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Treating Inflammatory Bowel Disease During Pregnancy

Dr. Buch:
Treating inflammatory bowel disease, or IBD for short, during pregnancy can be a tricky process, so active patient education and having specialized knowledge could be a great benefit to those undergoing treatment.

This is *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch. Today we are joined by Dr. Eugenia Shmidt to talk about IBD during pregnancy. Dr. Shmidt is the lead author of the article, titled "Inflammatory Bowel Disease and Pregnancy," that was published in the *American Journal of Gastroenterology* in 2022. She is also an assistant professor in the Division of Gastroenterology, Hepatology, and Nutrition at the University of Minnesota.

Welcome to the program, Dr. Shmidt.

Dr. Shmidt:
Hello. Thank you so much for having me.

Dr. Buch:
So let's jump right in, Dr. Shmidt. What are the consequences that a patient could face during pregnancy if they have inflammatory bowel disease that is active?

Dr. Shmidt:
Yeah, this is a super important question, and the keyword in your question is "active." So I'd like to kind of start by answering a slightly different question, which is what can a woman with IBD expect if she's pregnant and does not have active disease? And the answer to that is easy. She can expect the same outcomes that she would have had if she didn't have a diagnosis of IBD. However, if she does have active disease, that's when adverse pregnancy outcomes can happen. And so those adverse outcomes are increased risk for C-section, increased risk for gestational diabetes, even in the setting of not taking corticosteroids, and increased risk for preterm pre-labor rupture of membranes, so early delivery. And then outcomes from the PIANO registry did show that women who have active disease during pregnancy are at higher risk for early pregnancy loss, meaning miscarriages, so these are some very serious adverse pregnancy outcomes that can happen in a setting of active disease, and so that is why the mantra of preconception and pregnancy management counseling is to avoid all active disease in the setting of IBD during pregnancy.

Dr. Buch:
Can you just tell us a little bit more about that registry?

Dr. Shmidt:
Yeah. So the PIANO registry stands for Pregnancy Inflammatory Bowel Disease and Neonatal Outcomes. It is the largest US-based registry that examines women who have IBD and who are pregnant. It follows these women prospectively and specifically answers the question of which medications are safe to continue through pregnancy in women who have IBD. This registry is a national collaborative effort that's spearheaded by Dr. Uma Mahadevan at the University of California, San Francisco.

Dr. Buch:
And continuing with our thoughts from before, you kind of led into that, but what steps should a patient follow preconception?

Dr. Shmidt:
Yeah. So once a woman is pregnant, in a way the horse is out of the barn. The major impact that we as physicians can make on a woman who, in the setting of pregnancy, really happens in the preconception phase. So if a woman has IBD and expresses interest in

getting pregnant, there are many things that need to be done. So first of all, it's important to ensure that disease management is optimized; that basically she has been in a steroid-free remission for at least three months prior to conception, and you want to make sure that remission is confirmed endoscopically and with other objective markers, such as C-reactive protein in serology.

If she's interested in getting pregnant and has been trying to get pregnant for a while, you want to make sure that she's referred to a fertility specialist sooner rather than later. Typically, we recommend referral to a fertility specialist after six months of unprotected intercourse if she is less than 40 years of age. If she's greater than 40 years of age, then referral to a fertility specialist after four months of unprotected intercourse is appropriate. You want to make sure that you address other fertility factors like possible scar tissue that may have occurred after getting a J pouch, say in the setting of ulcerative colitis or with scar tissue in the setting of Crohn's disease. We know that those women have higher rates of infertility and so should be referred to an infertility specialist sooner.

You want to make sure that all of your key players are on board so to speak. If there's a history of a prior pregnancy complication, then it's important to have a maternal-fetal medicine specialist or a high-risk obstetrician on board. Make sure that her nutrition status is optimized. And if there's a history of J pouch surgery for ulcerative colitis, getting a consultation with a colorectal surgeon is important, as well.

Of course, the safety of medications is a really big piece that should be addressed in the preconception phase. If the patient is on methotrexate, you want to make sure that she's been off of it for at least three months prior to conception, and that is true for small-molecule medications, as well. These are the new ones that have been recently approved by the FDA. Examples of these are ozanimod or upadacitinib. Other medications that should be optimized, as well if the patient is on biologic therapy, it would be prudent to check serum drug levels and make sure that they are optimized prior to conception. Azathioprine monotherapy can be continued. If the patient is on tofacitinib, which is another small molecule, then again you want to avoid that use because there's a paucity of data on the safety of that.

And then in terms of healthcare maintenance, you're not really going to be doing much healthcare maintenance during the pregnancy phase, so this is the time to address this in advance, so make sure that the patient is up-to-date with respect to her vaccines; that drugs, alcohol, or tobacco use are not in the picture; make sure that she's up-to-date with her colon cancer surveillance, as well.

