

## 1-MINUTE CONSULT

### GREGORY T. BRENNAN, MD

Gastroenterology Fellow, Department of Medicine, Division of Gastroenterology, University of California Irvine Medical Center, Irvine, CA

### ALEX DUONG

Student, Department of Medicine, Division of Gastroenterology, University of California Irvine Medical Center, Irvine, CA

### EMILY T. NGUYEN, PharmD

Pharmacist, Department of Pharmacy, University of California Irvine Medical Center, Irvine, CA

### DOUGLAS L. NGUYEN, MD

Associate Professor, Department of Medicine, Division of Gastroenterology, University of California Irvine Medical Center, Irvine, CA



BRIEF ANSWERS  
TO SPECIFIC  
CLINICAL  
QUESTIONS

## Q: Are anti-TNF drugs safe for pregnant women with inflammatory bowel disease?

**A:** Yes, anti-tumor necrosis factor (anti-TNF) therapy for inflammatory bowel disease (IBD) can be continued during pregnancy.

IBD is often diagnosed and treated in women during their reproductive years. Consequently, these patients face important decisions about the management of their disease and the safety of their baby. Clinicians should be prepared to offer guidance by discussing the risks and benefits of anti-TNF agents with their pregnant patients who have IBD, as well as with those considering pregnancy.

### STUDIES OF THE POTENTIAL RISKS

Anti-TNF agents are monoclonal antibodies. Infliximab, adalimumab, and golimumab are actively transported into the fetal circulation via the placenta, mainly during the second and third trimesters. Certolizumab crosses the placenta only by passive means, because it lacks the fragment crystallizable (Fc) region required for placental transfer.<sup>1</sup>

#### Effects on pregnancy outcomes

In a 2016 meta-analysis,<sup>2</sup> of 1,242 pregnancies in women with IBD, 482 were in women on anti-TNF therapy. It found no statistically significant difference in rates of adverse pregnancy outcomes including congenital abnormality, preterm birth, and low birth weight.

A meta-analysis of 1,216 pregnant women with IBD found no statistically significant differences in rates of spontaneous or elective abortion, preterm birth, low birth weight, or congenital malformation in those on anti-TNF therapy vs controls.<sup>3</sup>

A systematic review of 58 studies including more than 1,500 pregnant women with IBD who were exposed to anti-TNF agents concluded that there was no association with adverse pregnancy outcomes such as spontaneous abortion, preterm delivery, stillbirth, low birth weight, congenital malformation, or infection.<sup>4</sup>

A retrospective cohort study of 66 pregnant patients with IBD from several centers in Spain found that anti-TNF or thiopurine therapy during pregnancy did not increase the risk of pregnancy complications or neonatal complications.<sup>5</sup>

#### Effects on newborns

Cord blood studies have shown that maternal use of infliximab and adalimumab results in a detectable serum level in newborns, while cord blood levels of certolizumab are much lower.<sup>1,6</sup> In some studies, anti-TNF drugs were detectable in infants for up to 6 months after birth, whereas other studies found that detectable serum levels dropped soon after birth.<sup>1,7</sup>

Addressing concern about an increased risk of infection or dysfunctional immune development in newborns exposed to anti-TNF drugs in utero, a systematic review found no increased risk.<sup>4</sup> A retrospective multicenter cohort study of 841 children also reported no association between in utero exposure to anti-TNF agents and risk of severe infection in the short term or long term (mean of 4 years).<sup>8</sup> Additional studies are under way to determine long-term risk to the newborn.<sup>7</sup>

### THE TORONTO CONSENSUS GUIDELINES

The Toronto consensus guidelines strongly recommend continuing anti-TNF therapy

Active IBD poses a greater risk to mother and baby than continuing anti-TNF therapy

Douglas L. Nguyen, MD, has disclosed teaching and speaking for Abbvie and Janssen.

doi:10.3949/ccjm.85a.18037

during pregnancy in women with IBD who began maintenance therapy before conception.<sup>6</sup>

If a patient strongly prefers to stop therapy during pregnancy to limit fetal exposure, the Toronto consensus recommends giving the last dose at 22 to 24 weeks of gestation. However, this should only be considered in patients whose IBD is in remission and at low risk of relapse.<sup>6,9</sup>

Although anti-TNF drugs may differ in terms of placental transfer, agents should not be switched in stable patients, as switching increases the risk of relapse.<sup>10</sup>

### ■ BENEFITS OF CONTINUING THERAPY

Active IBD poses a significantly greater risk to the mother and the baby than continuing anti-TNF therapy during pregnancy.<sup>1,7</sup> The primary benefit of continuing therapy is to maintain disease remission.

