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, monoclonal antibody targeting \(\alpha 4\beta 7\) integrin. Unlike anti-TNF agents or immunomodulators, vedolizumab is gut selective, and works by inhibiting leukocyte migration into inflamed intestinal tissue via the \(\alpha 4\beta 7\) 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 \(\alpha 4\beta 7\) 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

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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

<table>
<thead>
<tr>
<th>Pregnancy outcome</th>
<th>Total number of VDZ exposed pregnanciesA (n=104)</th>
<th>Infliximab exposed pregnanciesB (n=106)</th>
<th>Non-biologic exposed pregnancies in IBDB (n=106)</th>
<th>US general populationC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live birth</td>
<td>80 (77%)</td>
<td>81 (81.8%)</td>
<td>82 (91.1%)</td>
<td>64.6%</td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>6 (6%)</td>
<td>1 (1.2%)</td>
<td>3 (3.7%)</td>
<td>4%</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>11 (11%)</td>
<td>16 (16.2%)</td>
<td>8 (8.9%)</td>
<td>10-17%</td>
</tr>
<tr>
<td>Elective/therapeutic termination</td>
<td>8 (8%)</td>
<td>2 (2.0%)</td>
<td>0 (0%)</td>
<td>18.4%</td>
</tr>
<tr>
<td>Still birth</td>
<td>1 (1%)</td>
<td></td>
<td></td>
<td>1%</td>
</tr>
<tr>
<td>Pre term birth (&lt; 37 weeks gestation)</td>
<td>15 (14%)</td>
<td>4 (3.8%)</td>
<td>5 (4.7%)</td>
<td>9-10%</td>
</tr>
</tbody>
</table>

AAvailable 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.
is 10-17% of clinically recognized pregnancies, and typically occurs in the first trimester. In the TREAT registry, the spontaneous abortion rate was 16% in infliximab exposed pregnancies, and 8.9% in non-biologic exposed pregnancies. 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. The pre-term birth rate in the United States has been found to be 9-10%. 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. The TREAT registry had a low pre-term birth rate of 3.8% in infliximab, and 4.7% in non-biologic exposed pregnancies. 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. 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. In the United States, the stillbirth rate is 1%. 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. 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%. 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. Folate is known to have protective effects against the development of neural tube defects and supplementation is recommended at conception and during pregnancy. 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. Studies have demonstrated placental transfer of anti-TNF biologic agents with the exception of certolizumab. In PIANO registry data, vedolizumab was present in the infant serum at birth, however was less than half that of the mother. This is in comparison to infliximab, where levels in the infant were found to be double that of the mother. 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. 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. 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.

In anti-TNF medications other than certolizumab, the rotavirus vaccination is avoided. 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
The Use of Vedolizumab in Pregnancy and Breastfeeding in Women with Inflammatory Bowel Disease

INFLAMMATORY BOWEL DISEASE: A PRACTICAL APPROACH, SERIES #107

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Breastfeeding

Breastfeeding is highly recommended by the American Academy of Pediatrics for at least the first 6 months of a baby’s life. In women with inflammatory bowel disease, breastfeeding has not been shown to have any adverse effects on disease activity. 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. 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. Drug levels have not exceeded 480 ng/ml or 1/100th 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.

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

13. Soler D, Chapman T, Yang LL, et al. The binding specificity and selective antagonism of vedolizumab, an anti-a4ß7 integrin therapeutic vaccines. 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. 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. No other known hospitalizations occurred for the other 99 infants despite in utero vedolizumab exposure.

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Answers to this month’s crossword puzzle:

C R A F T

O A B M I N O

L A X A T I V E S

C A J A L

D T I R

R D A I

S T U D Y

T O R S O

T E A

M I S

N Y E

B E T

T A M I N O

C E L I A C

I

R S K O E C

E S T

P R O B I O T I C S

A R Y N A R T

Z E N K E R S G A U

E N S G P U L S E S

T R A N S A M I N A S E S

A S O A L O N E U

T E A R

G A S T R I T I S