Fertility, pregnancy, and nursing in inflammatory bowel disease

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INTRODUCTION

Inflammatory bowel disease (IBD) can affect patients in their childbearing years and therefore has implications on fertility, pregnancy, and nursing.

This topic will review issues related to fertility in patients with IBD and the diagnosis and management of IBD in pregnant and nursing patients. The medical management of IBD in the general population is discussed in detail separately:

- (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis".)
- (See "Management of moderate to severe ulcerative colitis in adults".)
- (See "Management of the hospitalized adult patient with severe ulcerative colitis".)
- (See "Overview of the medical management of mild (low risk) Crohn disease in adults".)
- (See "Medical management of moderate to severe Crohn disease in adults".)

Our approach is consistent with a multidisciplinary guide to preconception counseling and caring for pregnant patients with IBD [1].

FERTILITY

Patients with quiescent IBD do not have decreased fertility as compared with the age-matched general population [2-6]. Low birth rates among patients with IBD are often due to patient choice rather than disease-related infertility [2,5]. (See "Overview of infertility".)

However, IBD can cause infertility in the following circumstances:

- Active inflammation in patients with Crohn disease may result in infertility due to inflammation involving the fallopian tubes and ovaries [6]. Perianal disease can also cause dyspareunia. (See "Female infertility: Causes", section on 'Fallopian tube abnormalities/pelvic adhesions'.)

- Medications may decrease fertility in male patients. As examples, methotrexate and sulfasalazine can cause reversible oligospermia. In addition, sulfasalazine is associated with reduced sperm motility and abnormal sperm morphology [7-10].

  However, studies suggest that anti-tumor necrosis factor (anti-TNF) therapy does not impair sperm quality [11].

- Surgery may impact fertility in patients with IBD. Proctocolectomy in males may lead to impotence or ejaculatory difficulties [12]. Restorative proctocolectomy with ileoanal anastomosis has been associated with dyspareunia and a reduction in fertility due to scarring and formation of adnexal adhesions [3,13,14]. (See "Surgical management of Crohn disease", section on 'Surgical approaches' and "Surgical management of ulcerative colitis", section on 'Surgical options'.)

  Female IBD patients with infertility may seek assisted reproductive technology (ART) treatment. A cohort study based on Danish health registries evaluated the chance of live birth in patients with IBD who underwent ART treatments [15]. Patients with ulcerative colitis had lower rates of successful pregnancy compared with patients without IBD (odds ratio [OR] 0.73, 95% CI 0.58-0.92). Patients who had surgery for Crohn disease were also less likely to have live birth following ART (adjusted OR 0.51, 95% CI 0.29-0.91).

PRECONCEPTION COUNSELING

Preconception counseling offers an opportunity for the clinician to address specific patient concerns regarding the risk of transmission of IBD or other diseases to their offspring, to optimize control of disease activity and nutritional status, avoid inappropriate medication cessation, and discontinue medications that may adversely affect pregnancy. (See "The preconception office visit".)

IBD risk in offspring — Although IBD follows a non-Mendelian pattern of inheritance, genetically determined factors contribute to IBD susceptibility. First-degree relatives of patients with IBD are approximately 3 to 20 times more likely to develop IBD as compared with the general population [16-19]. In a large national, registry-based cohort study with a median follow-up of 10 years, the risk of developing IBD was increased in offspring born to mothers with ulcerative colitis (HR 4.6, 95% CI 3.5-6.2) and mothers with Crohn disease (HR 7.7, 95% CI 5.7-10.5) compared with mothers without IBD; the impact of paternal IBD was not evaluated [20].

Clinical features of the disease also demonstrate a heritable pattern with concordance in disease location (eg, ileal versus colonic Crohn disease) and type (eg, fibrostenotic Crohn disease, fistulas) [21-26]. Subsequent generations may demonstrate "genetic anticipation" with the development of earlier onset of IBD and more severe disease as compared with their parents [19,27].

The role of genetic factors that increase susceptibility to IBD and genetic syndromes associated with IBD is discussed in detail separately. (See "Genetic factors in inflammatory bowel disease".)

Disease control — Female patients with IBD should attempt conception at a time when the disease is in remission. Patients who have active disease at conception are more likely to have active disease during pregnancy [28]. Data have suggested that patients with ulcerative colitis are more likely to have disease activity during pregnancy than patients with Crohn disease [29]. This may reflect the cytokine production of the placenta and its impact on ulcerative colitis. Having active disease is associated with a significant increase in the rate of preterm birth [30]. The risk of disease activity in the untreated patient should be discussed alongside the potential risk of any medications used during pregnancy to maintain remission. (See "Preterm birth: Definitions of prematurity, epidemiology, and risk factors for infant mortality".)

Medications — Medications that may affect fertility or adversely affect pregnancy should be discontinued, when possible, for patients planning pregnancy. The risks and benefits of fetal drug exposure versus discontinuation of medications and its attendant risk of flare should be specifically discussed. These risks and benefits are discussed in detail below. (See 'Medications during pregnancy and lactation' below.)

