# Chapter 8
# The Woman with Inflammatory Bowel Disease: Fertility, Pregnancy, and beyond


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## Overview

IBD is a chronic inflammatory condition that affects roughly 1.6 million people or 0.5% of the US population [1]. Patients are typically diagnosed in the second and third decades of life, with more than half of affected cases being women, many of whom are of childbearing age [2, 3]. These women often present with concerns about fertility, the immediate and long-term effects of the disease and its treatment on the fetus, and the impact of pregnancy on disease course and vice versa. There are also special considerations regarding babies who have been born to mothers with IBD, especially in the era of biologic therapy. The complexity of the disease and its treatment require a multidisciplinary tactic with the primary goal being to have the disease under control while keeping the mother and child safe. Providers should guide their patients by using evidence-based medicine while incorporating a shared decision-making approach.

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## Fertility

Many women with IBD have fertility concerns. There is also evidence showing that more women with IBD choose to remain childless, compared to the general population, due to misconceptions about pregnancy and IBD [4, 5, 6]. While the fertility rates in women with ulcerative colitis (UC) or Crohn's disease (CD) in remission are comparable to the general population, the rates may decrease in women with active IBD or prior pelvic surgeries like ileal pouch-anal anastomosis (IPAA) and proctectomy [7, 8]. This is probably related to inflammation and scarring of the fallopian tubes or ovaries. Dyspareunia may also play a role in patients who have perianal disease.

Women with IBD should be referred to a fertility specialist if they are unable to conceive after 6 months of timed intercourse. While assisted reproductive technology (ART) may not be as effective in these patients as in infertile women without IBD, especially if they have had prior surgeries, it is reassuring to know that chances of live birth are comparable to the general population when pregnancy does occur [9]. It is also important to remember that currently available medical therapies for IBD do not decrease fertility in women [10, 11].

Male fertility may also be affected, especially if they have impotence secondary to prior proctocolectomy or if they are being treated with medications such as methotrexate (MTX) and sulfasalazine. These drugs may cause reversible oligospermia. MTX can theoretically lead to mutation in sperm [12]. It is advisable to hold MTX therapy for 3 months and transition sulfasalazine to mesalamine 4 months before conception, because spermatogenesis takes 3–4 months [13, 14, 15, 16, 17, 18]. Mesalamine is not associated with oligospermia [13, 14]

## Preconception

All women with IBD should receive preconception counseling and family planning as part of their routine care with their gastroenterologist and obstetrician/gynecologist. Colorectal surgeons and maternal-fetal medicine specialists should also be involved in their care when appropriate. Preconception counseling provides an opportunity to review contraception, discuss healthcare maintenance, address patient's concerns regarding heritability to offspring, and optimize nutrition status. This is also an important time to emphasize smoking cessation and disease control while examining the safety of different IBD therapies during pregnancy and lactation. Preconception care reduces the risk of having an infant with low-birth-weight (LBW) and prevents IBD relapse in pregnant women by promoting smoking cessation and medication adherence [19].

### *Contraception*

Education regarding contraception should occur at preconception visits. Patients should be encouraged to use the safest and most effective option for reversible,

long-acting birth control. Options include an intrauterine device or an implant which can be hormonal or nonhormonal. Since IBD patients are at higher risk for venous thromboembolism (VTE), estrogen-containing contraception should be avoided if possible, especially in smokers and those with personal or family history of thromboembolic events.

## *Healthcare Maintenance*

Healthcare maintenance should be part of the routine IBD visits. Women are recommended to undergo regular Papanicolaou smears, stay up to date with recommended vaccinations, and avoid alcohol, tobacco use, narcotics, and recreational drugs. Cannabis is sometimes used in IBD patients to alleviate pain. However, its use should be discouraged in patients who are trying to conceive, pregnant, or breastfeeding due to its potential role in neurodevelopmental impairment in a growing fetus and infants, based on the recommendation by obstetric practice guidance [20]. Alcohol and smoking cessation improve parturition outcomes such as fetal alcohol spectrum disorder and smoking-associated LBW [21, 22].

