Seymour Katz, M.D., Series Editor

# The Use of Vedolizumab in Pregnancy and Breastfeeding in Women with Inflammatory Bowel Disease

Kerri Glassner

Bincy P. Abraham

Many women with inflammatory bowel disease (IBD) are diagnosed during their childbearing years. Accordingly, patients and their providers may experience significant anxiety about the impact of their disease course and medications on pregnancy and breastfeeding. Unfortunately, it is not uncommon to encounter a pregnant IBD patient who presents with active disease after stopping their medications, either by personal choice or on advice from their obstetrician or gastroenterologist. Active disease at the time of conception and during pregnancy has been associated with poor pregnancy outcomes including an increased risk of preterm birth, low birth weight, and fetal loss.[1-7] In fact, the greatest risk to the mother and fetus during pregnancy has been found to be active IBD, not the medications used to treat it.[7-10] Recently, there has been increased attention on the importance of preemptive counseling of women with IBD and their providers on the role of disease control on pregnancy outcomes.

Vedolizumab is a humanized immunoglobulin $G_1$ monoclonal antibody targeting α4ß7 integrin. Unlike anti-TNF agents or immunomodulators, vedolizumab is gut selective, and works by inhibiting leukocyte migration into inflamed intestinal tissue via the α4ß7 integrin expressed on circulating B and T lymphocytes.[11-14] Vedolizumab is FDA approved for the treatment of both ulcerative colitis and Crohn's disease. Animal studies have shown that mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1) is expressed by maternal vessels in the placenta and recruits α4ß7 expressing cells that are considered important for maternal fetal tolerance.[15] However, it is unknown what effect, if any, vedolizumab use in humans has on maternal placental vessels.

## Pregnancy Outcomes

Few studies have been published on the use of vedolizumab during pregnancy. A review of the literature identified 6 publications with a total of 104 pregnancies in women who received vedolizumab during conception and/or pregnancy with available birth outcome data which can be seen in Table 1.[16-21] Among these, there were 80 (77%) of

Kerri Glassner DO Bincy P. Abraham MD MS AGAF FACG Fondren Inflammatory Bowel Disease Program, Lynda K and David M Underwood Center for Digestive Disorders, Division of Gastroenterology and Hepatology, Houston Methodist Hospital and Weill Cornell Medical College

**Table 1. Pregnancy Outcomes in Women With Inflammatory Bowel Disease With and Without Biologic Exposure Compared to the United States General Population**

| Pregnancy outcome | Total number of VDZ exposed pregnancies[A] (n=104) | Infliximab exposed pregnancies[B] (n=106) | Non-biologic exposed pregnancies in IBD[B] (n=106) | US general population[C] |
|---|---|---|---|---|
| **Live birth** | 80 (77%) | 81 (81.8%) | 82 (91.1%) | 64.6% |
| **Congenital anomaly** | 6 (6%)<br>1 Hip dysplasia<br>1 Pulmonary valve stenosis<br>1 Hirschsprung's disease<br>1 Congenital hypothyroidism<br>1 Agenesis of the corpus callosum<br>1 Neural tube defect | 1 (1.2%)<br>1 ectrodactyly | 3 (3.7%)<br>1 down syndrome<br>1 heart murmur<br>1 cortical vision delay and delayed development of fine motor skills | 4% |
| **Spontaneous abortion** | 11 (11%) | 16 (16.2%) | 8 (8.9%) | 10-17% |
| **Elective/ therapeutic termination** | 8 (8%) | 2 (2.0%) | 0 (0%) | 18.4% |
| **Still birth** | 1 (1%) | | | 1% |
| **Pre term birth** (< 37 weeks gestation) | 15 (14%) | 4 (3.8%) | 5 (4.7%) | 9-10% |

[A]Available data from 6 studies on the use of vedolizumab during pregnancy in women with IBD.
[B]TREAT registry outcomes of women treated with infliximab during pregnancy compared with women not on biologic therapy during pregnancy.
[C]CDC reporting on pregnancy outcome data in the United States from 1990-2014.

pregnancies that resulted in at least one live birth, 6 (6%) congenital anomalies, 11 (11%) spontaneous abortions, 8 (8%) elective terminations, and 1 (1%) stillbirth or pregnancy loss at greater than 20 weeks gestation. There were 15 (14%) preterm births (less than 37 weeks gestation).