Dr. Buch:
Thank you for that. And, Dr. Shmidt, can we just focus a little bit more on the biologics and the safety of biologics during pregnancy?

Dr. Shmidt:
Yeah. So up until fairly recently there's been a pretty heated debate about the safety of biologics, particularly in the third trimester, and at this point the debate has ended, and at this point North America and Europe are both in agreement that biologics are safe in pregnancy and should be continued through the entire pregnancy. Now this data is truly supported by very robust findings from both the PIANO registry and also European trials. So for example, in the PIANO registry, there were 869 pregnant women who were exposed to biologics, and they found no difference in terms of pregnancy complications. And then recently published meta-analysis looking at 48 studies found that rates of various pregnancy outcomes were comparable to the general population. This is early pregnancy loss, preterm birth, stillbirth, low birth weights, and congenital malformations. So we do know that biologics are safe in pregnancy, and they should be continued in the third trimester, as well.

What gave people pause in the past is that we know that biologics do cross the placenta, and so baby is born with biologics in their system, so basically, that means that the baby is immunosuppressed as a result, but what we do know is that not continuing biologics in the third trimester increases risk for flaring, and we know that active disease has very serious negative outcomes. We also know that babies who had intrauterine exposure to biologics do quite well and do not have increased rates of infection, even among those who attend daycare. There's essentially no difference in terms of health outcomes in babies who had intrauterine exposure to biologics versus those who did not. And so if you put on the other side of the scale the risk for flaring, it's very clear that biologics are safe and should be continued throughout the entire duration of the pregnancy.

The only thing that I recommend is positioning the biologic or changing the schedule of the biologic so that it is due right at the time of delivery, so within 24 to 48 hours depending on the mode of delivery, and the reason for that is two-fold. One, it's to decrease transplacental transfer of the biologic in the third trimester, and the second reason is to decrease the risk of postpartum flare.

Dr. Buch:
Thank you very much for that very useful and very reassuring information.

For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Shmidt about inflammatory bowel disease, or IBD, during pregnancy.

Now, Dr. Shmidt, you talked about this earlier. What role does therapeutic drug monitoring especially have in pregnant patients with IBD?

Dr. Shmidt:
Yeah, this is a really great question. So the short answer really is that we don't know because we don't have prospective randomized data on this. However, we do know some key facts. We do know that infliximab levels increase in the second trimester of pregnancy, and so clearly, pregnancy seems to affect the clearance of this medication. Interestingly, we also know that 6-TG, which is a metabolite of 6-MP, tends to decrease in pregnancy.

So we do know that clearance of biologics, as well as immunomodulators, is affected by the pregnant state. And so for that reason, I do recommend checking biologic concentrations, as well as thiopurine metabolites at preconception and in the second trimester of pregnancy, and this is an opportunity to adjust the medication in order to make sure that the medication is appropriately dosed and on the right schedule.

Dr. Buch:
So moving on to a very important other topic, what should we know about lactation in women with IBD?

Dr. Shmidt:
The short answer is that breast is best, and there's no need to pump and dump. This is in women who are on biologics. So biologics are very, very large molecules, and they transfer into the milk in very, very minuscule amounts, much smaller amounts than what you would get through transplacental transfer. And we know that children who are breastfed and are exposed to these biologics have no adverse outcomes, and so it's important to know that breastfeeding is completely safe in the setting of biologic use. I will say that small molecules, on the other hand, have not been shown to be safe. We just don't have data on this. We do know that small molecules do transfer to breast milk, and the mode of administration is oral, so we know that it would have activity when ingested, so the recommendation is not to breastfeed in the setting of small molecule use. And again, some examples of small molecules are tofacitiniband and ozanimod.

Dr. Buch:
Before we conclude, Dr. Shmidt, are there any other thoughts you'd like to share with our audience today?

Dr. Shmidt:
I just want to emphasize that it is really important to make sure that a patient's IBD is well-controlled and is in remission at the time of conception. That is how we position the patient to have the best outcomes in pregnancy. And I also want to say that there's a lot of voluntary childlessness among patients with ulcerative colitis, and particularly Crohn's disease, and there are many myths out there about the safety of medications or the impact IBD might have on a pregnancy. And the truth is that in the vast majority of cases, it is absolutely safe to conceive, and most of the time pregnancy outcomes are just the same as they would be in the general population. So I just think it's important to inform the patient and make sure that she's making a decision based on what we actually know and not on what we actually fear.

Dr. Buch:
What an excellent discussion on IBD and pregnancy. I want to thank my guest, Dr. Eugenia Shmidt, for sharing her insights.

Dr. Shmidt, thanks so very much for joining us today.

Dr. Shmidt:
Thank you so much for having me.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit ReachMD.com/GIInsights where you can Be Part of the Knowledge. Thanks for listening and looking forward to learning with you next time.