## *Genetics*

CD and UC are observed to cluster within families; however, they do not obey the traditional Mendelian pattern of disease. Their pathogenesis is multifactorial and due to the dysregulated immune response to the gut microbiota in genetically susceptible hosts with possible environmental triggers such as antibiotics, infections, stress, and diet. Genome-wide association studies (GWAS) have led to the discovery of more than 200 genetic loci, which may play a role in IBD pathogenesis, with some genes implicated in both diseases while others being more specific to CD or UC [23]. Compared to the general population, the familial risk of IBD is about 8–12% when looking at first-, second-, and third-degree relatives with IBD [24, 25]. The chance of having IBD has been reported to be about 36% when both parents are affected [26]. Genetic influences are more substantial with CD compared to UC [27]. Disease concordance is higher in monozygotic (MZ) than dizygotic (DZ) twins implicating the role of genetics. The concordance rates for CD are about 20–56% in MZ and 0–7% in DZ twins. These rates for UC are about 6–19% and 0–5%, respectively [25]. These numbers indicate the importance of epigenetic and environmental factors in the pathogenesis of IBD in addition to genetics.

There is limited epidemiological data regarding other ethnic and racial groups because most data is based on Caucasians with an insufficient sample size of different ethnic and racial populations. While the highest incidence of IBD is in Caucasians, especially Ashkenazi Jews, IBD-associated hospitalization and mortality are more prevalent among non-Hispanic blacks [28, 29].

## *Nutrition and Supplements*

Nutrition should be optimized to achieve ideal body weight preferably before conception. Patients should be encouraged to eat a healthy, well-balanced diet. While nutrition consultation may be beneficial for all IBD patients before a planned pregnancy, it is highly recommended in patients with additional risk factors such as those with active disease, prior small bowel surgeries that influence the absorption of nutrients, and obese or underweight patients [30]. Inadequate gestational weight gain (GWG) is often a concern for women with IBD, especially when their disease is not well controlled. These patients have a twofold increased risk of infants with small-for-gestational-age and a 2.5-fold higher risk of preterm births [31].

Essential nutrients to address at preconception visits include folate, vitamin B12, vitamin D, and iron. These vitamins and minerals are often present in prenatal vitamins, which are routinely recommended in the general obstetric population, but a higher dose may be needed in some IBD patients. Folic acid deficiency during pregnancy can lead to neural tube defects in the fetus. Low levels may arise in patients on a low residue diet, small bowel involvement, or those being treated with sulfasalazine; therefore, supplementation with at least 2 mg/day is recommended [32]. Patients with CD who have undergone ileal resection or suffer from terminal ileum disease may be deficient in vitamin B12. Therefore, levels should be checked and replacement therapy initiated if needed. Similarly, vitamin D levels are often low in IBD patients, particularly during pregnancy, and they should be checked during preconception visits and supplemented accordingly [33]. Additionally, iron requirements are increased during pregnancy, making this a vital micronutrient. Iron replacement can be done via an oral or an intravenous route. Constipation may accompany oral iron supplementation, which may cause abdominal pain. If abdominal pain with constipation occurs after starting oral iron supplementation, patients can be treated with stool softeners and laxatives safely during pregnancy.

Women should limit their caffeine intake to 250 mg per day during preconception and conception phases. A growing number of herbal supplements are available over the counter for the treatment of IBD patients. Given the lack of robust data regarding the safety and efficacy of herbal remedies and the presence of significant methodological barriers in studies evaluating them, the use of these supplements should be discouraged in pregnant patients.

## *Disease Control*

In general, being in remission for at least 3 to 6 months, preconception significantly reduces the risk of an IBD flare intra- and postpartum. Quiescent disease at conception dramatically increases the chances of having a healthy pregnancy and delivering a healthy full-term baby. Pregnant patients with UC experience disease flare more commonly compared to CD, which mostly occurs during first and second

trimesters. In UC patients who become pregnant, it is estimated that one-third will remain in remission, one-third will improve, and one-third will worsen. While the exact etiology of this remains unclear, possible explanations include a shift from T-helper 1 (Th-1) to T-helper 2 (Th-2) cells which occurs to protect the fetus, smoking cessation, or undertreatment of UC at preconception [34].

