ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Update on Pregnancy in Patients With Inflammatory Bowel Disease

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G&H What is the current understanding of the relationship between inflammatory bowel disease and fertility?

AA Female patients whose inflammatory bowel disease (IBD) is under control and who have not undergone pelvic surgery have fertility rates that are comparable with those of women of the same age who do not have IBD. Thus, the risk of infertility in IBD and non-IBD women is comparable (approximately 6%-7%). Importantly, disease remission, and therefore control of inflammation, not only improves fertility rates but also leads to favorable outcomes of pregnancy.

G&H According to the research conducted to date, how does the presence of IBD affect pregnancy complications and outcomes?

AA Overall, a healthy mother with IBD means a healthy baby. Disease activity appears to increase the risk for adverse maternal and birth outcomes. There is also a higher rate of miscarriage, which is reported to be approximately 35%, among women with active IBD. Data regarding the effect of disease activity on pregnancy outcomes remain inconsistent, but, overall, physicians advise female patients to conceive while their disease is in remission and to continue their medication throughout pregnancy in order to maintain remission and also avoid worse pregnancy outcomes. Several studies have demonstrated that rates of fetal loss and preterm birth are higher in patients who conceive while their IBD is active.

G&H Why does the severity of IBD affect pregnancy complications or outcomes?

AA This issue is still being better understood, but we know that tumor necrosis factor (TNF)-α and other pro-inflammatory Th1 cytokines play a pivotal role in successful pregnancy. The current understanding is that the increase in natural pro-inflammatory cytokines that occurs with pregnancy, combined with an underlying immune-mediated inflammatory disease such as IBD, can potentially increase the risk for pregnancy-related adverse events. Studies have reported a higher risk of preterm birth, low birth weight, and small-for-gestational-age infants born to mothers with IBD regardless of disease activity, which could be the result of the natural surge of pro-inflammatory cytokines that are released during pregnancy and heightened with underlying bowel disease.

G&H According to the most recent research, how does pregnancy usually affect the disease course of IBD?

AA Typically, nearly approximately 80% of IBD patients who conceive while in remission remain so throughout pregnancy and postpartum. The best time for conception is when the disease is quiescent and in remission. Physicians should try to emphasize this message to their patients. Of the patients with IBD who conceive while their disease is active, approximately 65% continue to have active disease or, in fact, experience a worsening of their disease during pregnancy.

G&H How do the rates of IBD flare and relapse compare in pregnant and nonpregnant patients?

AA Studies have shown that the rates of IBD flare are similar in pregnant and nonpregnant patients with both

ulcerative colitis and Crohn's disease. For example, the relapse rate was 34% per year among pregnant women with ulcerative colitis and 32% per year in nonpregnant women with ulcerative colitis. Disease flares are typically and more frequently seen in the first 6 months of pregnancy and also in the first 3 months postpartum.

G&H Can pregnancy trigger IBD?

AA This is a difficult question to answer. Studies have not demonstrated that pregnancy causes IBD, but pregnancy can certainly be a trigger for the presentation of IBD. In other words, if a patient has underlying IBD that is subclinical, pregnancy and its natural increase in proinflammatory cytokines can potentially cause subclinical disease to become clinically active.

G&H How should patients with IBD (active or in remission) be treated if they become pregnant?

AA Generally, the rule of thumb is that any medication(s) used to achieve remission should be continued throughout the entirety of pregnancy without interruption, as the benefits currently outweigh any potential risks to either the mother or fetus.

G&H What safety data are currently available for the use of various IBD therapies, especially biologic and anti-TNF agents, during pregnancy?

AA As mentioned, IBD medications are generally safe to take during the conception period as well as during pregnancy and postpartum. An exception is methotrexate, which is teratogenic. There are also more limited data on some of the newer therapies, such as the Janus kinase (JAK) inhibitors, which is why physicians currently recommend avoiding these agents before or during pregnancy.

As for biologic agents (particularly anti-TNF therapies, for which the most data are available), we know that these therapies are safe and associated with reduced rates of flares and improved bowel disease activity, which in turn lowers the risk for adverse pregnancy outcomes as well as postpartum flares. Several large population-based studies and registries, such as the PIANO (Pregnancy and Inflammatory Bowel Disease and Neonatal Outcomes) registry, have demonstrated that there are no differences in adverse pregnancy outcome rates between women taking an anti-TNF agent compared with women who are not taking any IBD medications during pregnancy.

G&H Are there any specific risks associated with any of the IBD drugs?

AA The primary concern associated with biologic agents is that there is a potential risk for the development of the newborn's immune system and, therefore, related infections. Thus, live vaccines should be avoided for at least the first 6 to 9 months of life or until drug levels of the anti-TNF agent are undetectable in the baby. An exception is certolizumab pegol (Cimzia, UCB), which does not cross the placenta; therefore, the infection risk to the newborn is low, and live vaccines do not need to be avoided.

