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AGA SECTION

Inflammatory Bowel Disease in Pregnancy Clinical Care Pathway: A Report From the American Gastroenterological Association IBD Parenthood Project Working Group

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In the United States, approximately 0.5% of the population, or 1.6 million people, have inflammatory bowel disease (IBD)—Crohn's disease (CD) and ulcerative colitis (UC).[1,2] Of those, roughly half are women, and most will carry the diagnosis during their reproductive years.[3] Caring for this complex population is a challenge for the multidisciplinary group of providers involved, compounded by misinformation and differences in priorities. There is fear surrounding the impact of IBD and its therapies on pregnancy and infant outcomes, as well as fear surrounding the impact of pregnancy on IBD and maternal health.[4–6] Oftentimes, the default is to stop all therapies through pregnancy and lactation, despite the significant risk of worsening disease activity, which is the greatest known risk to pregnancy outcome.[7] By looking at only one part of the puzzle, the greater picture of maternal and infant health is missed. The challenge of improving care to the woman with IBD is best met with the power of information, collaboration, and shared decision-making.

The goal of the IBD in Pregnancy Clinical Care Pathway is to provide guidance on the continuum of care and best practices for managing patients with IBD who are either pregnant or have a desire to become pregnant. The Pathway outlines the entire care process—from preconception counseling through the postpartum phase. The Pathway was developed by a multidisciplinary working group, encompassing the full spectrum of providers that a pregnant female with IBD may seek treatment from before, during, and after pregnancy. The working group included representatives from the fields of gastroenterology, maternal–fetal medicine (MFM), teratology, and lactation, as well as patient stakeholders, and is backed by a multisociety team. The Pathway provides a practical resource for clinicians and health systems to guide the treatment for these patients and ensure a consistent and high level of care. (Figure 1 outlines the scope of the IBD in Pregnancy Clinical Care Pathway.)

Care Coordination Team

Ideally, a pregnant patient with IBD is monitored by both a gastroenterologist specializing in IBD and an MFM specialist, with assistance from nutritionists, lactation counselors, and colorectal surgeons, as needed. However, due to variations in access, availability, and preference, patients may receive their IBD care from a general gastroenterologist, nurse practitioner, physician's assistant, surgeon, primary care provider, or even the emergency department. Similarly, obstetric care may be provided by an MFM, general obstetrician, midwife, family practitioner, or no one at all for much of the pregnancy.[8] Some patients are newly diagnosed with IBD during pregnancy and may be directed to a gastroenterologist after an emergency department visit, hospital admission, or visit with their primary care provider or obstetrician/gynecologist (OB/GYN).

We understand that many patients and providers do not have access to IBD experts and MFM specialists, particularly outside of urban centers. However, any gastroenterologist, OB/GYN, or specialized physician's assistant, nurse practitioner, or midwife can follow the Care Pathway to optimize outcomes in this population.

Role of the Maternal–Fetal Specialist in Managing Inflammatory Bowel Disease in Pregnancy

The risks of IBD to a pregnancy are significant and manifold, including miscarriage, delivery of a small-for-gestational-age infant, premature delivery, poor maternal weight gain, and complications of labor and delivery (eg, preeclampsia, placental abruption, increased probability of cesarean delivery).[9–14] Therefore, we recommend consultation with an MFM specialist, if available, for every pregnant patient with IBD. This is especially relevant to those with prior laparotomy, ostomy, ileal pouch-anal

Abbreviations used in this paper: **ART, assisted reproductive technology; CD, Crohn's disease; IBD, inflammatory bowel disease; IPAA, ileal pouch-anal anastomosis; MFM, maternal–fetal medicine; OB/GYN, obstetrician/gynecologist; UC, ulcerative colitis.**