## *Medications*

Most medical therapies for IBD are considered safe for women planning a pregnancy with few exceptions. As a general rule, most treatments should be continued during the preconception phase to optimize fertility while maintaining remission. Aminosalicylates or 5-aminosalicylic acid (5-ASA) derivatives are generally safe during this period. Women on Asacol HD should be changed to an equivalent dose of an alternative mesalamine due to concerns over dibutyl phthalate in the enteric coating and its effect over reproductive biology in animal models [35]. Patients who are being treated with sulfasalazine should maintain folic acid supplementation at a dose of 2 mg per day.

Glucocorticoids, in general, should never be used as maintenance therapy, and patients who are planning to get pregnant should aim to achieve steroid-free remission for at least 3 months before conception using a steroid-sparing agent.

Thiopurines, 6-mercaptopurine (6-MP) or its prodrug azathioprine (AZA), should be continued if the patient has been in remission on these medications as monotherapy. In patients on dual therapy with thiopurines, the risk and benefits of stopping concomitant thiopurines should be considered given a higher risk of infections with combination therapy.

MTX is teratogenic and is an abortifacient. Therefore, effective contraception methods should be employed for all women of childbearing age while using this drug and the patient should receive adequate counseling regarding its teratogenicity in order to prevent unplanned pregnancy. For women planning to conceive, MTX must be stopped at least 3 months before conception. When alternative therapy is needed in the interim, remission should be maintained on the new drug for at least 3 months before conception.

There is a significant amount of evidence regarding the safety of anti-TNFs during pregnancy based on registry data. Although similar data is still not available for the other biologics such as vedolizumab and ustekinumab, the consensus appears to be that they are safe during pregnancy. Therefore biologic therapy with anti-TNFs [infliximab (IFX), adalimumab (ADA), golimumab (GOL), and certolizumab pegol (CZP)], integrin inhibitors [vedolizumab (VDZ)], and interleukin 12/23 inhibitor [ustekinumab (UST)] should be continued in patients already on them, due to the importance of maintaining remission during pregnancy. In patients who are on dual therapy, particularly with anti-TNFs and immunomodulators, one should consider checking the drug levels before conception, especially when planning to stop the immunomodulators.

Small molecule Janus kinase inhibitor, tofacitinib, is a relatively new drug, with limited safety data in pregnancy. Due to its short half-life, it is recommended that tofacitinib be discontinued for at least 1 week prior to planned conception to allow this drug to wash out [3].

In men, the majority of IBD medications are safe to continue during the preconception period, with only a few exceptions. Sulfasalazine should be switched to one of the 5-ASAs about 4 months before conception due to reversible oligospermia [36]. MTX, which has a theoretical mutagenic effect on sperm, should be held 3 months before conception [12].

## Conception

### *Disease in Remission*

About one-third of patients who have been in remission at conception may flare during pregnancy [37]. Flares occur at a similar rate in nonpregnant IBD patients over 9 months [38]. Disease flares should be managed aggressively to avoid complications such as preterm delivery and LBW. Patients who are in remission should be monitored with laboratory workup every semester. These include a complete blood count, a liver profile, and any other necessary labs which may be indicated due to their specific therapies. At the same time, maternal-fetal monitoring should include routine antepartum care with fetal growth ultrasound in the third trimester and checking the perineal area for any active disease [3]. Laboratory values must be carefully analyzed in pregnancy as hemoglobin and albumin values often decrease while erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are often elevated. Trends of ESR and CRP help for disease monitoring; however, fecal calprotectin is a more reliable marker for this purpose.