- Nonimmunosuppressive agents – Sulfasalazine causes reversible oligospermia that resolves within discontinuation of therapy. Oligospermia is not associated with 5-aminosalicylic acid (5-ASA) medications (eg, mesalamine). Male patients on sulfasalazine should therefore be transitioned to 5-ASAs four months prior to conception (table 1) [31,32]. (See 'Sulfasalazine and 5-aminosalicylic acid' below.)

- Immunosuppressive agents – In female patients, methotrexate is contraindicated because it is an abortifacient and potent teratogen. Methotrexate is associated with oligospermia but has not been associated with adverse fetal outcomes related to paternal exposure [33-35]. Because of the risk of oligospermia, male patients should discontinue methotrexate and use contraception for at least four months prior to conception. (See "Safety of rheumatic disease medication use during pregnancy and lactation", section on 'Methotrexate' and 'Medications during pregnancy and lactation' below.)

  Data on paternal exposure to immunomodulators and/or biologic agents around the time of conception have suggested that such agents were not associated with increased risk of adverse birth outcomes [36-38]. In a database study including 7453 males with immune-mediated inflammatory diseases (eg, inflammatory bowel disease, psoriasis/psoriatic arthritis) whose partners had conceived, exposure to thiopurines (relative risk [RR], 1.12; 95% CI 0.66-1.76), methotrexate (RR, 0.67; 95% CI 0.21-1.55), anti-tumor necrosis factor (anti-TNF) agents (RR, 1.14; 95% CI 0.81-1.57), or non-TNF targeting biologic agents (eg, vedolizumab, ustekinumab) (RR, 1.75; 95% CI 0.80-3.24) was not associated with increased risk of major congenital anomalies, preterm birth or low birth weight [37]. In a prior meta-analysis, periconception exposure to thiopurines in male patients was not associated with congenital anomalies [36]. These findings lend support for the safety of these biologics and immunomodulators at the time of conception for male patients.

  We do not routinely recommend that male patients on thiopurines discontinue treatment unless the couple has a history of infertility or miscarriages that is otherwise unexplained. In such cases, if analysis of male factor infertility suggests abnormal semen quality, and no other factor is identified, a trial of thiopurine discontinuation can be considered. (See 'Azathioprine and mercaptopurine' below and "Causes of male infertility".)

  Data on the effect of thiopurines on female fertility are lacking.

  Cyclosporine does not appear to reduce male fertility or to have a demonstrable effect on sperm [39]. (See "Safety of rheumatic disease medication use during pregnancy and lactation", section on 'Cyclosporine' and 'Cyclosporine' below.)

Nutrition and supplements — Consultation with a nutritionist should be considered to offer advice on eating a well-balanced, healthy diet. We obtain nutrition consultation for patients with risk factors for reduced gestational weight gain such as those with active disease and surgical changes impacting absorption. [40]. Folic acid is important for neural tube development during pregnancy. Folate supplementation (2 mg daily) should be recommended in patients with IBD on low residue diets, with ileal involvement, and patients on medications that interfere with folic

acid metabolism (eg, sulfasalazine) [6,41]. (See "Preconception and prenatal folic acid supplementation".)

Patients with IBD are at risk for iron and vitamin B12 deficiency. Furthermore, iron requirements increase during pregnancy. Iron and B12 levels should therefore be checked in the first trimester and supplementation should be provided as needed. (See "Vitamin and mineral deficiencies in inflammatory bowel disease" and "Nutrition in pregnancy: Dietary requirements and supplements".)

PREGNANCY AND LACTATION

Patients with IBD are at an increased risk for worse obstetric and medical outcomes compared with the age-matched general population [42-44].

Effect of pregnancy on IBD — For patients with quiescent IBD at conception, the course of IBD is approximately the same as in nonpregnant patients [45]. Patients with Crohn disease have a similar disease course during pregnancy and the postpartum as nonpregnant patients with IBD. However, for patients with ulcerative colitis, there is an increased risk of disease flare compared with a patient with Crohn disease. The reason for this is unclear and may be associated with smoking cessation, cytokines secreted by the placenta or undertreatment of ulcerative colitis patients prior to pregnancy [29].

Approximately one-third of patients with quiescent disease at conception relapse during the pregnancy, similar to the general IBD population [46]. Relapses are more common during the first trimester. However, remission achieved during pregnancy is likely to be sustained throughout the remainder of the pregnancy.

In contrast, approximately 70 percent of patients with active disease at conception are likely to have continued or worsening symptoms during pregnancy [47,48]. (See "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults", section on 'Acute complications'.)

The events occurring during one pregnancy do not correlate with the course in subsequent pregnancies [49]. However, pregnancy may be protective in the long term, as suggested by lower relapse rates up to ten years following pregnancy compared with rates prior to pregnancy [50,51]. As parity increases, the risk for surgery to treat IBD also decreases, though this may simply be because healthier patients are more likely to have multiple pregnancies [50].