Among women with active IBD at the time of conception, one-third will have improvement in disease activity during the course of their pregnancy, one-third will have no change, and one-third will have worsening of disease activity. But if IBD is in remission at the time of conception, it will remain in remission in nearly 80% of women during pregnancy.<sup>1</sup>

Women with active IBD are at increased risk of preterm delivery, low birth weight, and intrauterine growth restriction.<sup>1,2,5</sup> Also, women with IBD have an increased risk of venous thromboembolism, particularly if they have active disease during pregnancy.<sup>1</sup> Therefore, achieving and maintaining remission are

vital in the management of the pregnant patient with IBD.

### ■ CONSIDERATIONS AFTER BIRTH: BREAST-FEEDING AND VACCINATION

Breast-feeding is considered safe. Minuscule amounts of infliximab or adalimumab are transferred in breast milk but are unlikely to result in systemic immune suppression in the infant.<sup>7</sup>

Live-attenuated vaccines should be avoided for the first 6 months in infants exposed to anti-TNF agents in utero.<sup>1,7,11</sup> All other vaccines, including hepatitis B virus vaccine, should be given according to standard schedules.<sup>6</sup>

### ■ OUR RECOMMENDATIONS

The goal of managing IBD in women of reproductive age is to minimize the risk of adverse outcomes for both mother and baby. We recommend a team approach, working closely with a gastroenterologist and a high-risk-pregnancy obstetrician, if available.

Patients should continue anti-TNF therapy during pregnancy because evidence supports its safety. If a woman wants to stop therapy and is at low risk of relapse, we recommend giving the last dose at 22 to 24 weeks of gestation, then promptly resuming therapy postpartum.

Live-attenuated vaccines (eg, influenza, rotavirus) should be avoided for the first 6 months in babies born to mothers on anti-TNF therapy. ■

### ■ REFERENCES

1. Ananthakrishnan AN, Xavier RJ, Podolsky DK. *Inflammatory Bowel Diseases: A Clinician's Guide*. Chichester, UK: Wiley; 2017. doi:10.1002/9781119077633
2. Shihab Z, Yeomans ND, De Cruz P. Anti-tumour necrosis factor alpha therapies and inflammatory bowel disease pregnancy outcomes: a meta-analysis. *J Crohns Colitis* 2016; 10(8):979–988. doi:10.1093/ecco-jcc/jjv234
3. Narula N, Al-Dabbagh, Dhillon A, Sands BE, Marshall JK. Anti-TNF alpha therapies are safe during pregnancy in women with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis* 2014; 20(10):1862–1869. doi:10.1097/MIB.0000000000000092
4. Nielsen OH, Loftus EV Jr, Jess T. Safety of TNF-alpha inhibitors during IBD pregnancy: a systematic review. *BMC Med* 2013; 11:174. doi:10.1186/1741-7015-11-174
5. Casanova MJ, Chaparro M, Domenech E, et al. Safety of thiopurines and anti-TNF-alpha drugs during pregnancy in patients with inflammatory bowel disease. *Am J Gastroenterol* 2013; 108(3):433–440. doi:10.1038/ajg.2012.430
6. Nguyen GC, Seow CH, Maxwell C, et al; IBD in Pregnancy Consensus Group; Canadian Association of Gastroenterology. The Toronto consensus statements for the management of inflammatory bowel disease in pregnancy. *Gastroenterology* 2016; 150(3):734–757.e1. doi:10.1053/j.gastro.2015.12.003
7. Gisbert JP, Chaparro M. Safety of anti-TNF agents during pregnancy and breastfeeding in women with inflammatory bowel disease. *Am J Gastroenterol* 2013; 108(9):1426–1438. doi:10.1038/ajg.2013.171
8. Chaparro M, Verreth A, Lobaton T, et al. Long-term safety of in utero exposure to anti-TNF alpha drugs for the treatment of inflammatory bowel disease: results from the multicenter European TEDDY Study. *Am J Gastroenterol* 2018; 113(3):396–403. doi:10.1038/ajg.2017.501
9. de Lima A, Zelinkova Z, van der Ent C, Steegers EA, van der Woude CJ. Tailored anti-TNF therapy during pregnancy in patients with IBD: maternal and fetal safety. *Gut* 2016; 65(8):1261–1268. doi:10.1136/gutjnl-2015-309321
10. Van Assche G, Vermeire S, Ballet V, et al. Switch to adalimumab in patients with Crohn's disease controlled by maintenance infliximab: prospective randomised SWITCH trial. *Gut* 2012; 61(2):229–234. doi:10.1136/gutjnl-2011-300755
11. Saha S. Medication management in the pregnant IBD patient. *Am J Gastroenterol* 2017; 112(5):667–669. doi:10.1038/ajg.2017.22

ADDRESS: Douglas L. Nguyen, MD, Department of Medicine, Division of Gastroenterology, University of California Irvine Medical Center, 333 City Boulevard West, #400, Orange, CA 92868; douglaln@uci.edu