### *Active Disease*

Patients are more likely to experience a flare of disease during pregnancy if the disease is active at conception; this is especially so for patients with CD [39]. Women with IBD, especially non-Caucasian race and those with a history of IBD related surgery, are at a higher risk of adverse pregnancy outcomes such as venous thromboembolism (VTE), malnutrition, and the requirement for blood transfusion, compared to non-IBD patients [40, 41, 42]. Women with active CD, especially active perianal disease, have higher rates of fourth-degree perineal lacerations and cesarean deliveries [43]. Patients with active disease should have their medications adjusted to obtain remission, while being monitored more frequently with blood work, fecal calprotectin, and follow-up visits every 2 weeks through office visits,

electronic messaging, and telehealth encounters [3]. Maternal-fetal monitoring in these patients includes a nutrition consult, early screening for gestational diabetes in those being treated with steroids, cervical length screening (ultrasound at 18–22 weeks with obstetrics follow-up if length <25 mm), fetal growth surveillance every month (starting at 24 weeks), and third-trimester antepartum fetal surveillance (routine nonstress test and biophysical profile) [3].

Disease assessment with either imaging or endoscopy should only be undertaken in pregnancy when anticipated results may change patient management. Imaging modalities include X-ray, ultrasound, CT scan, and MRI. Diagnostic accuracy is comparable for both MRI and CT scans. If imaging study is needed, ultrasound and MRI without gadolinium (lack of safety data) are considered safe modalities, especially during the first trimester, while radiation exposure with X-ray and CT scans may be problematic and should be avoided whenever possible. Regarding endoscopic evaluation, unsedated flexible sigmoidoscopy is preferable and safe to perform during all trimesters but best avoided if possible in the first and third trimesters. If colonoscopy is necessary, it should be performed under obstetric anesthesiology monitoring [11]. When procedural sedation is needed, propofol is considered safe; however, benzodiazepines should be avoided. Patients should be placed in the left lateral decubitus position to avoid aorto-caval compression, and fetal monitoring should occur before, during, and after endoscopy.

## *Medications*

The goal of IBD therapy during pregnancy is to maintain remission in order to improve maternal-fetal outcomes. Table 8.1 provides a summary for specific dosing recommendations and safety of IBD drugs during pregnancy and lactation using the LactMed database and the new US Food and Drug Administration's (FDA) Pregnancy and Lactation Labeling Rules, keeping in mind that pregnancy categories (i.e., A, B, C, D, X) are no longer used [44, 45]. One should remember that the long-term effects of the newer medications on the offspring of women treated during pregnancy are lacking, and some recommendations regarding the newer therapies are based on limited data.

Medications that are typically safe to continue during pregnancy are aminosalicylates, thiopurines, and biologic therapies. MTX should never be used, and tofacitinib should be avoided if possible. Mesalamines are considered safe during pregnancy. Animal models have raised concern over mesalamine teratogenicity with phthalate-containing compounds (e.g., coating of Asacol HD); however, human studies have not been able to demonstrate this [35]. In light of this, a switch to an alternative mesalamine of an equivalent dosage should be made. Mesalamines are overall safe and preferred over sulfasalazine, but if sulfasalazine is chosen, then 2 mg of folic acid should be supplemented.

Glucocorticoids are often necessary for the treatment of active disease states; however, maintenance use should be avoided in all IBD patients, particularly during

**Table 8.1** Pregnancy and lactation safety of commonly used drugs in IBD [3, 11, 44, 45]

| Drug class | Pregnancy safety | Preconception recommendation | Conception recommendation | Breast milk transfer | Breastfeeding safety |
|---|---|---|---|---|---|
| *Aminosalicylates* | Low risk | Switch Asacol HD to alternate mesalamine due to the presence of DBP (teratogenic in animals) in its enteric coating.<br>If using sulfasalazine, add 2 mg per day of folic acid supplementation (mesalamine formulations are preferred) | Same as preconception recommendations | Poor excretion into breast milk (metabolites do appear in breast milk) | Acceptable (monitor breastfed infant for diarrhea) |
| *Budesonide* | Low risk | Short course for flare | Short course for flare | Detected in small concentration | Acceptable |
| *Prednisone* | Moderate risk (increased risk of gestational diabetes, PROM, preterm birth, and congenital defect) | Short course for flare | Short course for flare | Dose-dependent levels detected in breast milk (for high-dose therapy, prednisolone is preferred) | Acceptable (delay breastfeeding 1–2 hours after a dose) |
| *Thiopurines* | Low risk (monotherapy is preferred if possible) | Monotherapy is preferred (increased infection risk with dual therapy) | Monotherapy preferred (increased risk with dual therapy)<br>Avoid introduction during pregnancy, given the delayed onset of action and the risk of pancreatitis | Detected in small concentration | Acceptable (delay breastfeeding 4 hours after a dose) |
| *Methotrexate* | Contraindicated (teratogenic and abortifacient) | Avoid 3–6 months prior to conception | Contraindicated | Detected in small concentration | Contraindicated |