In addition, the use of combination therapy, such as a biologic agent and a thiopurine, has been associated with nearly a 3-fold higher risk for infant infections compared with the use of a biologic agent without a thiopurine. Reducing the exposure of the thiopurine or not utilizing combination therapy may be associated with better outcomes and a decrease in the risk of infection for the newborn. However, this decision should be weighed carefully with maintaining disease control.

G&H Might any other drug effects manifest later on in pregnant patients or their children?

AA A recent prospective study by Matro and colleagues examined women receiving treatment for IBD and their infants, and detected low concentrations of infliximab (Remicade, Janssen), adalimumab (Humira, AbbVie), certolizumab pegol, natalizumab (Tysabri, Biogen), and ustekinumab (Stelara, Janssen) in breast milk samples. Breast-fed infants of mothers on these biologic agents, immune modulators, or combination therapy were found to have similar risks of infection as well as similar rates of achieving developmental milestones, compared with infants of mothers who were not on these therapies or who did not breastfeed. Thus, overall, the use of these therapies did not have a negative impact on developmental milestones at 12 months, which were, in fact, comparable with infants of mothers who did not breastfeed and/or were not exposed to biologic therapy.

G&H Should any other IBD drugs be avoided during pregnancy?

AA There have been mixed reports regarding whether corticosteroids such as prednisone should be avoided during pregnancy, as older studies have suggested a higher risk, for example, for cleft palate in newborns. More recent studies have not reported this risk. Overall, physicians recommend that corticosteroids do not necessarily need to be avoided, but that, similar to nonpregnant patients, long-term use of corticosteroids for maintenance treatment should be avoided in pregnant patients. However, short courses may be needed and may be appropriate for a woman with a disease flare during pregnancy. Long-term or high-dose corticosteroid use during pregnancy is associated with a risk for gestational diabetes.

The other drugs of concern are immune modulators, specifically thiopurines, which include azathioprine and

6-mercaptopurine. For a woman who is having a disease flare and considering her treatment options, physicians should recommend that the patient avoid starting a thiopurine during pregnancy if she is not already on it, primarily because of the concern of possible adverse reactions such as pancreatitis or bone marrow suppression as well as a slow onset of therapeutic benefit. If a patient was taking a thiopurine before becoming pregnant, physicians should recommend continuing the therapy.

G&H Should IBD treatment be adjusted in any way postpartum?

AA Often, pregnant women will stay on their medication throughout pregnancy but as soon as a healthy baby is delivered, they discontinue their treatment. Physicians should emphasize to their patients that the risk for disease flare postpartum is approximately 20% and that flares often occur in the first 3 to 6 months postpartum. Therefore, it is important that medications be continued even after delivery.

Furthermore, there is no need to time medications, including biologic agents or thiopurines, with breastfeeding. For example, the practice of "pump and dump" for 4 hours after taking a thiopurine is an old recommendation, and because breast milk drug levels are extremely low and negligible, this is no longer advised.

G&H Are there any other considerations that should be kept in mind when managing pregnant IBD patients?

AA As mentioned, it is important to emphasize that a healthy mother means a healthy baby. Too often, physicians focus so much on the pregnancy that they forget about the importance of controlling and maintaining remission of the bowel disease itself. Management of a pregnant patient means ensuring that the disease is quiescent and in remission even preconception, if possible.

It is also important to keep in mind that pregnancy limits the diagnostic workup and studies that can be performed if the patient is flaring (eg, in terms of colonoscopy or certain cross-sectional imaging studies).

G&H What other advice should be given to IBD patients who are planning to become pregnant?

AA Ideally, patients should have a discussion with their care providers early on regarding appropriate disease management, including health care maintenance, as well as medication management. As mentioned, methotrexate, for example, is teratogenic, so female patients should avoid using this drug for at least 3 to 6 months even prior to conception. It is also important to ensure good interdisciplinary consultation that includes, in addition to gastroenterology, early discussion with obstetrics, maternal fetal medicine, and primary care. Lastly, appropriate health care maintenance, including immunizations, pap smears, and baseline colonoscopy, is important.

G&H What research is still needed in this area?

AA More data are needed on the safety of some of the newer biologic agents that have a different mechanism of action, such as anti-adhesion agents, anti–interleukin-12 and/or -23 agents, and JAK inhibitors or oral small molecules, many of which are being used in women of childbearing age. Patients are often concerned about the safety of their therapies while pregnant, and we believe that they are safe because the disease is being controlled and based on current pregnancy and safety data, but it would be helpful to have as much robust data as we have with anti-TNF agents.

G&H Are there any ongoing or upcoming studies that you would like to highlight?

AA There are several ongoing registries, such as the OTIS (Organization of Teratology Information Services) registry and the PIANO registry, which are collecting and describing much-needed data. Of note, these registries have collected data on the use of IBD drugs with different mechanisms of action and, overall, have found safety profiles and pregnancy and birth outcomes similar to those of anti-TNF agents.

Dr Afzali has served as a consultant/speaker for AbbVie, UCB, Takeda, Pfizer, and Janssen; has served on the advisory boards for AbbVie, UCB, Takeda, Janssen, and Celgene; and has received research grant support from AbbVie, Janssen, Takeda, and Celgene.

Suggested Reading

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