Based upon data from the CDC, the live birth rate in 2008 among an estimated 6,578,000 pregnancies in women in the United States was 65% and is shown in Table 1.[22] Previous data from pregnancies among women with IBD showed the live birth rate to be 60%, lower than in women without IBD.[5] More recent data from the TREAT registry following women with IBD who were treated with infliximab as well as those without biologic exposure, found a much higher live birth rate of 91.1%, Table 1.[23] Based upon the available data in women with IBD using vedolizumab during pregnancy, the live birth rate of 77% appears to be higher than that of both women in the general United States population, and of that seen in certain studies of pregnancy outcomes in women with IBD.[5,16-22] The differences seen in live birth rates may be related to other factors including small sample size, outcome reporting, or closer monitoring of mothers on biologic therapy. In the general population, the rate of spontaneous abortion or miscarriage

*(continued on page 16)*

(continued from page 14)

is 10-17% of clinically recognized pregnancies, and typically occurs in the first trimester.[24] In the TREAT registry, the spontaneous abortion rate was 16% in infliximab exposed pregnancies, and 8.9% in non-biologic exposed pregnancies.[23] The overall rate of spontaneous abortions in women with IBD on vedolizumab appears to be similar to that of both the general population and infliximab exposed pregnancies.[16-21, 23-24] The pre-term birth rate in the United States has been found to be 9-10%.[25] Previous studies have shown that there is an increased risk of premature delivery in patients with inflammatory bowel disease, especially those with more severe disease activity.[1,26-27] The TREAT registry had a low pre term birth rate of 3.8% in infliximab, and 4.7% in non-biologic exposed pregnancies.[23] In vedolizumab exposed women the pre-term birth rate was higher at 14%, but comparable to other studies of pregnancy outcomes in women with IBD.[5] The higher rate of pre-term birth seen in the vedolizumab group compared to the TREAT registry may be explained by the fact that vedolizumab is often a second or third-line therapy used in patients with severe disease after having failed multiple biologics. It is known that more severe disease activity correlates with an increased risk of pre-term birth.[7] In the United States, the stillbirth rate is 1%.[28] The current literature on vedolizumab is similar, with a stillbirth rate of 1%.

Major structural birth defects occur in 3-5% of births in the United States.[29-31] In the TREAT registry, women treated with infliximab had a congenital anomaly rate of 1.2% compared to women without biologic exposure who had a rate of 3.7%.[23] In women exposed to vedolizumab the rate of congenital anomalies appears to be slightly higher at 6%. However, none of the congenital anomalies were felt to be related to vedolizumab's mechanism of action. Hip dysplasia, pulmonary valve stenosis, and Hirschsprung's disease occurred in three infants, one infant was born with congenital hypothyroidism, and there was a single case of agenesis of the corpus callosum and left frontal polymicrogyria in a healthy volunteer who received a single dose of vedolizumab 79 days prior to conception. Investigators felt that all of the congenital anomalies were unrelated to vedolizumab use. Of the elective terminations, one patient underwent an induced abortion due to a neural tube defect. This patient was also taking sulfasalazine which inhibits folate synthesis.[32] Folate is known to have protective effects against the development of neural tube defects and supplementation is recommended at conception and during pregnancy.[33-34] In analyzing the congenital anomalies as a whole, no two babies developed the same anomaly, and there is no evidence of an association with vedolizumab's mechanism of action, making any causal effect unlikely.

### *Infant outcomes*

IgG antibody transfer is known to increase from week 16 of gestation, with the majority of transfer occurring during the third trimester.[35-36] Studies have demonstrated placental transfer of anti-TNF biologic agents with the exception of certolizumab.[37-38] In PIANO registry data, vedolizumab was present in the infant serum at birth, however was less than half that of the mother[39]. This is in comparison to infliximab, where levels in the infant were found to be double that of the mother.[40] Previously physicians have recommended the discontinuation of biologic medications in the third trimester due to fear of an increased risk of infection and other adverse outcomes in the exposed infant. However, exposure to anti-TNF therapy in the third trimester of pregnancy in the PIANO registry was not associated with an increased risk of infection in the infant.[41] In addition, recent studies have shown that there is no increased risk of pre-term birth or low birth weight among women receiving anti-TNF therapy during the third trimester of pregnancy.[42] An increased risk of pre-term birth or low birth rate was however associated with disease activity. Infants exposed in utero to immunomodulator and biologic therapy did not exhibit developmental delay compared to unexposed infants, with development scores in some categories actually higher in the exposed infants.[43-44]

