

Pregnancy and Inflammatory Bowel Disease

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Abstract: Many patients with inflammatory bowel disease (IBD), whether Crohn's disease or ulcerative colitis, are of reproductive age. Young women with IBD are usually very worried about their fertility, the activity of their disease during pregnancy, the heritability of the disease to their unborn child, and the effect of their underlying IBD on the pregnancy itself. Additionally, patients express concerns about using IBD medications during pregnancy, fearing that the medications may negatively affect the fetus. For this reason, it is of the utmost importance that gastroenterologists and patients with IBD be aware of the effect of IBD on pregnancy, the effect of pregnancy on IBD, and the effect of IBD medications on the fetus and on pregnancy outcomes. Increasing the awareness of patients with IBD about the importance of maintaining disease remission at the time of conception and throughout pregnancy is key to improving the outcomes of both mothers and fetuses. This article addresses the fertility of patients with IBD, the effect of pregnancy on disease activity, and the effect of IBD on pregnancy. Also discussed are which IBD medications can be used during conception and pregnancy and which medications must be avoided.

Fertility in Inflammatory Bowel Disease

Fertility remains a topic of concern among many patients with inflammatory bowel disease (IBD).¹ Female patients whose IBD is under control and who have not previously undergone pelvic surgery have fertility rates comparable with those of women of the same age who do not have IBD. Disease remission not only improves fertility rates^{2,3} but also, as most studies have shown, leads to more favorable outcomes of pregnancy.

The fertility rates of patients with ulcerative colitis who have not undergone intestinal surgery are not diminished when compared with those of individuals who do not have IBD.⁴⁻⁶ Surgery for ulcerative colitis usually comprises a total abdominal colectomy

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with or without pelvic dissection and the creation of an ileal J-pouch anal anastomosis. If the latter part of the surgery is performed, pelvic adhesions tend to form in female patients, affecting fallopian tube patency and consequently leading to tubal obstruction and diminished fecundity. Fertility is the natural ability to produce offspring, whereas fecundity is the potential for reproduction, influenced by gamete production, fertilization, and carriage of the pregnancy to term. The decreased rates of fecundity (ie, the inability to conceive naturally) are not related to the underlying IBD but are purely a consequence of the surgery. This effect has also been seen in patients with familial adenomatous polyposis who have undergone the same surgery, with pelvic dissection and creation of an ileal pouch anal anastomosis.⁷

For this reason, it is strongly recommended that young women who have not completed their families avoid pelvic dissection until later in life. Patients who require surgery should undergo subtotal colectomy, placement of an end-ileostomy, and the creation of a Hartmann pouch. If the patient is not too far away from completing her family, it is recommended that she do so before pursuing the latter steps of the operation and undergoing the creation of an ileal J-pouch and an ileo-anal anastomosis. On the other hand, if completion of her family is far away, it may not be surgically feasible to allow many years to pass between the stages of the J-pouch surgery, and *in vitro* fertilization would be an option for the patient in the future. Most important is that the patient proceed with the best option for her health. Additionally, it has been shown that the fertility rates of patients who undergo an open ileal J-pouch anal anastomosis are even more compromised than those of patients who undergo the operation laparoscopically.⁸ Another option for female patients of childbearing age that does not affect fecundity is the creation of an ileorectal anastomosis.⁹ Although disease may return in the rectum, it can be controlled with topical therapies, and the pelvis has been spared surgery.