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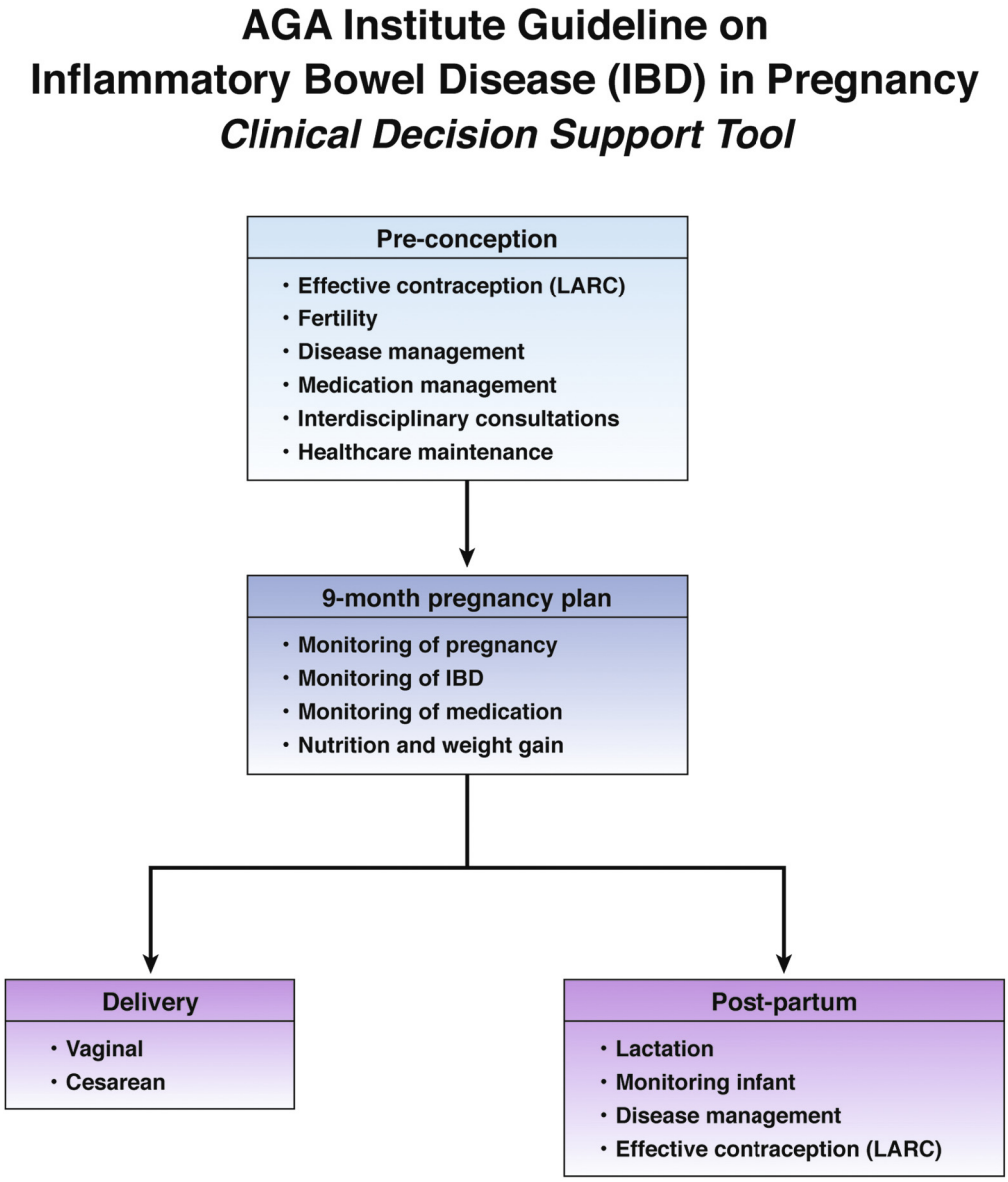


Figure 1. Overview of IBD in Pregnancy Clinical Care Pathway. LARC, long-acting, reversible contraception.

anastomosis (IPAA, or "J-pouch") surgery, and presentation suggesting the need for cesarean delivery, prior cesarean delivery, treatment with biologic or combination therapy, current active disease or recent hospitalization, perianal disease, or a history of adverse pregnancy outcomes.[15] The MFM specialist can determine the type of monitoring needed and the frequency of return visits. In most cases, it will be the general obstetrician who attends the delivery.

Role of the Gastroenterologist

The patient's gastroenterologist should coordinate her IBD care and see the patient once in the first or second trimester and thereafter during her pregnancy, as appropriate for her disease severity and pregnancy status. The gastroenterologist should also coordinate with the patient's obstetric provider who will lead the pregnancy-related care. Finally, the patient should be provided with a clear and easily understandable consensus plan for managing her disease during conception, pregnancy, and postpartum. As the patient may see multiple covering providers during her pregnancy, a clear plan can help empower her to obtain the very best care for herself and her child.