In anti-TNF medications other than certolizumab, the rotavirus vaccination is avoided.[7,45] Vedolizumab however, is not an immunosuppressant and does not pose the same risk for live virus vaccinations. In fact, patients themselves are able to receive live virus

vaccines.[46-47] Thus, infants exposed to vedolizumab should be able to receive the rotavirus vaccination. In one study of vedolizumab exposed mothers, 9 infants were inadvertently administered the rotavirus vaccination and none experienced any adverse outcomes.[16]

Of the studies that reported data on the outcomes of infants born to vedolizumab exposed mothers with IBD, there was only 1 hospitalization reported during the first year of life for fever of unknown origin.[16] No other known hospitalizations occurred for the other 99 infants despite in utero vedolizumab exposure.

### *Breastfeeding*

Breastfeeding is highly recommended by the American Academy of Pediatrics for at least the first 6 months of a babies' life.[48] In women with inflammatory bowel disease, breastfeeding has not been shown to have any adverse effects on disease activity.[49] Several studies have assessed the transfer of anti-TNF agents, the anti-integrin natalizumab, and interleukin 12-23 inhibitor ustekinumab to breast milk. Although all were found to be present at low levels, exposed infants had similar rates of growth, milestone achievement, and infection risk compared with non-breastfed or unexposed infants.[50] In two small studies of ten lactating women with inflammatory bowel disease, vedolizumab has been found to be present in breast milk in small amounts.[51-52] Drug levels have not exceeded 480 ng/ml or 1/100$^{th}$ of the comparable serum levels. Fully breastfed infants primarily consume secretory IgA with a low content of IgG. Although vedolizumab may be transferred to breast milk, it is not used orally and is unlikely to be bioavailable in the newborn's stomach. The minute quantity of vedolizumab is suspected to undergo proteolysis in the newborn's digestive tract. All infants exposed to vedolizumab in breast milk reached normal developmental milestones at 3.5 to 10 months and there was no increase in general or intestinal infections.[51-52]

## CONCLUSIONS

Current evidence supports the safety and benefits of continuing vedolizumab during pregnancy and breastfeeding. The rates of live birth and miscarriage are similar to those seen in the general population. The pre-term birth rate appears to be higher than that of the general population, but similar to previous studies of pregnancy outcomes in women with IBD. The congenital anomaly rate is slightly higher than that of the general population, however reassuringly, none of the anomalies have been felt to be related to vedolizumab's mechanism of action. Although vedolizumab has been found to be present in infant serum at birth and in breastmilk, there has not been any increase in infection, and infants reached normal developmental milestones. In addition, newborns administered the live rotavirus vaccination did not have any adverse effects. Although the current data is reassuring, larger studies are still needed to confirm these findings. ■