The fertility rates of patients with Crohn's disease in remission are similar to the rates of individuals who do not have IBD.¹⁰ In a recent systematic review by Tavernier and colleagues, the fertility rates of patients with Crohn's disease were found to be lower than those of the general population, but it is important to note that this decrease was not related to underlying IBD but rather to voluntary childlessness for fear of a bad outcome.⁵ Ovarian reserve in young women (<30 years of age) with Crohn's disease in remission is comparable with the reserve of young women who do not have IBD. In female patients with Crohn's disease who are older than 30 years, the ovarian reserve is significantly decreased. This decrease is even more pronounced in those in whom Crohn's disease involves the colon.¹¹

Effect of Inflammatory Bowel Disease on Pregnancy

Patients with IBD, whether Crohn's disease or ulcerative colitis, tend to have pregnancy outcomes worse than those of women without IBD. Studies have further shown that the chances of a poor pregnancy outcome in patients with Crohn's disease are higher than those in patients with ulcerative colitis.

In a population-based study of 2377 pregnant patients with Crohn's disease, the numbers of preterm births, newborns who were small for gestational age, and cesarean section deliveries were higher in this cohort than in individuals without IBD.^{12,13} Similarly, in a cohort of 2637 pregnant patients with ulcerative colitis, the numbers of preterm births, newborns who were small for gestational age, and cesarean section deliveries were noted to be higher in the cohort with ulcerative colitis than in individuals without ulcerative colitis. In addition to these poor pregnancy outcomes, it was noted that the number of preterm deaths was higher in the pregnant patients with ulcerative colitis than in controls without ulcerative colitis.¹⁴ Secondary analysis of the patients with ulcerative colitis showed that more severe disease worsened pregnancy outcomes, but the same analysis failed to show that severity of disease had an effect on the pregnancy outcomes of patients with Crohn's disease.

A smaller prospective study by Bortoli and colleagues comparing pregnant patients who had IBD (145 with Crohn's disease and 187 with ulcerative colitis) with individuals who did not have IBD demonstrated that IBD had no effect on rates of abortions, preterm delivery, cesarean section births, and congenital abnormalities and had no effect on birth weight.¹⁵ The majority of the patients with IBD (87% of those with Crohn's disease and 79% of those with ulcerative colitis) who were included in this study had disease that was in remission at the time of conception and remained in remission throughout the pregnancy (86% of those with Crohn's disease and 74% of those with ulcerative colitis).¹⁵ A similar study involving 461 pregnant patients with IBD showed different results, demonstrating that IBD increases the risk of pregnancy complications associated with worse pregnancy outcomes but does not lead to worse newborn outcomes.¹⁶ Patients with IBD were more likely to have a spontaneous abortion, eclampsia, preeclampsia, placenta previa, abruptio placentae, or prolonged premature rupture of membranes. In this study, disease activity was not associated with a worse outcome; however, a diagnosis of IBD, a history of intestinal surgery for IBD, and not being white were found to be independent predictors of worse outcomes.¹⁶

A case-control study by Molnar and colleagues looked at patients who had a pregnancy before their diag-

nosis of IBD and a pregnancy again after their diagnosis.¹⁷ The investigators compared the pregnancy outcomes of each patient before and after her IBD diagnosis and found that after a diagnosis of IBD, preterm birth and low birth weight were more common than before a diagnosis of IBD. Disease activity, the location and extent of disease, the presence of perianal complications, and the mode of delivery did not affect pregnancy outcomes.¹⁷

Data regarding the effect of disease activity on pregnancy outcomes remain inconsistent, but most physicians advise their female patients to conceive while their disease is in remission and to continue their medications throughout the pregnancy in order to maintain remission and avoid worse pregnancy outcomes.¹⁸ Some studies have demonstrated that rates of fetal loss and preterm birth are higher in patients who conceive while their IBD is active. In patients whose IBD was active during pregnancy, higher rates of preterm birth and low birth weight were noted.¹⁹⁻²¹ As previously described, the studies by Molnar and colleagues and Mahadevan and colleagues did not demonstrate an association between worse pregnancy outcomes and disease activity.^{16,17} It has been reported that the children of patients with ulcerative colitis whose disease was active during pregnancy have a higher risk of developing childhood illnesses.¹⁷