Roles of Additional Providers

Although not all patients will have access to specialty care, additional care providers during pregnancy and postpartum may include a nutritionist, particularly in patients with active disease, significant surgical changes, or inadequate maternal weight gain; a psychologist to provide support for the anxiety and depression that are increased in both IBD and pregnancy[16,17]; and a lactation specialist knowledgeable in IBD medications. When the infant is born, a pediatrician will need to be involved and should be aware

of potential complications the infant may experience, as well as vaccination and breastfeeding recommendations.

Family Planning and Preconception Counseling

Family planning for all women with IBD should include consultation with their gastroenterologist, OB/GYN, and, if appropriate, an MFM specialist and a colorectal surgeon. Three- to six-month remission before conception reduces the risk of a flare-up during pregnancy and in the postpartum period, making contraception an important part of the discussion.[18] In-person preconception care improves adherence to medications, enhances smoking-cessation efforts, reduces relapse during pregnancy, and lowers the risk of having a low-birth-weight infant.[19] Such care should focus on optimizing nutrition status, maintaining iron and folic acid supplementation, and achieving an ideal weight, if possible.

Contraception

The patient's OB/GYN should be actively engaged in decisions regarding contraception. The safest and most effective birth control option is long-acting, reversible contraception, which may include a hormonal or nonhormonal intrauterine device or a contraceptive implant. The authors prefer non–estrogen-containing contraception, given the increased risk of venous thromboembolism in IBD. However, low-dose estrogen oral contraceptive pills may be an option if the patient does not have a personal or family history of blood clots or other risk factors for thromboembolic events. Active small bowel inflammation, extensive resection, or rapid bowel transit may decrease oral contraceptive pill efficacy.[20]

Genetic Risk

Preconception counseling and evaluation are key components of the care of the woman with IBD who is of childbearing age (Figure 2).[19] The genetic risk of IBD is an important topic that will frequently arise during preconception counseling, and patients typically overestimate the risk of having a child affected by IBD. In European cohort studies, the genetic risk of CD is higher than that of UC. Incidence rate ratios represent the relative risk of IBD; however, absolute risk is an easier and more comprehensible concept to discuss with patients. The concordance rates in monozygotic twins range from 20%–56% for CD and from 6%–19% for UC.[21] With maternal CD, the incidence rate ratio for CD in offspring is 6.3, whereas the incidence rate ratio for UC in an offspring with maternal UC is 3.7. Having multiple family members affected by IBD will increase the risk, as will young age at diagnosis. The absolute risk of an offspring developing CD in the setting of maternal CD is 2.7%, whereas the risk of UC in the setting of maternal UC is 1.6%.[22] Based on 2 small studies, the risk of IBD has been suggested to exceed 30% when both parents have the disease.[23,24] These rates may be higher in cases of multiple affected family members and in certain ethnic groups. Studies suggest that the risk of IBD is 3-fold higher in non-Hispanic whites[25] and 2- to 4-fold higher in Ashkenazi Jews compared to non-Jewish ethnic groups, although the risk among non-European populations has not been well-characterized amid rising global incidence.[26] Numerous genetic associations with IBD have been identified, but the development of IBD is only rarely attributable to single genes, and there are no genetic tests available to predict whether one's offspring will develop IBD.

Fertility Concerns

Among women with CD and UC whose disease is in remission and who have never had surgery, fertility rates are equal to those in the general population. However, women who have had IPAA surgery, proctectomy, and permanent ostomies have decreased fertility due to inflammation and scarring of the fallopian tubes.[27–30] Laparoscopic rather than open IPAA surgery may improve fertility rates.[31,32] Women with active IBD may also have decreased fertility.[33] A review of fertility in IBD reported that 17% of women with IBD are voluntarily childless[5] compared to 6% of women in the general population.[34] The choice to remain childless appears to be largely due to incorrect information about pregnancy and IBD. Medical therapy for IBD, including all biologic therapies, steroids, thiopurines, methotrexate, and mesalamine, does not decrease fertility.[15,35–37]

