small observational studies have demonstrated that their use during pregnancy result in outcomes that are similar to pregnant patients with IBD not on these medications and do not increase the risk of congenital malformations. However, a review of the FDA database of reported adverse events with entanercept, IFX, and ADA revealed 34 types of congenital anomalies in total and suggested 19 (56%) of those were part of the VACTERL
(vertebral abnormalities, anal atresia, cardiac defects, tracheoesophageal, renal, and limb abnormalities) spectrum. This study had several major limitations, including the voluntary reporting of adverse events which could result in reporter bias while the total number of pregnant patients treated with anti-TNFα agents was unknown, precluding any calculation of a true incidence. More recently, Casanova et al performed a retrospective, multi-center study comparing the safety of 66 women exposed to biologic agents while controlling for disease activity using clinical scores (Harvey-Bradshaw index and Mayo Score). Compared to patients not exposed to immunosuppressive agents, anti-TNFα agents did not increase pregnancy (27.7% vs. 30.3%) or neonatal complications (23.3% vs. 21.2%) suggesting they are safe to use in pregnancy.

The safety of anti-TNFα agents in pregnant women with IBD is further supported by findings from the PIANO study (Pregnancy in IBD and Neonatal Outcomes), which is a large prospective registry of pregnant women with IBD created to evaluate the safety of biologic and immunosuppressant medications (azathioprine/6-MP). Overall, medication exposure did not increase congenital abnormalities. When adjusted for disease activity, the use of anti-TNFα agents were associated with increased spontaneous abortions (RR 2.56; 95% CI=1.01-3.31) and increased C-sections (RR 1.23 1.02-1.48). The increase in spontaneous abortions may represent reporting bias as anti-TNF exposed patients likely enrolled earlier in pregnancy. In addition, patients exposed to combination therapy had increased rates of preterm birth (RR 1.83; 95% CI=1.01-3.31).

Role of anti-TNFα Antibodies in Immune System Development

IFX and ADA are immunoglobulin G (IgG) antibodies to TNF and can potentially neutralize the critical role that TNFα plays in immune system defense and development. Fetal immunity is obtained by transfer of antibodies, such as IgG, from the maternal to fetal circulation during pregnancy. The levels of fetal immunoglobulins rise in linear fashion from at least 13 weeks gestation, with maximal transfer in the third trimester. IgG1 is the most efficiently transferred Ig subclass.

TNFα is essential for macrophage activation, phagosome activation, differentiation of monocytes into macrophages, recruitment of neutrophils, and granuloma formation. Therefore, therapy with TNF blockers is associated with an increased risk of granulomatous and intracellular infections. In addition, there is evidence that TNFα is involved in secondary lymphoid tissue development, including formation of lymphoid follicles and germinal centers.

Placental Transfer of Anti-TNFα Agents

Given the importance of TNFα in preventing infection, as well as immune development, there is concern about the placental transfer of anti-TNFα antibodies and the impact on neonatal immune defense. The placental transfer of biologic agents were first reported in a case report of significant IFX levels being detected in the offspring of a mother who was exposed to IFX throughout her pregnancy with the last dose being given two weeks prior to delivery. These levels persisted for up to 6 months. This was followed by a case series of four patients who received IFX at 30 weeks gestation or less. Three of the neonates had IFX levels that were two to three-fold higher than in the peripheral blood of their mothers.

More recently, the issue of placental transfer of anti-TNFα agents were further addressed by measuring serum concentrations of anti-TNFα antibodies in 31 pregnant women with IBD receiving IFX (n=11), ADA (n=10), or CZP (n=10). Levels of the biologic agents were measured in the infant, cord blood, and mother at birth and then in the infant until levels were undetectable. At a median of 35 and 38.5 days from maternal dosing, the median neonatal IFX level at birth was 160% (range 87%-400%) and neonatal ADA level at birth 179% (range 98%-293%) that of the mother, respectively. Drug levels could be detected in the infant for up to 6 months, but no congenital abnormalities were detected. Neonatal concentrations of CZP were only 3.9% (range, 1.5%-24%) of the mothers’ at birth at a median last dose of 19 days before delivery. CZP is a pegylated Fab fragment and does not have an Fc portion, so active transport of this drug across the placenta via the FcRN (Fc receptor) does not appear to occur.

Neonatal Response to Vaccines

Because the IFX and ADA can persist in the infant for up to 6 months, exposure and response to routine neonatal
vaccines remains a concern. This is evidenced by a case of a 28 year-old female with refractory Crohn’s disease who received IFX throughout her pregnancy. Her baby was born healthy and received a Bacillus Calmette-Guérin (BCG) vaccine at 3 months of age, but soon after died from disseminated BCG. Thus, it is recommended that live virus vaccines (including rotavirus, intranasal influenza vaccine, and BCG) be withheld for 6 months from birth in neonates that have had in utero exposure to IFX or ADA. In the United States, the rotavirus vaccine is typically given at 2 months of age and is the only live virus vaccine routinely offered in that time frame. However, the administration of standard inactivated neonatal vaccines is not discouraged since there are no reported adverse events associated with these vaccines. In addition, there is evidence that infants with neonatal exposure to biologics can still mount an appropriate response to these vaccinations.