The risk of giving birth to a child with a congenital anomaly among mothers with IBD remains controversial. In a study by Dominitz and colleagues, mothers with ulcerative colitis were at an increased risk for delivering children with congenital anomalies.²² Results were similar in a meta-analysis conducted by Cornish and colleagues.¹³ This analysis showed that patients who had IBD were more likely to have children with congenital anomalies (odds ratio [OR], 2.37; 95% CI, 1.47-3.82), and subgroup analysis demonstrated that this risk was seen only in mothers with ulcerative colitis.¹³ This meta-analysis was driven primarily by the study of Dominitz and colleagues. To date, the factors that may contribute to this possible increased risk of congenital anomalies are unknown.

Effect of Pregnancy on Inflammatory Bowel Disease

In most female patients (~80%) with IBD who conceive while their disease is in remission, the IBD tends to remain in remission throughout the pregnancy and in the postpartum period.²³ Of the patients with IBD who conceive when their disease is active, 66% continue to have active disease or experience worsening of their IBD. In up to 45% of patients with ulcerative colitis who conceive while their disease is active, the colitis worsens during pregnancy; in 24%, the colitis continues to be active but stable, and in the remainder of patients, the disease goes back into remission.²⁴ Among patients with Crohn's dis-

ease who conceive while their disease is active, the disease goes into remission in one-third, remains stably active in one-third, and worsens in one-third.²⁴

Studies have shown that the rates of IBD flare are similar in pregnant and nonpregnant patients with IBD—both ulcerative colitis and Crohn's disease. The relapse rate was 34% per year among pregnant patients with ulcerative colitis, compared with 32% per year among patients with ulcerative colitis who were not pregnant.²⁰ A prospective trial by Pedersen and colleagues found that the rates of disease flare were similar in pregnant patients with Crohn's disease who conceived while their disease was in remission and in nonpregnant patients with Crohn's disease.²⁵ Rates of relapse were higher in pregnant women with Crohn's disease who conceived while their disease was active than in nonpregnant patients with Crohn's disease (50% vs 33%, respectively).²⁵ Results of the study were different for patients with ulcerative colitis; patients with ulcerative colitis who were pregnant had a higher risk for disease flare during pregnancy (relative risk, 2.19; 95% CI, 1.25-3.97) and in the postpartum period in comparison with matched nonpregnant controls, even though the patients had conceived while their disease was in remission (hazard ratio, 2.74; 95% CI, 1.61-4.65).²⁵ Disease flares were more frequent in the first 6 months of pregnancy and in the first 3 months of the postpartum period.

The approach to patients with IBD who experience disease flares during pregnancy is very similar to the evaluation for nonpregnant patients with IBD. Similarly, the management of IBD flares in pregnant patients is similar to the management of flares in nonpregnant patients with IBD. Most medications used to treat IBD are relatively safe during pregnancy with a few exceptions, detailed in the following section. In terms of the evaluation of pregnant patients with IBD who experience symptoms suggestive of active disease, the use of ultrasound studies for imaging is preferred, and these studies can be used to evaluate the small bowel. Magnetic resonance imaging is also a safe option; however, it is better to avoid the use of gadolinium in the first trimester of pregnancy because of its possible teratogenicity, although it has been shown to be safe in a single prospective study by De Santis and colleagues.²⁶ If endoscopic evaluation is necessary, a flexible sigmoidoscopy with the patient unsedated is usually the recommended procedure.²⁷ As with any surgery during pregnancy, it is recommended to operate on pregnant patients during the second or third trimester if surgical intervention is needed.

