My Treatment Approach to Management of the Pregnant Patient With Inflammatory Bowel Disease

Susie W. Ng, MD, and Uma Mahadevan, MD

Abstract

Inflammatory bowel disease (IBD) is frequently diagnosed in women of childbearing age. Of paramount concern are questions about the effect of the disease on a woman’s ability to conceive and carry the pregnancy safely to term, as well as the effect of the disease and its therapies on the health of the fetus. For health care providers, there is also the issue of medication dose adjustments and management of flares during pregnancy. Growing experience with IBD in pregnancy suggests that most women will have good outcomes; however, concerns and uncertainty remain for both the patient and the physician. This article outlines our approach to the treatment of these patients with respect to preconception counseling and management during pregnancy and the postpartum period.
endocrinologist for evaluation and assistance in management. In our experience, the medications commonly used to assist the reproductive process do not significantly affect IBD activity.

**AFTER CONCEPTION**

**Effect of IBD on Pregnancy**

Most studies suggest that women with IBD have higher rates of pregnancy complications compared with age-matched controls. Complications include increased risk of preterm delivery, low birth weight, spontaneous abortion, and peripartum complications, including preeclampsia. Disease activity at conception and during pregnancy is associated with higher rates of adverse pregnancy outcomes, but even patients with quiescent disease are at elevated risk for complications throughout their pregnancy compared with the general population. Furthermore, maternal complications, such as venous thromboembolism and malnutrition, occur more frequently in women with IBD. Therefore, we recommend that all women with IBD be followed as high-risk obstetric patients.

The decision regarding mode of delivery should be made on an individual basis between the patient and her obstetric provider. Generally, patients with active perianal disease should be encouraged to have a cesarean delivery owing to the risk of exacerbating disease. Although cesarean delivery for the patient with an ileal pouch-anal anastomosis is recommended in some centers, studies have suggested that vaginal delivery may be safe. Patients without these conditions can be safely considered for vaginal delivery. We caution women against delaying or refusing cesarean delivery if labor is prolonged and the obstetrician recommends delivery. Forceps delivery and uncontrolled tears can affect pelvic floor function. In the patient with compromised bowel habits, this can have a substantial impact in the future.

**Effect of Pregnancy on IBD**

Women are not at increased risk for disease flare while pregnant or during the postpartum period compared with the nonpregnant patient with IBD. Earlier studies had reported higher rates of disease flares in pregnancy and the peripartum period, but this observation was likely confounded by medication cessation during pregnancy or while breastfeeding and resumption of tobacco smoking after delivery. In the national pregnancy registry Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO), we observed a significantly higher rate of disease activity in patients with ulcerative colitis (UC) compared with Crohn disease. This same effect has been reported in a European study as well. Although the reasons for this are unclear (perhaps owing to secretion of pro-UC cytokines by the placenta), we are particularly mindful of disease activity in our patients with UC.

If a patient develops a disease flare during her pregnancy, the evaluation and management of symptoms are similar to those of the nonpregnant patient with IBD. Stool studies should undergo laboratory testing to exclude infection, particularly *Clostridium difficile*, which is more prevalent during the peripartum period. If imaging is needed, ultrasound or magnetic resonance imaging is preferred over computed tomography to avoid exposing the developing fetus to radiation. Contrast agents, such as gadolinium, should be avoided in the first trimester because this compound has been associated with teratogenic effects in animal models. We have used contrast imaging successfully in the second and third trimesters, but after discussion with our radiology colleagues. Endoscopic evaluation should be performed by unsedated flexible sigmoidoscopy if possible. A full colonoscopy is rarely required during pregnancy, but, if so, it should be performed with anesthesia support and fetal monitoring. Surgery should be considered for severe bleeding, medically refractory disease, or obstruction, if needed. The American College of Obstetricians and Gynecologists recommends that nonemergency operations should be performed during the second trimester, when preterm contractions and spontaneous abortion are least likely.

**MEDICATIONS**

Most medications used for the treatment of IBD are considered compatible with pregnancy and breastfeeding. In general, the act of stopping medications and precipitating a possible disease flare poses a greater risk to the fetus than any potential adverse effects of most medications themselves. Therefore, we advise patients to have a thoughtful discussion with
their gastroenterologist before making any changes to their treatment regimen. It has been our experience that patients who have a medication plan before conception are much more adherent to recommended therapies than patients who attempt to create a treatment plan after conception. We generally address the issue of conception during routine office visits so that the patient knows to contact us before conception and is comfortable with their therapy. We also emphasize that they should check with their gastroenterologist before discontinuing any IBD medications, even if this was a recommendation made by their obstetrician or pediatrician.