| | | | | | |
|---|---|---|---|---|---|
| *Cyclosporine* | Limited data (risk of preeclampsia, maternal hypertension, gestational diabetes, preterm birth, and LBW) | Standard dose when used for salvage therapy | Standard dose when used for salvage therapy | Detected with variable levels | Acceptable (monitor infant levels) |
| *Infliximab* | Low risk (monotherapy) | Standard dose | Last dose 6–10 weeks before EDD or 4–5 weeks if monthly dosing (resume 48 hours postpartum) | Detected in small concentration | Acceptable |
| *Adalimumab* | Low risk (monotherapy) | Standard dose | Last dose 2–3 weeks before EDD or 1–2 weeks if weekly dosing (resume 48 hours postpartum) | Detected in small concentration | Acceptable |
| *Certolizumab pegol* | Very low risk (monotherapy; not actively transported through the placenta) | Standard dose | No need to change the dosing schedule<br>No placental transfer | Detected in small concentrations in some women | Safe (absorption from infant GI tract unlikely) |
| *Golimumab* | Low risk (monotherapy) | Standard dose | Time last dose 4–6 weeks before EDD (resume 48 hours postpartum) | Detected in small concentration | Acceptable |
| *Natalizumab* | Low risk | Standard dose | Time last infusion 4–6 weeks prior to EDD (resume 48 hours postpartum) | Detected in small concentration | Acceptable |
| *Vedolizumab* | Low risk | Standard dose | Time last dose 6–10 weeks prior to EDD or 4–5 weeks if monthly dosing (resume 48 hours postpartum) | Detected in small concentration | Acceptable |

(continued)

**Table 8.1** (continued)

| Drug class | Pregnancy safety | Preconception recommendation | Conception recommendation | Breast milk transfer | Breastfeeding safety |
|---|---|---|---|---|---|
| *Ustekinumab* | Limited data (probably low risk) | Standard dose | Time last dose 6–10 weeks prior to EDD or 4–5 weeks if monthly dosing (resume 48 hours postpartum) | Detected in small concentration | Acceptable |
| *Tofacitinib* | Limited data | Discontinue at least 1 week prior to conception | Avoid if possible (especially during first trimester) | Unknown | Unknown |
| *Amoxicillin/ clavulanic acid* | Low risk | Standard dose | Preferred over other antibiotics during pregnancy<br>Avoid as maintenance therapy | Detected in breast milk | Acceptable |
| *Ciprofloxacin* | Low risk (arthropathy in animals) | Standard dose | Avoid as maintenance therapy | Detected in small concentration (short course likely safe) | Acceptable (delay breastfeeding 3–4 hours after dose; monitor infant for diarrhea and/or candidiasis) |
| *Metronidazole* | Low risk (risk of cleft lip) | Standard dose | Short courses. Avoid in the first trimester if possible. Avoid as maintenance therapy | Detected in breast milk (mutagenic) | Contraindicated |
| *Rifaximin* | Limited data (teratogenic in animal studies) | Avoid if possible | Avoid if possible (malformation in animal models) | Poorly absorbed orally and unlikely to reach breast milk | Unknown (alternative agent is preferred) |

**EDD* estimated date of delivery

pregnancy due to higher rates of adverse maternal-fetal outcomes. These adverse outcomes may include preterm delivery, higher cesarean section rates, LWB, and an increased risk of gestational diabetes [46].