Management of the Pregnant Patient With Inflammatory Bowel Disease

It is of the utmost importance that patients conceive while their IBD is in remission. It is equally important

Table. Pregnancy Categories of Inflammatory Bowel Disease Medications

| Category | Inflammatory Bowel Disease Medications |
|----------|--|
| A | — |
| B | Sulfasalazine Mesalamines (except for delayed-release mesalamine and olsalazine) Anti-tumor necrosis factor α agents (infliximab, adalimumab, certolizumab pegol, golimumab) Metronidazole |
| C | Delayed-release mesalamine Olsalazine Anti-integrin (natalizumab) Corticosteroids Ciprofloxacin, rifaximin |
| D | 6-Mercaptopurine, azathioprine |
| X | Methotrexate Thalidomide |

for patients to maintain remission during pregnancy and in the postpartum period by strictly adhering to their medications. IBD medications are safe to take during the conception period and during pregnancy except for 2 medications: methotrexate and thalidomide (Thalomid, Celgene). Both of these are teratogenic (category X) and must be used with extreme caution in women of child-bearing potential because they should be discontinued months before conception. The safety of each of the IBD medications is discussed below, and the pregnancy categories are listed in the Table.

Aminosalicylates

The use of mesalamine products is safe during pregnancy despite their presence in cord blood. No abnormalities were seen in the fetuses of mothers who took up to 3 g of mesalamine daily during pregnancy.²⁸ The different mesalamine formulations are classified as either category B or category C.²⁹ Delayed-release mesalamine (Asacol, Actavis) and olsalazine (Dipentum, Alaven) are considered category C drugs, and the remainder of the aminosalicylates are category B medications. Delayed-release mesalamine is considered a category C drug because of the dibutyl phthalate that is found in the capsule's coating. In animal studies, very high doses of dibutyl phthalate led to skeletal and urogenital tract malformations in male newborns. This outcome has not been demonstrated in human offspring.³⁰ Olsalazine is considered a category C drug in pregnancy because there are no data on its use during pregnancy.

In early studies, it was suggested that sulfasalazine may be teratogenic because it crosses the placenta. Larger

studies demonstrated that despite this characteristic, sulfasalazine did not cause fetal abnormalities and was safe to use during pregnancy. Sulfasalazine is currently categorized as a category B drug. As is recommended for nonpregnant patients, it is essential that pregnant patients taking sulfasalazine also take folic acid because sulfasalazine inhibits folate synthesis.³¹ Women taking sulfasalazine who are planning to conceive should take 1 mg of oral folic acid twice daily in the prenatal period (at least 3 months before conception) and during pregnancy to avoid defects in the fetal neural tube.³² In a meta-analysis, Rahimi and colleagues demonstrated that mesalamine and sulfasalazine did not cause an increased risk of congenital malformations, premature birth, spontaneous abortions, or low birth weight.²⁸

Thiopurines

The drug 6-mercaptopurine and its prodrug azathioprine are classified as category D drugs in pregnancy. These medications are detected in fetal blood, reaching levels as high as 5% of the maternal drug level.³³ In animals, thiopurines were found to be teratogenic; however, in animal studies, thiopurines were administered either intravenously or intraperitoneally (rather than orally), and the doses administered were much higher than those used in humans.³⁴ Results of human studies in terms of the safety of thiopurine use in pregnancy have been conflicting. Nonetheless, it is recommended that thiopurine drugs be continued in pregnancy with the goal of keeping the mother's IBD under control. Older studies demonstrated that thiopurine use in pregnancy leads to congenital anomalies, perinatal mortality, low birth weight, babies who are small for gestational age, and preterm deliveries; however, these studies may have been confounded by maternal illness.^{35,36} On the contrary, newer studies and studies of patients with transplants show that the use of thiopurines does not pose an increased risk to fetuses and that thiopurines are safe to continue in pregnant patients.³⁷⁻⁴⁰ Interim analysis of the ongoing prospective PIANO (Pregnancy in IBD Neonatal Outcomes) Registry confirmed that the use of thiopurines does not lead to worse fetal outcomes.⁴¹ Jharap and colleagues recently performed a prospective study examining the effect of pregnancy on thiopurine metabolism and the effect of thiopurine use on exposed fetuses.⁴² At birth, all newborns had a normal Apgar score, and none had major congenital abnormalities; however, 60% of the newborns had anemia.⁴²