**Methotrexate and Thalidomide**
The 2 exceptions to IBD medications being safely continued in pregnancy are methotrexate and thalidomide, which are both Food and Drug Administration category X agents and are absolutely contraindicated in pregnancy. We do not routinely manage patients taking thalidomide, but for the many patients taking methotrexate as monotherapy or as combination therapy with biological agents, we advise discontinuing the drug at least 6 months before attempting conception. Methotrexate is also excreted in breast milk and can interfere with cellular metabolism; therefore, it is contraindicated in breastfeeding.

**Aminosalicylates**
Most aminosalicylates are category B and are considered safe in pregnancy. These include most formulations of mesalamine, such as Pentasa and Lialda (both from Shire US Inc), as well as sulfasalazine and balsalazide. Osalazine, Asacol, and Asacol HD (Actavis) are category C agents. Both Asacol and Asacol HD contain dibutyl phthalate in the coating, which has been associated with congenital anomalies in animals. Currently, Asacol HD is commercially available, but Asacol is no longer manufactured. Delzicol (Warner Chilcott), a new formulation of Asacol without dibutyl phthalate, was recently released and is a category B agent. Women receiving sulfasalazine who are pregnant or attempting to conceive should take supplemental folic acid, 2 mg daily, to prevent folate deficiency. Mesalamine suppositories and enemas are well tolerated and can be used during pregnancy. There is no evidence to suggest that the use of medicinal enemas during pregnancy is associated with an increased rate of miscarriage or preterm labor.

**Corticosteroids**
Prednisone and budesonide are category C agents but can be used in the setting of disease flares. There may be a small increased risk of orofacial clefts in infants exposed to corticosteroids during the first trimester, but there does not seem to be a major teratogenic risk. Prednisone (or more specifically its metabolite prednisolone) is minimally excreted in breast milk, and prednisone and budesonide are considered compatible with breastfeeding.

**Thiopurines**
Azathioprine/6-mercaptopurine (AZA/6-MP) has demonstrated teratogenicity in animal studies, although no consistent pattern of birth defects has been identified in humans. Nonetheless, these agents are pregnancy category D. In our practice, if AZA/6-MP is monotherapy, we will continue it throughout pregnancy. If the patient is taking a thiopurine as part of combination therapy with an anti-tumor necrosis factor agent, we will consider stopping it in the patient with long-standing remission. It should be recognized that stopping AZA/6-MP during pregnancy may not change outcomes given that fetal exposure during organogenesis has already occurred by the time the patient realizes she is pregnant, so the risk of flaring should be weighed against the unclear benefit of stopping thiopurines. We do not administer AZA/6-MP for the first time during pregnancy given the (very small) risk of pancreatitis or bone marrow suppression. Azathioprine/6-MP is excreted at low levels in breast milk, with maximal excretion during the first 4 hours of drug ingestion. Azathioprine/6-MP is believed to be compatible with lactation, but mothers are advised to wait 4 hours after taking the medication before breastfeeding. This is not always possible with a newborn, in which case we still give patients the option of breastfeeding because transfer is minimal.

**Biological Agents**
In general, these agents are compatible with pregnancy and breastfeeding. Infliximab,
adalimumab, and certolizumab are all Food and Drug Administration pregnancy category B. Natalizumab is pregnancy category C. Experience with this group of drugs is increasing. To date, there has not been a consistent pattern of adverse pregnancy outcomes or birth defects observed in exposed individuals. Infliximab and adalimumab are IgG1 antibodies that are actively transported across the placenta by the FcRn receptor on the placenta and are detectable in newborns for up to 6 months after birth. Certolizumab is a pegylated Fab’ fragment that is not actively transported across the placenta during pregnancy, resulting in minimal drug levels detected in infant and cord blood. Natalizumab is an integrin receptor antagonist and IgG4 antibody that would be expected to actively cross the placenta as well. Available data, mostly in patients with multiple sclerosis, do not suggest an increase in birth defects.33 The PIANO registry has now enrolled more than 1200 pregnant patients with IBD, of whom more than 500 have been exposed to a biological agent.20 The risk of birth defects does not seem to be increased based on exposure to medication (biological agents, AZA/6-MP, or combination therapy) compared with those not exposed to these medications.

