ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Overview of Pregnancy in Patients With Inflammatory Bowel Disease

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G&H Currently, how do pregnancy outcomes typically compare between patients who have inflammatory bowel disease and those who do not?

UM Women with inflammatory bowel disease (IBD) are as likely to become pregnant as those without IBD unless they have had surgery in the pelvis or have active disease. Thus, the ability to conceive is fairly similar. However, once pregnant, women with IBD, even those in remission, are more likely to have a miscarriage, preterm birth, low birth weight, complications of labor and delivery (eg, preeclampsia), and small-for-gestational-age infants.

G&H What is the relationship between disease activity and pregnancy complications?

UM Disease activity is the most significant risk factor for the development of a pregnancy complication in a patient with IBD. Patients with active disease are up to 3 times or more likely to have a complication than those with inactive disease. Studies that have looked at disease activity did not scope women when they were pregnant, so they could have had an undetected, low level of inflammation. However, even if there is not active inflammation, having IBD impacts the patient's immune system, as does pregnancy. This interaction may lead to more difficult pregnancies.

G&H Does pregnancy seem to affect Crohn's disease and ulcerative colitis the same?

UM In PIANO (A Multicenter National Prospective Study of Pregnancy in IBD and Neonatal Outcomes), my colleagues and I found that pregnant patients with ulcerative colitis were more likely to have active disease than pregnant patients with Crohn's disease. This finding has been reported in other studies as well. There is something about pregnancy that seems to trigger ulcerative colitis. I have had many patients with ulcerative colitis who flare only when they are pregnant, and they have been scoped and have had completely normal endoscopy findings prior to pregnancy.

Thus, women can flare during pregnancy even if they are doing well before, which is why they need to be monitored closely, particularly when they have ulcerative colitis. However, population-based data suggest that approximately one-third of pregnant women may flare during pregnancy, which is similar to the rate of flare in the general population. If patients are in remission going into pregnancy, they are likely to stay that way.

Pregnancy can also trigger IBD, in particular ulcerative colitis. Thus, patients may be diagnosed during pregnancy.

G&H What are the most recent data on the use of biologics in pregnant patients who have IBD?

UM My colleagues and I reported findings from the PIANO registry that were recently released online ahead of print publication in the journal *Gastroenterology.* The

PIANO registry is a 1700-patient prospective registry of women with IBD on various medications. Our article reported on 1490 completed pregnancies, of which 1431 ended in live birth. There were 242 patients on thiopurines, 642 on biologic monotherapy, and 227 on combination biologic and thiopurine therapy; thus, altogether, 869 patients were on biologics. The key finding was that being exposed to either a thiopurine or a biologic did not result in an increase in birth defects, spontaneous abortion, preterm birth, low birth weight, or infant infection in the baby over the first year of life. Exposure also did not adversely affect developmental milestones.

There has been a push to stop biologics in the second trimester because of placental transfer; however, these and other data from the PIANO registry show that there is no increase in harm with continuing biologics during pregnancy. In addition, European data show that stopping biologics early can lead to the mother flaring, which can result in adverse outcomes in the infants.

G&H What research has been conducted recently on the use of biologics specifically during breastfeeding?

UM We have found that mothers can breastfeed on biologics without any harm to the infant. My colleagues and I have published findings on breastfeeding showing that biologics do cross into breast milk, but in very trivial levels. Therefore, it is not necessary to adjust biologics when breastfeeding; it was not associated with an increase in infection.

G&H Has there been any research specifically on the use of the newer drugs ustekinumab and vedolizumab in pregnant patients with IBD?

UM Several of the patients in the PIANO registry used those drugs, and the drugs did not seem to have an increased risk of adverse outcomes. Other studies, both from the safety monitoring of the manufacturers and from other researchers, have also suggested that there is no increase in adverse events with the use of ustekinumab (Stelara, Janssen) or vedolizumab (Entyvio, Takeda) during pregnancy. Monoclonal antibodies are large and should not cross the placenta during the first trimester, when the organs of the baby are forming. Thus, there should not be an increase in birth defects. However, beginning around week 14, the placenta develops a receptor that actively transports antibody from mother to baby. In the early second trimester, an antibody given to the mother will start to cross. This transfer is most efficient in the third trimester, which is why babies are born with detectable levels of drug.

We have found that babies exposed to infliximab in utero have the highest levels of drug, approximately 2.4 times the maternal level at birth, and that the drug takes approximately 6 months to clear. With exposure to adalimumab and ustekinumab in utero, babies have 1.4 times the maternal drug level at birth, and these drugs take a little less time to clear. Interestingly, even though vedolizumab is an immunoglobulin G1 antibody, drug levels in the baby at birth are only 40% to 70% of that of the mother.

G&H Could you discuss any other recent research involving neonatal outcomes and the use of biologics during pregnancy?

UM My colleagues and I examined babies who were exposed to biologics in utero and found that their responses to the inactive vaccines for *Haemophilus influenzae* B and tetanus toxoid were similar to those of unexposed infants, which is good. If an infant was exposed to a biologic in utero, it is recommended that he or she not receive live vaccine for the first 6 months of life. Live vaccines are contraindicated for people taking biologics because of the potential for developing an infection. Nevertheless, 40 babies in the PIANO registry were exposed to the rotavirus vaccine, the only live vaccine given in the United States during the first 6 months of life, and they were all fine.

We also looked at whether going to day care was harmful to babies exposed to biologics in utero, and found that they had no increase in infections.

In addition, we found that infants of IBD patients who were on biologics during pregnancy had equivalent or superior scores for all developmental milestones using the nationally validated Ages and Stages Questionnaire. It is not surprising that the offspring of women with IBD have higher scores compared with the national population, as developmental milestones can be very dependent on socioeconomic status and the participants of the PIANO registry were of higher socioeconomic status. However, even within the PIANO registry, when comparing infants of IBD patients exposed to biologics with infants of IBD patients not exposed to biologics, there was a suggestion that the biologic-exposed babies did better on their developmental milestones. A possible, but theoretical, explanation is that the more strongly inflammation is controlled, the better the baby's neural pathways are formed during the critical first few weeks of life.

G&H Are there any risks associated with the use of other IBD drugs during pregnancy?

UM Methotrexate is known to cause birth defects and pregnancy loss. Thus, it is generally recommended that

women stop methotrexate at least 3 months prior to considering pregnancy.

We do not have a lot of data on the use of the newer IBD drug tofacitinib (Xeljanz, Pfizer) in pregnant patients with IBD. Tofacitinib is an oral medication, so it can potentially cross the placenta in the first trimester and cause birth defects. In fact, birth defects were seen in animals given high doses of tofacitinib. However, research is needed specifically in humans.

G&H Should any adjustments be made to IBD treatment during pregnancy or postpartum?

UM If a patient is on sulfasalazine, folic acid should be increased to 2 mg per day instead of 1 mg per day because folate deficiency can be harmful to the infant. Otherwise, thiopurines, biologics, and mesalamine can be continued as appropriate throughout pregnancy. If patients are on multiple medications, doctors should assess whether all of the therapies are needed. For example, mesalamine is likely not needed in a patient on a biologic. Some patients on thiopurines for antibody formation and biologics may be stable with good serum trough levels of the biologic and so can stop thiopurines during pregnancy. All of these treatments can also be continued postpartum because patients can breastfeed on them.

G&H What are the most important questions that remain in this area?

UM Most data in the PIANO registry involve anti–tumor necrosis factor agents. More research is needed on the use of ustekinumab, vedolizumab, and tofacitinib during pregnancy. Although I feel fairly confident about ustekinumab and vedolizumab use during pregnancy, more data are needed regarding tofacitinib safety during this time.

An important question is how children exposed to IBD drugs fare in the long term. The PIANO registry has followed children up to 4 years of age, and they seem to be doing well with no increased health or developmental issues. However, what about children up to 18 years of age, and what if they develop IBD themselves? My colleagues and I have published on a mother who was on infliximab during pregnancy whose child needed infliximab at 12 years of age. We wondered if the child would reject the drug or respond to it. The child did respond to infliximab and did quite well.

We are now following children to 18 years of age in the PIANO registry to learn more. We are also still enrolling patients in the PIANO registry, so anyone interested can e-mail us at PIANO@ucsf.edu. We are particularly looking for pregnant women with IBD on biologics or small molecules and/or who have had coronavirus disease 2019 (COVID-19) or who have received any of the COVID-19 vaccines.

G&H Has there been any research on pregnant patients with IBD who had COVID-19?

UM I am not aware of research specifically on pregnant patients with IBD who had COVID-19, but pregnant women in general who become infected with COVID-19 are known to have a significantly increased risk for adverse outcomes. Therefore, it is recommended that women who are pregnant take extreme precautions to avoid infection. A more controversial question is whether pregnant women should receive any of the COVID-19 vaccines. Pregnant women were not part of the clinical trials for the vaccines; however, the Centers for Disease Control and Prevention, the American College of Obstetrics and Gynecologists, and the Society for Maternal-Fetal Medicine have recommended that pregnant women should have access to the vaccines, particularly if they are high risk (eg, frontline health care workers or other essential workers).

Disclosures

Dr Mahadevan serves as a consultant for AbbVie, Janssen, Takeda, and Pfizer.

Suggested Reading

Mahadevan U, Dubinsky MC, Su C, et al. Outcomes of pregnancies with maternal/paternal exposure in the tofacitinib safety databases for ulcerative colitis. *Inflamm Bowel Dis*. 2018;24(12):2494-2500.

Mahadevan U, Long MD, Kane SV, et al; Crohn's Colitis Foundation Clinical Research Alliance. Pregnancy and neonatal outcomes after fetal exposure to biologics and thiopurines among women with inflammatory bowel disease [published online November 20, 2020]. *Gastroenterology*. doi:10.1053/j.gastro.2020.11.038.

Mahadevan U, McConnell RA, Chambers CD. Drug safety and risk of adverse outcomes for pregnant patients with inflammatory bowel disease. *Gastroenterology*. 2017;152(2):451-462.e2.

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. *Inflamm Bowel Dis*. 2019;25(4):627-641.

Mao EJ, Sheibani S, Martin C, et al. Preventive health care among postpartum women with inflammatory bowel disease: results from the PIANO registry. *Inflamm Bowel Dis*. 2019;25(4):797-802.

Matro R, Martin CF, Wolf D, Shah SA, Mahadevan U. Exposure concentrations of infants breastfed by women receiving biologic therapies for inflammatory bowel diseases and effects of breastfeeding on infections and development. *Gastroenterology*. 2018;155(3):696-704.