Methotrexate

Although methotrexate is an immunomodulator, like the thiopurines, it is a category X drug in pregnancy and should be discontinued during pregnancy. Many physicians avoid using methotrexate in young women of repro-

ductive potential because of its major teratogenic effect.⁴³ When it is given, patients are instructed to employ at least one form of contraception to avoid pregnancy. Because of its long half-life, methotrexate persists for long periods of time in the tissues of patients who use it, and it should be discontinued at least 6 months before conception to allow enough time for it to be eliminated from the body.⁴⁴ The fetuses of mothers who conceive while on methotrexate or mothers who continue to take this medication during pregnancy (at least during the first trimester, when organogenesis occurs) are at extremely high risk for being born with multiple congenital anomalies and possibly with methotrexate embryopathy syndrome, which is characterized by limb abnormalities, small and low-set ears, micrognathia, intrauterine growth retardation, and hypoplastic supraorbital ridges; sometimes, these children are also mentally retarded.

Biologic Agents

Biologic medications for IBD include anti-tumor necrosis factor α (anti-TNF) medications and an anti-integrin medication. The anti-TNF drugs include infliximab (Remicade, Janssen Biotech), adalimumab (Humira, AbbVie), certolizumab pegol (Cimzia, UCB), and golimumab (Simponi, Janssen Biotech), and all of these medications are considered category B drugs in pregnancy. The anti-integrin natalizumab (Tysabri, Biogen Idec) is considered a category C drug in pregnancy.

Anti-Tumor Necrosis Factor Medications Infliximab, a chimeric mouse/human immunoglobulin (Ig) G1 antibody, crosses the placenta after 20 weeks of gestation, with the highest rate of transfer across the placenta occurring in the third trimester. For this reason, this drug does not interfere with organogenesis, which occurs during the first trimester of pregnancy. Infliximab has not been shown to increase the risk of fetal malformations, miscarriage, and neonatal complications among patients with Crohn's disease.^{45,46}

Adalimumab is a fully human IgG1 anti-TNF antibody, and, like infliximab, it crosses the placenta after 20 weeks of gestation. There have been no increased rates of spontaneous abortion, stillbirth, congenital malformations, or preterm delivery among pregnant patients who have been exposed to adalimumab.^{44,47,48} Golimumab is similar to adalimumab in that it is a fully human IgG1 anti-TNF antibody.

Unlike the other 3 anti-TNF agents, certolizumab pegol is a Fab' fragment of humanized monoclonal anti-TNF antibody that is linked to polyethylene glycol. Certolizumab pegol does not contain the Fc portion of the antibody and does not cross the placenta.⁴⁹

It has been shown that anti-TNF medications do not increase the risk of pregnancy complications in comparison

with thiopurines and in comparison with not taking IBD medications. On the contrary, the use of thiopurines or anti-TNF agents is associated with fewer neonatal complications, which stresses the importance of maintaining disease remission in pregnant women with IBD.⁴⁰ Similar outcomes were demonstrated in the PIANO Registry analysis, in which children born to mothers who were treated with adalimumab or certolizumab pegol monotherapy were not found to have an increased risk of congenital anomalies, delayed infant growth, developmental problems, or infections.⁴¹ However, the risk for infection was higher in the children of mothers treated with combination therapy (an anti-TNF agent and a thiopurine).⁴¹ There have been concerns that anti-TNF medications may cause a defect in the maturation of the newborn immune system, resulting in an increased risk of infection.⁵⁰ Animal studies, however, failed to show a defective infant immune system in children whose mothers were treated with anti-TNF therapy throughout pregnancy.⁴⁹