Referral for assisted reproductive technology (ART) treatments should be individualized, depending on the patient's age, IBD type, and history of IBD surgery. Women with CD who are over the age of 30 years may have decreased ovarian reserve.[38,39] In general, IBD patients who have tried unsuccessfully to conceive for 6 months should be referred for infertility evaluation, particularly if they have had pelvic surgery.[40] IBD medications have no effect on egg freezing or ART efficacy; in the authors' experience, hormones used as part of ART have no adverse effect on IBD activity. ART in women with CD and UC is not as effective as in infertile women in the general population.[41–43] Similarly, among women with CD who have had CD surgery, ART is less effective than in women with CD who have never had surgery.[41] The decreased efficacy of ART is likely due to a lesser chance of achieving a chemical pregnancy (positive human chorionic gonadotropin 2 weeks after embryo transfer).[43] Once pregnant, women with CD and UC have equal chances of achieving a live birth compared to women in the general population who underwent ART.[43]

Health Care Maintenance

Women need to be up-to-date with their Papanicolaou smears, vaccines, and routine health care maintenance before pregnancy. Cessation of smoking, alcohol, opioids, and recreational drug use should be encouraged. Meta-analyses of randomized trials have shown that provider-led interventions can not only reduce the number of women smoking during pregnancy, but also improve birth outcomes.[44,45] Abstaining from alcohol during pregnancy removes the risks of alcohol-related birth defects,

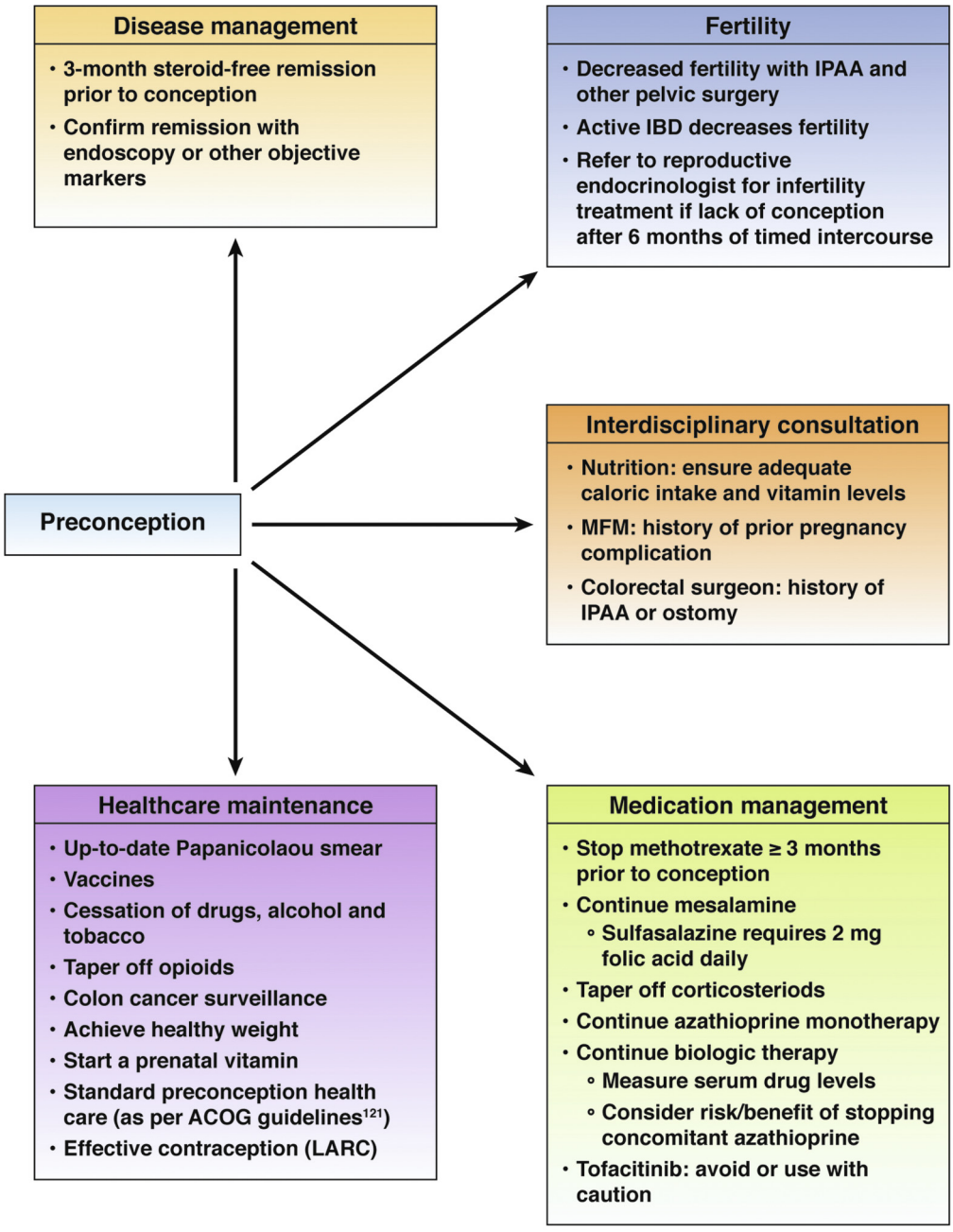


Figure 2. Pregnancy planning and conception. ACOG, American College of Obstetricians and Gynecologists; LARC, long-acting, reversible contraception.