## References

1. Kammerlander H, Nielsen J, Kjeldsen J, et al. The effect of disease activity on birth outcomes in a nationwide cohort of women with moderate to severe inflammatory bowel disease. Inflamm Bowel Dis 2017;23(6):1011-1018.
2. Van der Woude CJ, Ardizzone S, Bengtson MB, et al. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. J Crohns Colitis 2015;9:107-24.
3. Bengtson MB, Solberg IC, Aamodt G, et al. Relationships between inflammatory bowel disease and perinatal factors: both maternal and paternal disease are related to preterm birth of offspring. Inflamm Bowel Dis 2010;16:847-55.
4. Miller JP. Inflammatory bowel disease in pregnancy: a review. J R Soc Med 1986;79:221-5.
5. Mahadevan U, Sandborn WJ, Li DK, et al. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. Gastroenterol 2007;133:1106-12
6. Norgard B, Hundborg HH, Jacobsen BA, et al. Disease activity in pregnant women with Crohn's disease and birth outcomes: a regional Danish cohort study. Am J Gastroenterol 2007;102:1947-1954.
7. Mahadevan U, Robinson C, Bernasko N, et al. Inflammatory bowel disease in pregnancy clinical care pathway: a report from the American gastroenterological association IBD parenthood project working group. Gastroenterol 2019;156:1508-1524.
8. Mahadevan U, Cucchiara S, Hyams JS, et al. The London position statement of the World Congress of Gastroenterology on biological therapy for IBD with the European Crohn's and Colitis Organization: pregnancy and pediatrics. Am J Gastroenterol 2011;106:214-23.
9. Mahadevan U, Martin C, Sandler R, et al. Piano: A 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy. Gastroenterol 2012;142:S-149.
10. Chaparro M, Verreth A, Lobaton T, et al. Long-term safety of in utero exposure to anti-tnfa drugs for the treatment of inflammatory bowel disease: results from the multicenter European TEDDY study. Am J Gastroenterol 2018;113:396-403.
11. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013;369:699-710.
12. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2013;369:711-21.
13. Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. Gut 2017;66:839-851.
14. Soler D, Chapman T, Yang LL, et al. The binding specificity and selective antagonism of vedolizumab, an anti-a4ß7 integrin therapeutic