Effect of IBD on pregnancy — Pregnant patients with IBD may be at increased risk for antepartum hemorrhage, low birth weight infants, and premature delivery [42,44,52-55].

However, the risk of congenital abnormalities does not appear to be increased [42,56,57].

The degree of disease activity may account, in part, for the poor pregnancy-related outcomes [56,58]. The risk of poor pregnancy outcomes in patients with IBD is greatest in those who have active disease at the time of conception, and in whom remission may be difficult to achieve during pregnancy [4,56,58-62]. As an example, in a Danish cohort study, the risk of preterm birth increased if the mother was hospitalized during pregnancy (odds ratio [OR] 1.4), and if the first hospitalization for ulcerative colitis occurred during pregnancy (OR 3.4) [56].

Patients with IBD should be followed as high-risk obstetric patients, particularly in the third trimester, and if the disease is active. (See "Overview of antepartum fetal assessment" and "Spontaneous preterm birth: Overview of risk factors and prognosis", section on 'Chronic medical disorders'.)

Effect of lactation on IBD — Breastfeeding does not independently affect the course of disease in IBD after adjusting for an increase in disease activity due to cessation of IBD medications. However, data suggest that over 50 percent of female patients with IBD do not breastfeed their children either because of a clinician recommendation, fear of medication interactions, or personal choice [63]. It is therefore important to discuss the benefits of breastfeeding as well as the compatibility of several anti-inflammatory and immunosuppressive medications with breastfeeding as discussed below. (See "Infant benefits of breastfeeding" and 'Medications during pregnancy and lactation' below and "Breastfeeding: Parental education and support".)

EVALUATING DISEASE ACTIVITY DURING PREGNANCY AND LACTATION

Laboratory studies — Fecal calprotectin is a stool marker of intestinal inflammation that can be measured in pregnant patients to assess disease activity [64-68]. In a cohort study including 85 pregnant patients with IBD, a fecal calprotectin level ≥250 mcg/g during the second trimester was associated with higher rates of low birth weight (35 versus 4 percent) [67]. (See "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults", section on 'Stool studies'.)

Endoscopy and imaging studies — Endoscopy or imaging studies may be indicated during pregnancy for the diagnosis of suspected IBD or for the assessment of disease severity, or diagnosis and management of complications in patients with established IBD. However, it is important to consider the risks, benefits, and optimal timing of such a diagnostic evaluation in pregnant or nursing patients. (See "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults", section on 'Diagnosis' and "Clinical manifestations, diagnosis, and

prognosis of Crohn disease in adults", section on 'Diagnostic evaluation' and "Management of the hospitalized adult patient with severe ulcerative colitis", section on 'Pretreatment evaluation'.)

The safety and efficacy of endoscopic procedures during pregnancy have not been extensively studied. Endoscopy should be performed during pregnancy only if there is a strong indication (eg, significant bleeding) or if the information is critical for making treatment decisions (eg, establish the diagnosis of IBD in a pregnant patient with chronic diarrhea or stage disease if new therapies are needed). Flexible sigmoidoscopy, which can be performed without sedation or colonic preparation, is low risk in pregnancy in any trimester [69]. While there are several reports of colonoscopies being performed during pregnancy without complications, experience is relatively limited compared with sigmoidoscopy [69,70]. Obstetrical staff should be closely involved and the degree of maternal and fetal monitoring should be individualized. Recommendations for procedural sedation for endoscopy in pregnant and nursing patients are discussed in detail separately. (See "Gastrointestinal endoscopy in adults: Procedural sedation administered by endoscopists", section on 'Special populations'.)

Radiographic studies involving ionizing radiation (eg, computed tomography enterography, abdominal radiographs, small bowel follow-through) should be avoided in pregnancy if possible. These studies can be performed if they are necessary for maternal management and if there is no alternative imaging modality available. Several techniques can be used to minimize fetal radiation exposure. Magnetic resonance (MR) enterography is the preferred diagnostic modality in the absence of institutional expertise with ultrasound for IBD because it avoids the ionizing radiation of computed tomography. While MR enterography can be done in any trimester, intravenous gadolinium crosses the placenta [71]. The theoretical risk to the patient needs to be weighed against the additional imaging benefit of using gadolinium. However, oral contrast is routinely used. (See "Diagnostic imaging in pregnant and lactating patients".)

MEDICATIONS DURING PREGNANCY AND LACTATION

The choice of anti-inflammatory and immunosuppressive use during pregnancy and lactation should be based upon their relative safety and indications as well as the risk of relapse of IBD if the medications are discontinued.

Active IBD itself is associated with poor pregnancy outcomes, and therefore the risks associated with discontinuing some medications (eg, azathioprine, anti-tumor necrosis factor [anti-TNF] agents) are higher than the known risks of the medications themselves. (See "Safety of rheumatic disease medication use during pregnancy and lactation".)

The recommendations on lactation are consistent with the Drugs and Lactation Database of the US National Library of Medicine (LactMed) unless noted otherwise. LactMed is a free, online resource for information on maternal and infant levels of drugs, possible effects on breastfed infants and on lactation.

Antibiotics — Antibiotics, metronidazole and ciprofloxacin, are frequently used in the management of patients with inflammatory bowel disease. (See "Overview of the medical management of mild (low risk) Crohn disease in adults", section on 'Antibiotics' and "Medical management of moderate to severe Crohn disease in adults", section on 'The acutely ill patient with Crohn disease'.)

The use of metronidazole should be limited to short courses. A number of studies have suggested that metronidazole is not associated with an increased risk of congenital anomaly or cancer [72,73]. However, long-term use in pregnancy remains controversial because it is carcinogenic in rodents and mutagenic in bacteria [74,75]. In a study of 922 patients exposed to metronidazole in pregnancy, there was no association with congenital anomalies, preterm birth, or low birth weight [76].

Metronidazole is excreted into breast milk and is a possible mutagen. Breastfeeding should be avoided for 12 to 24 hours after a single oral dose. [77]. Ciprofloxacin is not recommended in pregnant patients and in children under age 18 as it affects growing cartilage and can cause arthropathy. However, among 200 pregnancies exposed to fluoroquinolones (including ciprofloxacin), the incidence of adverse events were similar to controls [78].

Ciprofloxacin is excreted into breast milk, but short courses of ciprofloxacin are probably safe during breastfeeding due to the low concentration in breast milk [77].

Amoxicillin-clavulanic acid has a favorable safety profile and is considered acceptable for use during pregnancy and lactation [79]. Rifaximin has no published safety data in human pregnancy or lactation. Per their label, animal studies have revealed evidence of teratogenicity at doses about 0.9 to 5 times (rats) and 0.7 to 33 times (rabbits) the recommended human doses of 600 to 1650 mg per day [80]. It should be avoided in pregnancy. There are no published pregnancy safety data for probiotics in IBD. However, there are several large ongoing trials regarding the use of specific probiotics in all pregnancies to improve outcomes including preterm birth and infant infections and allergies [81].

Sulfasalazine and 5-aminosalicylic acid — Sulfasalazine and 5-aminosalicylic acid (5-ASA) drugs can be used during pregnancy and lactation.

The incidence of decreased birth weight, prematurity, spontaneous abortion, stillbirths, or congenital anomaly is similar in children born to mothers taking sulfasalazine compared with the general population [82]. Sulfasalazine and its sulfapyridine metabolite can be found in umbilical cord blood at similar concentrations to maternal blood. However, these concentrations do **not** cause significant displacement of bilirubin from albumin [83,84]. As a result, sulfasalazine does not have to be discontinued during pregnancy.

Folate supplementation (2 mg daily) should be recommended in patients on sulfasalazine as it interferes with folic acid metabolism [6]. (See 'Nutrition and supplements' above.)

Studies suggest that 5-ASA agents by themselves are safe during pregnancy [85-88]. Enteric coating of mesalamine with dibutyl phthalate (DBP) has been associated with skeletal malformations and adverse effects on the male reproductive system in fetal animal models exposed to high doses of DBP [89]. However, at this time there is no commercial preparation with DBP in the coating (table 1). (See "Sulfasalazine and 5-aminosalicylates in the treatment of inflammatory bowel disease" and "Occupational and environmental risks to reproduction in females: Specific exposures and impact", section on 'Bisphenol A and other phenols'.)

Sulfasalazine and 5-ASAs are excreted in breast milk in low concentrations. Infants whose mothers are on sulfasalazine and 5-ASAs should be monitored for the development of diarrhea, a rare complication of breastfeeding [77,90,91].

Glucocorticoids — Glucocorticoids are considered low risk in pregnancy and should be administered for the same indications as a nonpregnant patient with IBD. The lowest possible dose of systemic glucocorticoids should be used and they should not be considered an alternative to standard maintenance therapy. (See "Safety of rheumatic disease medication use during pregnancy and lactation", section on 'Glucocorticoids' and "Spontaneous preterm birth: Overview of risk factors and prognosis".)

Although older studies have demonstrated a threefold increase in the risk of cleft palate after maternal exposure to glucocorticoids, the absolute risk is low (0.2 to 0.4 percent) [92] and multiple other studies have not confirmed that risk [93]. In addition, as palatal closure is usually complete by the 12th week of pregnancy, the risk is limited to administration during the first trimester. (See "Etiology, prenatal diagnosis, obstetric management, and recurrence of cleft lip and/or palate".)

Fetal adrenal insufficiency and low birth weight have also been associated with glucocorticoids [94]. However, adrenal insufficiency of the fetus following maternal administration of glucocorticoids is rare as rapid maternal metabolism of prednisolone, binding to serum proteins, and conversion to inactive metabolites by placental 11 beta-hydroxysteroid

dehydrogenase results in relatively low fetal concentrations [95,96]. However, long-term administration of high doses of glucocorticoids (>20 mg) is associated with adrenal insufficiency and warrants close neonatal monitoring. (See "Overview of antepartum fetal assessment".)

Glucocorticoids have the potential for exacerbating pregnancy-induced hypertension, gestational diabetes, and preterm delivery from premature rupture of membranes [97]. Therefore, pregnant patients on glucocorticoids should be appropriately monitored for these complications [92,98]. (See "Gestational hypertension" and "Gestational diabetes mellitus: Glucose management and maternal prognosis" and "Gestational diabetes mellitus: Obstetric issues and management" and "Preterm prelabor rupture of membranes: Clinical manifestations and diagnosis".)

Although low levels of prednisone and its metabolite, prednisolone, can be measured in breast milk, these are unlikely to be clinically significant. In one study, following a dose of prednisolone 50 mg IV, an average of 0.025 percent was recovered from breast milk [99].

Azathioprine and mercaptopurine — Thiopurines, azathioprine and mercaptopurine, should be continued during pregnancy if they are monotherapy [100,101]. In a meta-analysis of 3045 patients with IBD, thiopurine exposure was associated with preterm birth (odds ratio [OR] 1.7, 95% CI 1.3-2.2), but not with congenital abnormalities or low birth weight [36]. In addition, discontinuing azathioprine and mercaptopurine is associated with a high rate of relapse and active IBD is itself associated with an increased risk of low birth weight [101-108].

Azathioprine and mercaptopurine are detectable in breast milk but studies have demonstrated that levels in breast milk are low and metabolites are undetectable in breastfed neonates [109,110]. Although data are limited, these studies suggest that breastfeeding is safe. Breastfeeding can be continued while on azathioprine and mercaptopurine after a detailed discussion of the risks and benefits of breastfeeding [6]. (See "Safety of rheumatic disease medication use during pregnancy and lactation", section on 'Azathioprine and 6-mercaptopurine'.)

Cyclosporine — Cyclosporine is effective at inducing remission in patients with severe steroid refractory ulcerative colitis during pregnancy [58]. When the administration of cyclosporine is necessary during pregnancy, the minimum dose should be used. (See "Management of the hospitalized adult patient with severe ulcerative colitis".)

In a meta-analysis, cyclosporine was not associated with an increase in risk of congenital malformations but was associated with increased rates of prematurity [111]. A higher incidence of small for gestational age infants has also been reported. However, it is unclear if fetal growth restriction and prematurity were due to cyclosporine or due to the mother's underlying disease.

Cyclosporine is excreted in breast milk, and therapeutic levels have been reported in breastfed infants [112,113]. However, as the amount of transfer is minimal, cyclosporine can be used in the breastfeeding mother and infant levels of drug can be monitored if concern for toxicity. (See "Safety of rheumatic disease medication use during pregnancy and lactation", section on 'Cyclosporine'.)

Methotrexate — Methotrexate is contraindicated in pregnancy as it is a potent abortifacient, and its use during pregnancy is associated with multiple skeletal abnormalities. Female patients who plan to conceive should, therefore, discontinue methotrexate and use contraception for at least three months, and ideally six months, prior to conception.

The rate of congenital malformations due to maternal methotrexate use is estimated to be 9 to 17 percent [114,115]. The risk of methotrexate-induced developmental toxicity is highest at 8 to 10 weeks of gestation and with doses ≥10 mg per week.

Breastfeeding is contraindicated in patients on methotrexate as it is excreted into breast milk and can accumulate in neonatal tissues [6,116]. (See "Safety of rheumatic disease medication use during pregnancy and lactation", section on 'Methotrexate'.)

Anti-tumor necrosis factor agents — Experience with anti-TNF agents used to treat IBD during pregnancy is reassuring [117-122]. The Toronto Consensus on Management of IBD in pregnancy recommended that pregnant patients on anti-TNF monotherapy for maintenance should continue therapy throughout pregnancy [123]. Switching from a combination of a biologic plus thiopurine therapy to anti-TNF monotherapy may be considered in very select low-risk patients. Low-risk patients are those in sustained remission prior to pregnancy (ie, symptomatic, glucocorticoid-free remission with endoscopic healing for at least three months duration) and no history of multiple medication failures, significant perianal disease, or multiple surgeries.

Data have consistently suggested that the use of anti-TNF agents throughout pregnancy may lower the risk of a disease flare [122,124]. In a population-based study including 5293 pregnancies exposed to anti-TNF agents from conception, use of anti-TNF therapy beyond 24 weeks was associated with lower risk of a maternal IBD flare compared with stopping anti-TNF therapy, after adjusting for factors such as IBD type and glucocorticoid use (35.8 versus 39 percent; adjusted risk ratio [aRR] 0.93, 95% CI 0.86-0.99) [122]. In addition, continuing anti-TNF agents beyond 24 weeks was not associated with increased risk of adverse pregnancy outcomes (ie, stillbirth, low birth weight, preterm birth).

The use of anti-TNF agents (alone or in combination with thiopurines) during pregnancy does not appear to increase the risk of severe infection for the child [119,122]. In a study with mean

follow-up of four years that included 841 children born to mothers with IBD, the rate of severe infection was similar in children exposed to anti-TNF agents in utero compared with unexposed children (1.6 versus 2.8 percent per person-year; HR 1.2, 95% CI 0.8-1.8) [119].

Use of anti-TNF therapy during pregnancy has not been associated with an increased risk of adverse pregnancy outcomes, and continuing anti-TNF therapy beyond 24 weeks may lower the risk of preterm birth [122,125-129]. In a study including 5293 pregnancies exposed to anti-TNF agents from conception, use of anti-TNF therapy beyond 24 weeks was associated with lower risk of preterm birth compared with stopping anti-TNF therapy (7.6 versus 8.9 percent; aRR 0.82, 95% CI 0.68-0.99) [122]. In an analysis of data from a prospective cohort (Pregnancy in IBD and Neonatal Outcomes Registry [PIANO]) including 1490 pregnant patients (ie, 242 patients exposed to azathioprine, 642 patients exposed to biologics, 227 patients exposed to combination therapy, and 379 patients unexposed), use of biologic, thiopurine, or combination therapy was not associated with increased risk for congenital malformations, spontaneous abortion, preterm birth, low birth weight, or infections at one year [129]. Patients with ulcerative colitis tended to have higher rates of disease activity compared with patients with Crohn disease. (See "Safety of rheumatic disease medication use during pregnancy and lactation".)

Infliximab — Infliximab is compatible with use during conception in male and female patients and throughout pregnancy [118,123]. Rates of live births, miscarriages, and therapeutic terminations do not appear to be significantly different in patients exposed to infliximab during pregnancy compared with the general population [126,130-132].

Infliximab should be continued throughout pregnancy to avoid flares. Discontinuation of therapy can lead to increased disease activity and increased adverse outcomes to the child [122,124]. The dose should ideally be given so that the patient is due for the next dose soon after delivery. For example, if the dosing schedule is every eight weeks, the infliximab dose is timed to be given between weeks 30 to 34; alternatively, if the dosing schedule is every four weeks, the dose is timed to be given between weeks 35 to 37. Infliximab is considered compatible with breastfeeding as it is excreted in trace amounts in human milk and is poorly absorbed orally, thus reducing the potential for systemic adverse effects [6,133].

Infliximab crosses the placenta [134]. The exact timing is unclear, but in general, maternal antibodies are actively transported across the placenta by the neonatal Fc receptor (FcRn) beginning in the early to mid-second trimester, with the highest fetal concentration in the third trimester near term. High levels of infliximab have been detected in the cord blood of newborns [134,135], and this raises concern about an increased risk of infection and a suboptimal response to vaccinations in the newborn [136]. However, in a cohort study including 179

pregnant patients with IBD, infants born to mothers on biologic therapy did not have lower rates of adequate serologic response to *Haemophilus influenza B* (HiB) or tetanus toxin following vaccination compared with infants unexposed to biologic therapy (HiB group: 71 versus 50 percent, and tetanus toxoid group: 80 versus 75 percent) [137]. In addition, the median cord blood concentrations of infliximab were similar in infants with an adequate serologic response to the vaccines compared with infants without an adequate response.

Live vaccines should not be given to infants exposed to infliximab, adalimumab, golimumab, or natalizumab, as newborns may have detectable serum levels of drug for up to nine months [123,134,138]. All other vaccinations can be given on schedule. (See "Standard immunizations for children and adolescents: Overview", section on 'Routine schedule'.)

Adalimumab — Adalimumab is considered compatible with use during conception and throughout pregnancy [123]. In observational studies, the incidence of congenital malformations, spontaneous abortion, stillbirth, and preterm delivery was not increased in pregnant patients exposed to adalimumab [134,135,139]. Adalimumab actively crosses the placenta as well [134].

Limited evidence suggests that adalimumab is compatible with breastfeeding. While it can be detected in breast milk, levels are low and it has not been demonstrated to adversely affect the nursing infant [140].

Certolizumab — Certolizumab is a PEGylated Fab fragment of a humanized anti-TNF-alpha monoclonal antibody. Unlike other anti-TNF agents, which are actively transferred across the placenta in the third trimester, there is minimal placental transfer of certolizumab to the infant during pregnancy as it does not have an Fc component to bind to the FcRn on the placenta [134].

Certolizumab can therefore be used through conception and continued throughout pregnancy until delivery. Although there are limited data, certolizumab pegol may also be compatible with breastfeeding as it is minimally excreted into breast milk [118]. There is no need to adjust vaccine schedules in infants exposed to certolizumab in utero.

Other anti-TNF agents — We typically continue golimumab in patients with ulcerative colitis who are pregnant or breastfeeding. (See "Overview of dosing and monitoring of biologic agents and small molecules for treating ulcerative colitis in adults", section on 'Tumor necrosis factor inhibitors'.)

Other biologic agents

- Vedolizumab – We typically continue vedolizumab in pregnant patients to avoid disease flares. Limited data on vedolizumab use during pregnancy suggested that vedolizumab was not associated with an increased risk of miscarriage, stillbirth, or congenital anomalies [141,142]. In an observational, case-control study including 73 patients with IBD (79 pregnancies), miscarriage rates were not significantly different for patients given vedolizumab compared with patients given anti-TNF agents or a control group who were not exposed to biologics or immunomodulators (16 versus 13 and 10 percent, respectively) [141]. Stillbirth rates were not significantly different for patients treated with vedolizumab compared with anti-TNF agents or with an unexposed control group. In addition, data from 25 pregnancies in patients with IBD found no increase in congenital anomalies [142].

  For patients who are breastfeeding, we also continue vedolizumab therapy. Vedolizumab is detectable at very low levels in breastmilk, which is similar to other biologic therapies [143]. (See 'Anti-tumor necrosis factor agents' above.)

- Ustekinumab – There are limited safety data in Crohn disease, but safety registries in psoriasis report a 1.7 percent rate of fetal malformations, similar to what would be expected in the general population [144]. There are limited human data on lactation safety, but again, it is the author's practice to continue use during breastfeeding in the healthy term infant.

- Risankizumab – We typically continue risankizumab in pregnant patients to reduce the risk of a disease flare. Limited studies did not show an increased risk of adverse pregnancy outcomes or infant adverse effects with use of risankizumab during pregnancy or lactation [145].

- Natalizumab – There are limited safety data on the use of natalizumab during pregnancy and lactation. The risk of congenital malformations was not increased in 164 pregnancies in patients with Crohn disease or multiple sclerosis on natalizumab during the first trimester [146].

Small molecules

- Tofacitinib – There are limited data on use of tofacitinib, and we avoid its use, particularly in the first trimester, in pregnant patients and breastfeeding mothers given teratogenicity documented in animals.

- Upadacitinib – We avoid the use of upadacitinib in pregnant patients. Upadacitinib crosses the placenta in the first trimester, and animal data show teratogenicity at doses equal to and less than the daily human dose [147].

Antidiarrheal drugs — Antidiarrheal drugs should be avoided, especially early in pregnancy. Antidiarrheals should only be used for severe diarrhea that cannot be controlled with dietary manipulation and bulking agents (eg, kaolin/pectin, psyllium).

Diphenoxylate with atropine and loperamide are not teratogenic in animal studies but there are no controlled studies in humans. Case reports have reported fetal malformations in infants exposed to diphenoxylate with atropine during the first trimester, but it is unclear if this was causal [148,149].

Loperamide is compatible with nursing [77]. However, there are no data for diphenoxylate. Diphenoxylate-atropine should therefore be used only in short, infrequent courses, at low doses while breastfeeding an older infant.

Anticoagulants — Pregnancy and the puerperium, as well as a diagnosis of IBD, are well-established risk factors for deep vein thrombosis (DVT) and pulmonary embolism (PE), which are collectively referred to as venous thromboembolic disease (VTE). Patients should receive VTE prophylaxis during any hospitalization and after cesarean delivery [1]. Prevention of VTE and the use of anticoagulants in pregnant patients are discussed separately. (See "Venous thromboembolism in pregnancy: Prevention" and "Use of anticoagulants during pregnancy and postpartum".)

SURGERY

Complications associated with IBD that warrant surgery in a pregnant patient include acute refractory colitis, perforation, abscesses, severe hemorrhage, and obstruction [6]. There are limited data pertaining to the risk of surgery in pregnant patients with IBD [150,151]. Surgery has been associated with preterm labor and spontaneous abortions, possibly related to inadvertent uterine manipulation, but complications are rare [6,152,153]. When possible, medical treatment should be intensified prior to considering surgery [154]. (See "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults", section on 'Acute complications' and "Surgical management of Crohn disease".)

Nonurgent surgery that cannot wait until delivery is ideally performed in the second trimester. The timing of nonobstetric surgery for pregnant patients is discussed separately. (See "Nonobstetric surgery in pregnant patients: Patient counseling, surgical considerations, and obstetric management", section on 'Timing of surgery'.)

MODE OF DELIVERY

Patients with active perineal disease or rectal involvement with Crohn disease should undergo cesarean delivery in order to avoid perineal trauma from vaginal birth that can trigger or worsen existing perineal disease [123,155]. The mode of delivery in all other patients with inflammatory bowel disease should be dictated by obstetric necessity. In patients with an ileoanal anastomosis or J pouch, many advocate planned cesarean delivery as well, though data suggest no long-term worsening of pouch function [155].

Vaginal delivery can be attempted in patients with a colostomy, ileostomy, or continent ileostomy and has not been associated with an increased risk of ostomy complications [6,156]. (See "Ileostomy or colostomy care and complications".)

POSTPARTUM CARE

Some studies have reported an increased risk of postpartum flares [29,157,158]. Risk factors for disease flares may include hormonal fluctuations, discontinuing IBD medications during lactation, and resuming tobacco use [158]. For patients with a clear pregnancy plan who continue medications during lactation, follow-up should occur within six months following delivery or sooner if symptoms develop or worsen prior to the visit.

Normal physiologic changes and routine maternal care in the postpartum period are discussed separately. (See "Overview of the postpartum period: Normal physiology and routine maternal care".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Ulcerative colitis in adults" and "Society guideline links: Crohn disease in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5^{th} to 6^{th} grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10^{th} to 12^{th} grade reading

level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Inflammatory bowel disease and pregnancy (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Background** – IBD can affect patients in their childbearing years and therefore has implications for fertility, pregnancy, and nursing. (See 'Introduction' above.)

  Patients with quiescent IBD do not have decreased fertility compared with the general population. However, fertility in patients with IBD may be affected by active inflammation, medications, and prior surgery. (See 'Fertility' above.)

  During pregnancy, patients with ulcerative colitis have more disease activity than patients with Crohn disease. Pregnant patients with IBD are at an increased risk for worse obstetric and pregnancy-related outcomes compared with the general population, even with disease in remission. (See 'Pregnancy and lactation' above.)

- **Preconception counseling** – The course of IBD during pregnancy is determined in part by the activity of the disease at conception. Patients in remission at the time of conception are likely to remain in remission during pregnancy. In contrast, up to 70 percent of patients with active disease at conception are likely to have continued or worsening symptoms during pregnancy. (See 'Disease control' above.)

- **Diagnostic evaluation during pregnancy** – Endoscopy should be performed during pregnancy only if there is a strong indication or if the information is critical for making treatment decisions. An unsedated flexible sigmoidoscopy is considered low risk. Magnetic resonance enterography is the preferred diagnostic modality in pregnant patients with IBD in the absence of institutional expertise with ultrasound for IBD. (See 'Evaluating disease activity during pregnancy and lactation' above.)

- **Medication use** – The choice of anti-inflammatory and immunosuppressive medications during pregnancy and lactation should be based upon their relative safety and indications

as well as the risk of relapse of IBD if the medications are discontinued. (See 'Medications during pregnancy and lactation' above.)

- **Mode of delivery** – Patients with perineal disease or rectal involvement with Crohn disease should undergo a cesarean delivery. The mode of delivery in all other patients with IBD should be dictated by obstetric necessity. (See 'Mode of delivery' above.)

- **Surgery in pregnant patients** – Complications associated with IBD that warrant surgery in a pregnant patient include acute refractory colitis, perforation, abscesses, severe hemorrhage, and obstruction. Although data are limited, surgery is associated with premature labor or spontaneous abortion, possibly related to inadvertent uterine manipulation. (See 'Surgery' above.)

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GRAPHICS

Sulfasalazine and 5-aminosalicylic acid (5-ASA) formulations

Medication	Trade name (US or as noted)	Strength of commonly available oral preparations (mg)
Oral 5-aminosalycylic acid (5-ASA) derivatives		
Sulfasalazine		
Non enteric-coated tablet (scored)	Azulfidine, Sulfazine, Salazopyrin*	500
Suspension	Salazopyrin*	250 per 5 mL*
Enteric-coated tablet (not scored)	Azulfidine EC, Sulfazine EC, Salazopyrin EN-tabs*	500
Mesalamine[¶]		
Delayed release enteric-coated tablet	Asacol[Δ ◇], Asacol HD[◇]	400[Δ], 800
Capsule containing delayed release tablet	Delzicol	400
Delayed and extended release tablet, multimatrix	Lialda, Mezavant*	1200
Capsule containing delayed release enteric-coated granules	Apriso	375
Controlled release capsule	Pentasa[§]	250, 500, 1000*
Enteric-coated delayed release granules (packet, sachet)	Salofalk*, Pentasa Sachet*	500, 1000, 1500, 2000 sachet*
Olsalazine capsule	Dipentum	250, 500*
Balsalazide		
Capsule	Colazal, Colazide*	750
Tablet	Giazo[¥]	1100

US: United States.

* Not available in US. Trade names shown are for products commonly available elsewhere (eg, Canada, United Kingdom, and Europe).

¶ Mesalamine is US generic name. Mesalazine is an international generic name.

Δ Asacol 400 mg tablets are no longer marketed in US. Asacol 400 mg delayed-release tablets and generic versions are available widely elsewhere.

§ According to US prescribing information, Pentasa capsules can be swallowed whole or opened and contents sprinkled over spoonful of applesauce or yogurt and swallowed immediately; capsule contents should not be crushed or chewed.

¥ US approval is limited to treatment of ulcerative colitis in male patients; failed to demonstrate efficacy in female patients.

Data courtesy of authors with additional data from: Ordás I, Eckmann L, Talamini M, et al. Ulcerative colitis. Lancet 2012; 380:1606.

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