Evidence for the safety of thiopurines during pregnancy is somewhat confusing. Although robust data are lacking regarding their risk during pregnancy, routine discontinuation is not recommended [47]. Thiopurines disrupt DNA replication and block the purine synthesis pathway, which is teratogenic to animals when given intravenously and intraperitoneal [48]. Some studies have demonstrated that thiopurine use during pregnancy for active disease or maintenance therapy may carry a higher risk of preterm birth and an increased risk of congenital malformations like atrial/ventricular septal defect and intrauterine growth restriction (IUGR) [49, 50]. However, more reliable data to date support their safety with no increased risk in maternal-fetal complications [51, 52, 53]. Since having active disease in pregnancy leads to poorer outcomes, the risks of stopping thiopurine treatment may be much higher compared to the possible adverse effects. Therefore, it is reasonable to continue the maintenance monotherapy. The overall safety of thiopurines is possibly attributable to the human placenta acting as a barrier to 6-MP and AZA and their metabolites [54]. During pregnancy, there is a shift in the metabolism of thiopurines resulting in lower concentrations of 6-thioguanine (6-TGN) level and higher levels of 6-methylmercaptopurine (6-MMP); however, toxicity does not result from this shift, and the postpartum levels revert to baseline [55]. Therapy with thiopurines should not be started during pregnancy to treat active disease because of the slow onset of action, risk of pancreatitis, and bone marrow suppression.

MTX, as discussed earlier, is contraindicated in pregnancy due to its teratogenic effects. It can lead to MTX embryopathy or fetal MTX syndrome, a combination of craniofacial defects, congenital limb anomalies, and developmental delays [12, 56].

There is limited data on the use of T-cell inhibitors like cyclosporine and tacrolimus in pregnant IBD patients, with most data derived from transplant patients. Cyclosporine may be needed as salvage therapy in severe acute steroid-refractory ulcerative colitis to avoid colectomy [57]. In comparison, cyclosporine use may not increase the risk of congenital malformation [58], but there may be an association with an increased prematurity rate. However, it is unknown if this is an effect of this medication or the woman's underlying condition [59]. Other reported adverse maternal-fetal outcomes include preeclampsia, maternal hypertension, gestational diabetes, preterm birth, and LBW; however, it has been safely used in the treatment of fulminant, steroid-refractory UC [60, 61]. Tacrolimus carries a lower risk of maternal hypertension but a higher incidence of neonatal hyperglycemia, hyperkalemia, renal injury, and approximately 4% rate of congenital malformations [62, 63, 64]. Placental transfer of calcineurin inhibitors to the fetus does occur, with levels in a newborn detected days after birth [65].

Despite the risk of placental transfer of IFX and ADA to the infant, anti-TNF therapy is considered safe and does not lead to adverse maternal-fetal outcomes. During pregnancy, IFX levels increase, while ADA levels remain stable after accounting for changes in albumin, body mass index (BMI), and CRP [66]. CZP is a pegylated anti-TNF agent that does not cross the placenta. Dosing and timing of

biologics should be adjusted, so that drug trough levels occur at the time of delivery without interruption of therapy if possible. Biologic therapy in utero does not confer an increased risk of severe infections in the short or long term [67]. Monotherapy is typically preferred due to a threefold increased risk of infections to infants on combination therapy with thiopurines [52, 68]. When using dual therapy before pregnancy with immunomodulators, the decision to switch to monotherapy rests upon disease severity and should be decided case by case.