It is important to make sure that children born to mothers who have received infliximab, adalimumab, or golimumab after the 20th week of gestation do not receive any live vaccinations during their first 6 months of life. These newborns are immunosuppressed because of the anti-TNF drugs that have crossed the placenta into their blood.⁵¹ Newborns have an immature reticuloendothelial system and are unable to clear antibodies, and infliximab, adalimumab, or golimumab will be detected in their blood. To date, there are no clear guidelines regarding when to hold anti-TNF medications in pregnant women. Some physicians stop infliximab, adalimumab, and golimumab at week 20 of gestation to minimize the transfer of these drugs across the placenta, whereas others give the last dose at 6 to 8 weeks before the estimated delivery date.^{52,53} It is important to keep in mind that maintaining disease remission in the mother is key, and the timing of holding anti-TNF therapy should be individualized for each patient.

Anti-Integrin Medication Natalizumab is a humanized monoclonal IgG4 antibody against the adhesion molecule $\alpha 4$ -integrin, and it is considered a category C medication in pregnancy. There are limited data on the use of this drug in pregnancy. The natalizumab global safety database review did not show an increase in birth defects in children whose mothers were exposed to natalizumab during pregnancy.⁵⁴ The multiple sclerosis literature described the pregnancy outcomes of 35 patients who accidentally became pregnant while being treated with natalizumab.⁵⁵ Of these patients, 29 had viable pregnancies; 28 gave birth to healthy children, and 1 child was born with hexadactyly. Of the remaining 6 patients, 1 decided to undergo an abortion and the other 5 had early miscarriages.⁵⁵ Analysis

of the PIANO Registry showed that of the 6 women with Crohn's disease who received natalizumab, all gave birth to healthy children.⁴¹

Antibiotics

A number of antibiotics are used to treat pouchitis as well as the complications of IBD, such as perianal Crohn's disease and intra-abdominal abscesses resulting from fistulizing Crohn's disease. Metronidazole and ciprofloxacin tend to be used in combination for adequate coverage of anaerobic and gram-negative rod infections in the previously mentioned conditions. Metronidazole is considered a category B medication, and its short-term use (5-7 days) is safe in pregnancy.⁵⁶ Ciprofloxacin is a category C medication and tends to cause arthropathies in children because of its affinity for bone and cartilage. Although rifaximin (Xifaxan, Salix) is not well studied in IBD, it has been used to treat pouchitis. It is considered a category C medication in pregnancy.⁵⁷ Amoxicillin/clavulanate is also used to treat pouchitis and is considered a category B medication in pregnancy.

Corticosteroids

Corticosteroids are often used to treat IBD flares. Studies pertaining to corticosteroid use in pregnancy have demonstrated conflicting results, and corticosteroids are currently considered category C drugs during pregnancy. Older studies have linked maternal corticosteroid use in the first trimester to orofacial cleft defects in newborns (OR, 3.35; 95% CI, 1.79-5.69), but newer and larger studies have disproved this finding (OR, 1.05; 95% CI, 0.8-1.38).⁵⁸⁻⁶¹ Older studies have also demonstrated that maternal corticosteroid use during pregnancy leads to low birth weight, premature delivery, fetal adrenal suppression, and increased intrauterine infections, but larger population studies have refuted these findings.^{59,62,63} Few data have been published in regard to the exact dosing of corticosteroids above which toxicity to the mother and/or fetus becomes clinically relevant. Because corticosteroids are often tapered over a short time, no strict guidelines exist. Rather, corticosteroid dosing is left to the discretion of the provider to maintain maternal health.

Conclusion

Maintaining remission of IBD before and throughout pregnancy is very important. Active disease contributes to decreased fertility, and although this finding is still controversial, active disease at the time of conception has been shown to lead to worse pregnancy outcomes. Surgery with pelvic dissection markedly affects fecundity, but if it is needed for a female patient's health, then alternative methods of conception, such as in vitro fertiliza-

tion, should be considered. All IBD medications except for thalidomide and methotrexate should be continued in young female patients who plan to conceive and those who are pregnant.

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