There is significant debate over when to stop antitumor necrosis factor agents during pregnancy. The theoretical risks of drug transfer to the infant must be weighed against the risk to the mother and infant if a flare occurs during pregnancy. Because certolizumab has minimal placental transfer, it can be continued throughout pregnancy with no adjustment made to medication timing or infant immunization schedules. There is evidence of placental transfer of infliximab as early as 26 weeks’ gestation, with detectable drug levels in cord blood at term birth.34 We also know that the FcRn is functioning as early as week 13 of gestation, so transfer may occur even earlier. In our practice, we try to manipulate the timing of infliximab doses so that the patient receives her last predelivery infusion during week 30 to 32 of gestation, followed by an infusion immediately after delivery. This method generally works well because there is little interruption to therapy. Adalimumab, on the other hand, has a 2-week dosing schedule, so a patient is at greater risk for disease flare when a scheduled injection is delayed. Therefore, we will continue treatment through week 36 to 38 of gestation. For natalizumab, these patients often have limited therapeutic options, and antibody development would be devastating; therefore, we generally continue therapy until week 37 to 38 of gestation and avoid infusion delays. For infliximab, adalimumab, and natalizumab, we send letters to the pediatrician and advise the mother that there should be no live vaccines for the first 6 months of life (all other attenuated vaccines should be given on schedule) and that the infant should be monitored for infection. At 1 year, in a preliminary analysis of the PIANO registry, we have not observed an increase in the rate of infections in those exposed to biological agents, and there seems to be no impairment in achieving developmental milestones.20

Infliximab and adalimumab have been detected in breast milk in miniscule amounts.35,36 Breastfeeding is considered compatible with the use of biological agents.

**RECOMMENDATIONS**

There are several key points that providers should keep in mind when treating IBD in women who are interested in conceiving or are pregnant (Table). Women with IBD who have not had pelvic surgery have similar chances of conceiving as women without IBD. Once pregnant, women with IBD are at increased risk for adverse outcomes and should be observed as high-risk obstetric patients, even in remission. Ideally, women should strive to achieve quiescent or stable disease before conception and to maintain it during pregnancy to reduce the risk of miscarriage and preterm birth. Preconception counseling, a medical therapy plan that the patient is comfortable following, and good communication with the treatment team should be established before pregnancy. Most IBD medications may be safely continued during pregnancy and lactation. Biological agent therapy may need to be adjusted in the third trimester but is generally well tolerated without significant adverse fetal outcomes. An interdisciplinary approach among the gastroenterologist, obstetrician, and, eventually, pediatrician is needed to ensure a healthy baby and a healthy mother.
TABLE. Key Points of IBD Management of the Pregnant Patient

<table>
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<tr>
<th>Period</th>
<th>Key points</th>
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<tr>
<td>Preconception counseling</td>
<td>Care should be established with a primary care provider, an obstetrician, and a gastroenterologist</td>
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<td>Medication that may be harmful to the fetus (eg, methotrexate) should be discontinued in favor of an alternative agent</td>
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<td>The patient should have a medication plan that she is comfortable with before conception and should understand the risks of NOT treating and the risks of the medication</td>
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<td>Disease activity should be stabilized and the patient should be receiving established maintenance therapy if appropriate</td>
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<td>Vaccinations and other health care maintenance should be up to date</td>
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<td>Laboratory values, such as complete blood cell count, B12, folic acid, iron, and vitamin D, should be checked and addressed if abnormal</td>
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<td>Conception</td>
<td>Rates of conception are similar in women with and without IBD (except in the setting of previous pelvic surgery)</td>
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<td>Increased disease activity may affect fertility and miscarriage rates; stable disease should be maintained</td>
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<td>Patients should be referred to a reproductive endocrinologist if concerted attempts to conceive are unsuccessful after 6 mo</td>
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<tr>
<td>Pregnancy</td>
<td>Increased disease activity may affect pregnancy outcome; stable disease should be maintained</td>
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<td>Appropriate maintenance therapy should be continued throughout pregnancy</td>
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<td>The schedule of biological agent dosing may be adjusted to minimize placental transfer to the fetus during the third trimester</td>
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<td>Women with IBD should be followed as high-risk obstetric patients given the increased risk of complications during labor and delivery</td>
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<td>Delivery</td>
<td>Generally, vaginal delivery is appropriate in women with IBD except those with active perianal disease</td>
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<td>Mode of delivery should remain an individualized decision between the patient and her obstetrician</td>
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<td>Postpartum</td>
<td>Most medications can be safely continued while breastfeeding</td>
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<td>Live vaccines should not be given in the first 6 mo to infants exposed to anti—tumor necrosis factor agents during pregnancy (except certolizumab)</td>
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<td>All other vaccines can be given on schedule</td>
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<td>The pediatrician should be aware of anti—tumor necrosis factor or other biological agent exposure during pregnancy so that fevers and infections in the newborn can be appropriately managed</td>
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**IBD** = inflammatory bowel disease.

**Abbreviations and Acronyms:** AZA/6-MP = azathioprine/6-mercaptopurine; IBD = inflammatory bowel disease; PIANO = Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes; UC = ulcerative colitis

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**Correspondence:** Address to Uma Mahadevan, MD, Department of Medicine, University of California, San Francisco, 1701 Divisadero St. #120, San Francisco, CA 94115 (umamahadevan@ucsf.edu).

**REFERENCES**