Integrin inhibitors (NTZ and VDZ) should overall be continued during pregnancy. There is limited data regarding the use of NTZ, an IgG4 anti-integrin, during pregnancy in IBD patients. NTZ safety profile from multiple sclerosis (MS) data supports continuation during pregnancy, with no worrisome adverse events in newborns except for anemia [69, 70]. Given the risk of IBD relapse when stopping the therapy and its associated detrimental effect on maternal-fetal outcomes, it is recommended to continue NTZ during pregnancy. This approach is supported by favorable results in MS literature and the PIANO registry for Crohn's disease pregnancy outcomes while on NTZ [71, 72, 52]. VDZ is a gut-selective a4b7 integrin inhibitor with much better safety data. Animal models have not demonstrated teratogenicity secondary to VDZ [73]. Trial data and post-marketing surveillance reports for VDZ were limited by sample size and follow-up; however, no safety concerns for pregnancy outcomes were identified from VDZ exposure [74]. In a case-control observational, multicenter study of 186 pregnancies in 164 women, no new safety signal was detected when VDZ was used during pregnancy [75]. Patients treated with VDZ have live birth and miscarriage rates similar to the non-IBD population. At the same time, infants reach typical developmental milestones with no significant infection rates and have only a slightly higher rate of congenital anomaly unrelated to VDZ use [76].

There is insufficient safety data for UST in pregnancy, with one case series demonstrating similar rates of live birth compared to the general population [77, 78]. Animal studies have not shown teratogenicity, and human data from dermatology literature have not implicated any fertility issues or congenital malformations [79, 80]. Based on the available data, it is recommended that UST should be continued during pregnancy, given the deleterious effects of a flare off therapy.

Tofacitinib may cross the placental barrier and lead to teratogenicity, as demonstrated in animal models at supratherapeutic doses [81]. Although data in human pregnancy are limited, maternal-fetal outcomes appear to mirror those of the general population [82]. Until more human data is available, tofacitinib should be avoided if possible, especially during the first trimester. Due to its short half-life, it has been recommended to discontinue tofacitinib for at least 1 week before conception to allow this drug to clear from the body. In patients who wish to continue this treatment due to their limited therapeutic options, providers should inform them regarding possible risks, benefits, and alternatives. Efforts should be made to avoid its use during the first trimester when possible because the organogenesis of the developing fetus occurs during this time.

Antibiotics are commonly being used in the treatment of abscesses, fistulizing CD, and pouchitis. Ciprofloxacin, metronidazole, amoxicillin/clavulanate, or

rifaximin is commonly used in managing these patients. Ciprofloxacin in high doses has been associated with bone and cartilage damage in animals and infrequently in humans; however, therapeutic doses are unlikely to pose a teratogenic risk [83, 84]. Metronidazole is carcinogenic in animals, but this has not been demonstrated in humans [85, 86]. Short-term use of metronidazole is probably safe during pregnancy due to the absence of reported significant teratogenicity in pregnant women [87, 88]. Amoxicillin/clavulanate can be used during pregnancy and is the preferred antibiotic as it does not lead to an elevated risk of congenital abnormalities in infants [89]. Rifaximin lacks adequate data in pregnant women but has been associated with malformations in animal studies when administered to pregnant rats and rabbits at supratherapeutic doses [90].

### *Surgery*

Surgical intervention may be required in patients with severe acute refractory ulcerative colitis, bowel perforation, severe gastrointestinal hemorrhage, abscess, or bowel obstruction. Increased parity has an inverse relationship with surgical interventions and clinical activity [34]. If surgery becomes necessary in patients with fulminant UC, a subtotal colectomy and Brooke ileostomy can be safely performed with low maternal-fetal morbidity and mortality [91]. Rarely, iatrogenic uterine manipulation may lead to spontaneous abortions or preterm labor. This type of surgical care is best accomplished by an experienced surgeon with a multidisciplinary team-based approach. Unless urgent, the ideal time to perform surgery is postpartum or second trimester if surgery cannot wait until delivery.

## Delivery and Postpartum Care

### *Mode of Delivery*

Most IBD patients can proceed with vaginal delivery unless there is a specific obstetric indication for cesarean delivery. If perianal disease (abscess, rectovaginal or anorectal fistula, anal fissure, or stenosis) is present or there was prior rectovaginal fistula, then cesarean delivery is recommended [92, 93]. When the estimated date of delivery (EDD) approaches, serial perineal inspections should be performed. Obtaining GBS cultures around 35 weeks of pregnancy presents an opportunity to check for active perianal disease [3].