antibody in development for inflammatory bowel diseases. J Pharmacol Exp Ther 2009;330:864-75.
15. Fernekorn U, Butcher EC, Behrends J, et al. Functional involvement of P-selectin and MAdCAM-1 in the recruitment of a4ß7 integrin expressing monocyte-like cells to the pregnant mouse uterus. Eur J Immunol 2004;34:3423-33.
16. Moens A, Van Hoeve K, Humblet E, et al. Outcome of pregnancies in female patients with inflammatory bowel disease treated with vedolizumab. J Crohns Colitis 2019;12-18.
17. Shitrit A, Ya'acov A, Livovsky D, et al. Exposure to Vedolizumab in IBD pregnant women appears of low risk for mother and neonate: a first prospective comparison study. Am J Gastroenterol 2019;00:1-4.
18. Mahadevan U, Vermeire S, Lasch K. et al. Vedolizumab exposure in pregnancy: outcomes form clinical studies in inflammatory bowel disease. Aliment Pharmacol Ther 2017;45:941-950.
19. Chambers C, Adams J, Xu R, et al. Results from the Vedolizumab pregnancy exposure registry: an OTIS pregnancy study. ACG 2018 Annual Scientific Meeting Abstracts.
20. Julsgaard M, Kjeldsen J, Baumgart DC. Vedolizumab safety in pregnancy and newborn outcomes. Gut 2017;66:1866-1867.
21. Sheridan J, Cullen G, Dohert G. Letter: Vedolizumab in pregnancy. J Crohns Colitis 2017;11:1025-6.
22. Ventura SJ, Curtin SC, Abma JC, et al. Estimated pregnancy rates and rates of pregnancy outcomes for the united states, 1990-2008. National Vital Statistics Reports 2012;60(7):1-21.
23. Lichtenstein GR, Feagan BG, Mahadevan U, et al. Pregnancy outcomes reported during the 13-year TREAT registry: a descriptive report. Am J Gastroenterol 2018;113(11):1678-1688.
24. Massalska D, Zimowski JG, Bijok J, et al. First trimester pregnancy loss: Clinical implications of genetic testing. J. Obstet. Gynaecol. Res 2017;43(1):23-29.
25. Martin JA, Osterman M. Describing the increase in preterm births in the united states, 2014-2016. NCHS Data Brief 2018;312:1-7.
26. Bush MC, Patel S, Lapinski RH, et al. Perinatal outcomes in inflammatory bowel disease. J Matern Fetal Neonatal Med 2004;15(4):237-41.
27. Reddy D, Murphy SJ, Kane SV, et al. Relapses of inflammatory bowel disease during pregnancy: in hospital management and birth outcomes. Am J Gastroenterol 2008;103(5):1203-9.
28. Hoyert DL, Gregory ECW. Cause of fetal death: data from the fetal death report, 2014. National vital stastistics reports 2016:65(7).
29. Mai C, Isenburg J, Langlois P, et al. Population-based birth defects data in the United States, 2008 to 2012: presentation of state-specific data and descriptive brief on variability of prevalence. Birth Defects Res A Clinc Mol Teratol 2015;103(11):972-993.
30. Marden PM, Smith DW, Mcdonald MJ. Congenital anomalies in the newborn infant, including minor variations. A study of 4,412 babies by surface examination for anomalies and buccal smear for sex chromatin. J Pediatr 1964;64:357.
31. Leppig KA, Werler MM, Cann CI, et al. Predictive value of minor anomalies. Association with major malformations. J Pediatr 1987;110(4):531.
32. Selhub J, Dhar GJ, Rosenberg IH. Inhibition of folate enzymes by sulfasalazine. J Clin Invest 1978;61(1):221-224.
33. Pitkin RM. Folate and neural tube defects. Am J Clin Nutr 2007;85(1):285S-288S.
34. Greenberg JA, Bell SJ, Guan Y, et al. Folic acid supplementation and pregnancy: more than just neural tube defect prevention. Rev Obstet Gynecol 2011;4(2):52-59.
35. Simister NE. Placental transport of immunoglobulin G. Vaccine 2003;21:3365-9.
36. Palmeira P, Quinello C, Silveira-Lessa AL, et al. IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol 2012;2012:985646.
37. Mahadevan U, Wolf DC, Dubinsky M, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2013;11(3):286-e24.
38. Mariette X, Forger F, Abraham B, et al. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, post-marketing, pharmacokinetic study. Annals of the Rheumatic Diseases 2018;77:228-233.
39. Mahadevan, U, Martin C, Kane S, et al. Do infant serum levels of biologic agents at birth correlate with risk of adverse outcomes? Results from the PIANO registry. Gastroenterol 2016;150(4):S91-S92.
40. Kathpalia P, Kane S, Mahadevan U. Detectable drug levels in infants exposed to biologics: so what? Gastroenterol 2016;151(1):25-26.
41. Mahadevan U, Martin C, Dubinsky M, et al. Exposure to anti-TNFa therapy in the third trimester of pregnancy is not associated with increased adverse outcomes: results from the PIANO registry. Gastroenterol 2014;146(5):S170.
42. Kammerlander H, Nielsen J, Knudsen T, et al. Anti-TNFa use during the third trimester of pregnancy in women with moderate-severe inflammatory bowel disease and the risk of preterm birth and low birth weight. Inflam Bowel Dis 2017;23(11):1916-1923.
43. Mahadevan U, Martin CF, Chambers C, et al. Achievement of developmental milestones among offspring of women with inflammatory bowel disease: the PIANO registry. Gastroenterol 2014;146(5):S1.
44. Roy A, Chambers C, Martin C, et al. Exposure to biologic therapy and childhood development among offspring of women with inflammatory bowel disease: results from the PIANO registry. Gastroenterol 2017;152(5):S85-86.
45. Julsgaard M, Christensen LA, Gibson P, et al. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. Gastroenterol 2016;151(1):110-119.
46. Food and Drug Administration. Entyvio. Prescribing information, 2014. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125476s022lbl.pdf. Accessed July 4, 2019.
47. Mahadevan U, Vermeire S, Lasch K, et al. Letter: vedolizumab drug levels in cord and maternal blood in women with inflammatory bowel disease-authors' reply. Aliment Pharmacol Ther 2018;48(3):388-389.
48. American Academy of Pediatrics. Breastfeeding and the use of human milk. Pediatrics 2012;129:e827-e841.
49. Moffat D, Illnycki A, Bernstein C. A population-based study of breastfeeding in inflammatory bowel disease: initiation, duration and effect on disease in the postpartum period: commentary. Am J Gastroenterol 2010;104:2517-23.
50. Matro R, Martin CF, Wolf D, et al. Exposure concentrations of infants breastfed by women receiving biologic therapies for inflammatory bowel disease and effects of breastfeeding on infections and development. Gastroenterol 2018;155:696-704.
51. Lahat A, Shitrit A, Naftali T, et al. Vedolizumab levels in breast milk of nursing mothers with inflammatory bowel disease. J Crohn Colitis 2018;12:120-123.
52. Julsgaard M, Kjeldsen J, Bibby B, et al. Vedolizumab concentrations in the breast milk of nursing mothers with inflammatory bowel disease. Gastroenterol 2018;154:752-754.

## Answers to this month's crossword puzzle: