ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Pregnancy Concerns in Women With Inflammatory Bowel Disease

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G&H Do women with inflammatory bowel disease have more complications during pregnancy than women who do not have this condition?

UM Women with inflammatory bowel disease (IBD) have more complications during pregnancy than women without IBD, regardless of whether the disease is active or inactive. Women with inactive IBD have more preterm births and more complications during labor and delivery than women without IBD. Disease severity also affects outcomes; preterm births were approximately 3 times more common among women with moderately to highly active disease than among those with inactive IBD.

G&H Why does IBD cause problems during pregnancy?

UM Although research has not conclusively proven why IBD is linked to complications, most likely several factors are at play. During active inflammation, the body is in an unhealthy state that may not support pregnancy. When active inflammation is severe, the body becomes more anemic, the albumin protein status worsens, and other issues arise that make carrying a child difficult. Simply put, too much active inflammation makes it difficult for the body to hold onto a child.

It is important to remember that pregnancy itself is an inflammatory state. The placenta produces cytokines that can worsen some forms of IBD, such as ulcerative colitis, during pregnancy. During the first trimester of pregnancy, the body experiences mild inflammation as the egg is implanted into the uterus. The second trimester typically is not characterized by excess inflammation. In the third trimester, the body goes into an inflammatory state as it prepares for delivery. This can aggravate already-existing immune-mediated inflammation.

Finally, nutrition may also play a role. If a woman has poor nutritional status as a result of active disease, that may also negatively impact the pregnancy.

G&H Is this heightened risk linked to preexisting IBD only, or can pregnancy also trigger IBD?

UM These complications are associated with preexisting IBD. Rarely, however, women can have their first flare during pregnancy. This situation tends to occur more often with ulcerative colitis than with Crohn's disease, possibly because of the changes that occur during pregnancy.

G&H You began studying pregnancy outcomes among women with IBD a few years ago. What led you to begin this research?

UM The first major study that I conducted in this area was spurred by the fact that the medication data available prior to the study were from individual tertiary care centers. The patients included in these studies could have been much sicker than typical patients in the community. Most studies were based on a single center or on large, population-based data sets for which tracing disease activity of the patients included was not feasible because it would require referring to hard-copy records.

G&H What data did you use in your study?

UM My colleagues and I conducted a community-based study using data from Northern California Kaiser Permanente hospitals. This population-representative data set

reflects the ethnic and demographic makeup of northern California, except at the extremes of income. The wealthiest and the poorest patients are not typically part of the Kaiser Permanente network, but all other economic levels are represented.

G&H How did you use these data to study pregnancy outcomes in IBD?

UM Using this population-representative cohort, we extracted data on major events and conducted chart reviews to examine the presence or absence of IBD, disease activity among those with IBD, complications, and other factors. Our objective was to examine the pregnancy outcomes among women both with and without IBD who were the same age and who were cared for at the same hospital.

G&H What were the most striking findings in that study?

UM We found that women with IBD had higher rates of miscarriage, preterm birth, low birth weight, and complications of labor and delivery than those without IBD. It was very interesting to observe that these rates were higher among women with IBD, regardless of disease activity.

G&H Did this finding alter your practice?

UM Yes, and many other physicians who treat this population also changed their approach. We realized that women with IBD should be followed as high-risk obstetric patients because of the increased risk of complications.

G&H Did you conduct further research?

UM Yes. One of the benefits of using data from Kaiser Permanente is the ability to match women of the same age who were treated at the same hospital, generating a sizeable data set. The drawback is that the analysis is retrospective. In addition, in this community-based setting, very few patients had been exposed to immunomodulators, and none had been exposed to biologic drugs. Therefore, once we had established the increased risk of pregnancy complications among women with IBD, we wanted to investigate the safety of the medications used to treat IBD.

G&H Could you describe your approach to studying the safety of IBD medications among pregnant women?

UM Seven years ago, we began a registry known as PIANO (A Multicenter National Prospective Study of Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes). In the PIANO registry, our objective was to determine the safety of IBD medications during pregnancy in a prospective manner. More than 30 sites joined the study through the Crohn's & Colitis Foundation of America, with the University of California at San Francisco as the lead study site. Pregnant women who enrolled in the study were followed through their pregnancy and the first year of their infant's life.

G&H What did the study show regarding medication risks?

UM In the first phase of the study, we found that biologic medications, azathioprine, and 6-mercaptopurine (6-MP) were not associated with an increased risk of birth defects or other adverse outcomes.

G&H Why did you decide to extend the study?

UM After the first 3 years of the study, we had a good understanding of what happens to pregnant women with IBD and their infants through the first year of life. However, adverse events may not manifest during the first year. We felt that it was important to continue following the children for an additional 3 years in order to chart whether children were reaching developmental milestones. Using the Ages and Stages Questionnaire, which monitors developmental milestones, we followed the children of women enrolled in the study until 4 years of age.