In patients with IPAA, there may be a temporary alteration in the pouch during the third trimester. While only a few cases may experience long-term problems, in most women, the functional status of the pouch returns to prepregnancy levels after pregnancy is over. The mode of delivery does not affect the outcome of the pouch function [94]. The risk of injury to the anal sphincter is higher with vaginal delivery

compared to cesarean section [95]. The decision to perform cesarean versus vaginal delivery in these patients should be made in a multidisciplinary team approach with a shared decision-making process to allow the patient's desire to be an integral part of the process and consider the potential risk of injury to the sphincter. All patients who undergo cesarean delivery should be on both mechanical (early ambulation and sequential compression devices) and pharmacologic (low molecular weight heparin) VTE prophylaxis, while mechanical alone is appropriate in patients after vaginal delivery [96]. The postpartum period carries the highest risk of VTE in pregnant patients, and extended thromboprophylaxis should be considered up to 3–6 weeks after birth [97, 3].

## *Breastfeeding*

Breastfeeding is generally recommended to all mothers, with few exceptions. Recommendations from the American Academy of Pediatrics should be followed, including exclusive breastfeeding for 6 months, which may be continued as complementary foods are added to the infant's diet [98]. Key exceptions on this list include women who are being treated with MTX, tofacitinib, rifaximin, and metronidazole with the former three options lacking robust pregnancy data and the latter being a potential mutagen with significant break milk concentration [45].

Along with standards for infant feeding, mothers should maintain optimal nutritional status by increasing daily caloric intake to 2300 to 2500 kilocalories (kcal) per day, which is 450 to 500 kcal above the average recommendation for nonpregnant women [99]. Breastfeeding mothers should eat a healthy, well-balanced diet. Omega-3 fatty acids, essential nutrients for infant development, should be supplemented by adding at least 200 mg per day because breast milk levels are dependent on maternal blood levels [100]. Nutritional consultation should be provided during this period for women who have an active flare or an ostomy to optimize nutritional status. Herbal galactagogue, particularly fenugreek, should be avoided in IBD patients due to the risk of bleeding and diarrhea [101]. Although many IBD medications can be detectable in breast milk, the overall safety profile is acceptable for most of them, given the low concentrations of less than 1% of maternal serum concentrations in breast milk. Specific considerations for lactation safety of commonly used IBD drugs according to the US National Library of Medicine LactMed database are detailed in Table 8.1.

## *Infant Monitoring*

Although the lack of significant congenital malformations is reassuring, pediatricians should be informed about biologics in utero when applicable. Fetal Fc receptor actively uptakes maternal IgG across the placenta as early as week 13 [102]. This

uptake rapidly increases during the third trimester and until delivery. The most efficiently transported subclass of immunoglobulin is IgG1, including IFX, ADA, GOL, VDZ, and UST, followed by IgG4, which includes NTZ [103]. Due to this active transportation, the drug level of medications such as IFX and ADA increases up to fourfold in the infant at birth compared to maternal levels and remains detectable for up to a year [68, 104]. This placental transfer does not occur with CZP, as this medication lacks the Fc portion. Because of detectable levels up to a year, infants who are exposed to biologics in utero, except for CZP, should not receive live vaccines for a minimum of 9 months or after drug level becomes undetectable in the infant. There are no contraindications to other recommended non-live vaccines for the newborns.

## Summary

The advent of new therapies has led to an exciting time in the management of women with IBD who wish to get pregnant and have a normal pregnancy course and a healthy baby. A favorable maternal-fetal outcome is achievable in most patients, but this can only be accomplished by addressing the misconceptions and misinformation among healthcare providers and patients. This goal can be reached by providing evidence-based data, emphasizing the importance of maintaining healthy nutrition, and having the disease in remission during preconception, conception, and postpartum phases. We hope this chapter offers guidance for healthcare providers to confidently formulate a successful standardized plan to achieve optimal pregnancy results using a multidisciplinary team-based approach.

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