### Anti-TNFα Therapy in the Third Trimester

Given the growing evidence of placental transfer of anti-TNFα agents in the neonate with persistent levels for up to 6 months, additional data is needed to determine if early cessation of anti-TNF therapy during pregnancy is beneficial to maternal and neonatal health. This issue was addressed in a recent study of 28 pregnant women who received their last dose of IFX or ADA before 30 weeks gestation. Among the 17 patients who received IFX, 12 (71%) of the patients in remission discontinued their therapy before 30 weeks and did not have a relapse of their disease. The remaining 5 (29%) patients continued their IFX until 30-34 weeks of gestation. Mothers who were restarted on their anti-TNFα agents post-partum did well, except for one patient who developed a reaction to IFX after resuming therapy 22 weeks post-partum and 2 others who switched to ADA due to side effects. All patients on ADA were in remission and had their medication discontinued prior to 26 weeks gestation with two of these patients having a relapse of their symptoms. One required treatment with steroids at 30 weeks gestation and the other had a C-section at 37 weeks gestation.

### Safety of Natalizumab During Pregnancy

Unlike TNFα antibodies, there is limited human data regarding the use of Natalizumab (NAT) in pregnant women with IBD. NAT is currently considered to be

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Table 1. Biologics for Inflammatory Bowel Disease Management During Pregnancy

<table>
<thead>
<tr>
<th>Medication</th>
<th>US FDA Category</th>
<th>Recommendations for Pregnancy</th>
<th>Recommendations for Breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>B</td>
<td>Low risk</td>
<td>Compatible</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>B</td>
<td>Low risk</td>
<td>Compatible</td>
</tr>
<tr>
<td>Infliximab</td>
<td>B</td>
<td>Low risk</td>
<td>Compatible</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>C</td>
<td>Limited human data</td>
<td>Limited human data, likely compatible</td>
</tr>
</tbody>
</table>

FDA category C in pregnancy. Recently, there was a prospective report of 35 pregnant women with multiple sclerosis who inadvertently got pregnant while taking NAT. All women received NAT at 8 weeks prior to their last menses and stopped the medication when they became aware of their pregnancy. There were a total of 28 healthy births with one child being born with hexadactyly. Five pregnancies ended in an early miscarriage and one woman decided to undergo an elective termination of pregnancy. In addition, the PIANO registry includes 6 women with NAT exposure during pregnancy with no observed increase rates of congenital abnormalities.

More recently, a study of T-lymphocyte chemotaxis rates in neonates that were exposed to NAT in utero, revealed a decreased response in the presence of a chemoattractant agent. Clinical implications of this finding are uncertain. Larger trials are needed to determine the safety and long-term impact of NAT use during pregnancy.

Breast Feeding with Anti-TNFα Agents

There is growing evidence that breast feeding while on therapy with anti-TNFα antibodies is safe. Earlier studies did not detect any drug levels in breast milk of mothers who were treated with anti-TNFα drugs. However, in a recent study of 3 patients, IFX levels in breast milk rose up to 101 ng/ml within 2-3 days of an infusion, which was roughly 1/200th of the level in blood. Similarly, milk ADA levels were less than 1/100 of the corresponding level in serum 3 days after injection of the drug. Thus, given the nanogram level of anti-TNFα drugs detected in breast milk, women are not discouraged from breast-feeding while on these drugs. There is no available data on the levels of NAT detected in breast milk.

SUMMARY/RECOMMENDATIONS

In summary, caring for a pregnant patient with IBD can be challenging as providing optimal medical therapy with biologics to control disease activity must be balanced with concerns regarding potential harm to the fetus and infant. Despite the growing evidence regarding the safety of biologics during pregnancy (Table 1) with respect to congenital malformations, the placental transfer of IFX and ADA raises concerns about the risk of infection and potential impact of these drugs on the development of the neonatal immune system. This risk must be weighed against the clear and well-documented risk to the fetus of preterm birth with maternal disease activity and the subsequent negative sequelae of preterm birth to childhood outcomes. Thus, timing of the last dose of the anti-TNFα agent needs to be individualized, with the goal of limiting the placental transfer of drug to the neonate while maintaining remission in the mother.

Based on the available data, it is our practice to give the last dose of IFX between 30-32 weeks gestation and ADA around 36 weeks gestation. In a patient with longstanding deep remission, stopping in the second trimester can be considered to minimize placental transfer, though this is not our practice. Given the minimal placental transfer of CZP, this can be continued as scheduled throughout pregnancy without adjustment. Regardless of the timing of the last dose of the biologic agent, live vaccines should be withheld for at least 6 months post-partum in infants exposed to IFX and ADA in utero. The use of anti-TNFα agents is compatible with breastfeeding. The pediatrician should also be alerted to monitor for infections in the exposed infant. Results from prospective trials with long-term follow-up will provide further insight into the impact of these drugs on newborn development and will help guide the appropriate use of these agents throughout pregnancy, particularly during the third trimester.

References