G&H Did you observe any problems linked to IBD drug exposure?

UM We found that there was no worsening of developmental milestones based on exposure to particular medications. In addition, children of women with IBD treated with biologics or azathioprine/6-MP did not have an increased risk of infection. However, among children of women with IBD treated with a combination of a biologic that crosses the placenta and either azathioprine or 6-MP, there was a slight increase in infections.

G&H What is your current study focusing on?

UM The elevated infection risk prompted a third phase, which is currently ongoing. We are continuing to follow mothers during pregnancy and their children through the first 4 years of life, but now we are also measuring placental drug levels. We want to see if there is a correlation between placental drug levels at birth and the risk of infection through the first year of life. We are also tracking the response of these children to vaccines and whether the drugs are transferred into breast milk.

We know that biologic drugs cross the placenta and are detectable at significant levels in infants during the first 6 months of life, except for certolizumab pegol (Cimzia, UCB), which crosses passively rather than actively because it is not a full antibody. Therefore, we need to better understand how these drugs affect newborns, if at all. In addition, we need safety data on new drugs such as vedolizumab (Entyvio, Takeda), ustekinumab (Stelara, Janssen Biotech; not approved for Crohn's disease), and golimumab (Simponi, Janssen Biotech). One of the benefits of the PIANO registry is that we can include these new drugs.

G&H What have you found so far?

UM As mentioned earlier, we have not seen an increase in birth defects associated with exposure to medication. This finding is based on more than 1400 mothers enrolled in the study, more than 600 infants exposed to biologic therapy, and more than 300 infants exposed to azathioprine/6-MP. In addition, we have not seen any problems with achieving developmental milestones. There is a suggestion of increased infection risk among babies exposed to both a biologic agent and an immune modulator, although certolizumab pegol appears to be safe. We have also seen minimal to no transfer of most drugs into breast milk, although this part of the study is still ongoing.

G&H How might your findings inform the care of pregnant women with IBD?

UM These results may reassure this population and their clinicians that these drugs do not need to be stopped during pregnancy or lactation. Stopping these drugs can lead to a disease flare, which can negatively impact pregnancy and the ability of the mother to care for the newborn postpartum. Biologic drugs typically are prescribed for women with active disease. If the medication is stopped, the patient may not be able to resume the same treatment because antibodies may develop or the patient may become resistant to the drug. Data indicating that these drugs pose a low risk for pregnant and lactating women may decrease the likelihood of women with IBD stopping these drugs during these times and putting their own health at risk.

A study from the Netherlands showed that women with IBD who receive counseling before pregnancy tend to maintain better health during pregnancy. Through this approach, women in cooperation with their obstetrician can establish a plan for how to manage their IBD during pregnancy. This decreases the likelihood that they will experience active disease during this time.

G&H What is your first recommendation to women with IBD who are intending to become pregnant?

UM For women with IBD, it is best for the disease to be in remission before becoming pregnant. If the disease is active, it can be harder to become pregnant and the risk of miscarriage is greater.

G&H What are some of the challenges in studying pregnancy outcomes in women with IBD?

UM The Crohn's & Colitis Foundation of America has been very generous in funding this work through 3 cycles of study. However, funding remains a challenge, with the bulk of the expense being shouldered by the participating study sites. The logistics of following so many enrollees and keeping the data organized is challenging, but has not been a limiting factor. The mothers enrolled in the study have been remarkably reliable about providing blood samples and being available for follow-up.

G&H Are you conducting any other studies in this area?

UM We are investigating whether IBD drug exposure in the mother diminishes immune function in babies by collecting data on vaccine response and T- and B-cell development. However, collecting adequate data takes a long time, so we do not yet have any conclusive evidence.

Dr Mahadevan is a consultant for Janssen, Takeda, UCB, AbbVie, and Prometheus. The PIANO registry is 100% funded by the Crohn's & Colitis Foundation of America.

Suggested Reading

Hassid B, Mahadevan U. The use of biologic therapy in pregnancy: a gastroenterologist's perspective. *Curr Opin Rheumatol.* 2014;26(3):347-353.

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 Organisation: pregnancy and pediatrics. *Am J Gastroenterol.* 2011;106(2):214-223.

Mahadevan U, Sandborn WJ, Li DK, Hakimian S, Kane S, Corley DA. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. *Gastroenterology.* 2007;133(4):1106-1112.

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):286-292.

Ng SW, Mahadevan U. My treatment approach to management of the pregnant patient with inflammatory bowel disease. *Mayo Clin Proc.* 2014;89(3):355-360.