developmental disabilities, and neurocognitive and behavioral issues.[46] Use of illicit or recreational drugs should also be discussed openly. Cannabis has been used in patients with IBD to improve pain and diarrheal symptoms. However, due to concern for adverse neurodevelopmental outcomes in the developing fetus and child, the American College of Obstetricians and Gynecologists and the Academy of Breastfeeding Medicine advise avoiding marijuana use during pregnancy and lactation.[47,48] Whereas it is prudent to conduct a risk–benefit analysis of opioid use in pregnancy, it is best to be off these agents during pregnancy. A systematic review of interventions that are not disease-modifying found limited evidence suggesting that relaxation and behavioral stress management programs may be promising in reducing IBD abdominal pain.[49]

Disease Management

Providers must check laboratory values and correct any abnormalities, as well as supplement folic acid. Corticosteroid use may increase the risk of gestational diabetes and adverse pregnancy outcomes[50] and should not be considered a reasonable maintenance therapy for pregnancy. Methotrexate needs to be stopped at least 3 months before conceiving due to its teratogenic effects.[37] If an alternate medication is needed, stability on the new medication for at

least 3 months should be achieved before attempting conception. Based on available data and balancing the risk to pregnancy of active disease, biologics and thiopurines used in the treatment of IBD are considered low risk during pregnancy and breastfeeding.[51] In the authors' opinion, serum drug levels of biologics should be measured and escalated or de-escalated as necessary before conception. Whereas the American Gastroenterological Association guidelines on therapeutic drug monitoring did not include a recommendation on prophylactic monitoring of patients in remission,[52] a subtherapeutic level may lead to flares in this vulnerable population and supratherapeutic levels may lead to increased transfer across the placenta.[53] Additionally, given the possibility of altered levels of biologics during pregnancy,[51] having a baseline level before conception is reasonable and may affect clinical management.

There are limited human data on the use of tofacitinib in pregnancy. Animal data demonstrate a clear risk of malformation at supratherapeutic doses, suggesting that this medication should be avoided, at least in the first trimester. The half-life of the drug is 3.2 hours,[54] therefore, a washout period of 1 week should be adequate before attempting conception. In the patient with limited treatment options who desires pregnancy, the medication information should be reviewed with all stakeholders—patient and provider(s)—and a consensus should be reached regarding continuation of the drug.

Nine-Month Plan

Vitamins and Nutrition in Pregnancy

The initial prenatal visit should include a discussion of lifestyle issues, nutrition and weight gain, disease activity, monitoring of maternal and fetal status, as well as flare management options. Ideally, this is a dynamic discussion started at the preconception consultation and reiterated during the initial prenatal visit.

Patients with IBD should follow the US Institute of Medicine guidelines for the general obstetric population, which include a recommendation for prenatal vitamins. In some women, prenatal vitamins containing iron may worsen the constipation that often accompanies normal pregnancy. For patients with IBD, this may also exacerbate abdominal pain. Patients should be informed that stool softeners (eg, docusate sodium, senna, bisacodyl, polyethylene glycol 3350) are compatible with use during pregnancy and also encouraged to increase their water intake. Castor oil, however, is contraindicated due to increased uterine contractions. Patients with IBD are at risk for iron and vitamin B-12 deficiency. Furthermore, given increased iron requirements during pregnancy, iron and vitamin B-12 levels should be checked in the first trimester and supplementation provided as needed. Patients unable to tolerate prenatal vitamins may need to rely on other vitamin supplementation, such as folic acid or vitamin B-12. It may also be useful to consult with a nutritionist for advice on eating a well-balanced, healthy diet. The consultation may include guidance on vitamin D as well as on folic acid, which 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, or on medications that interfere with folic acid metabolism.[55,56]

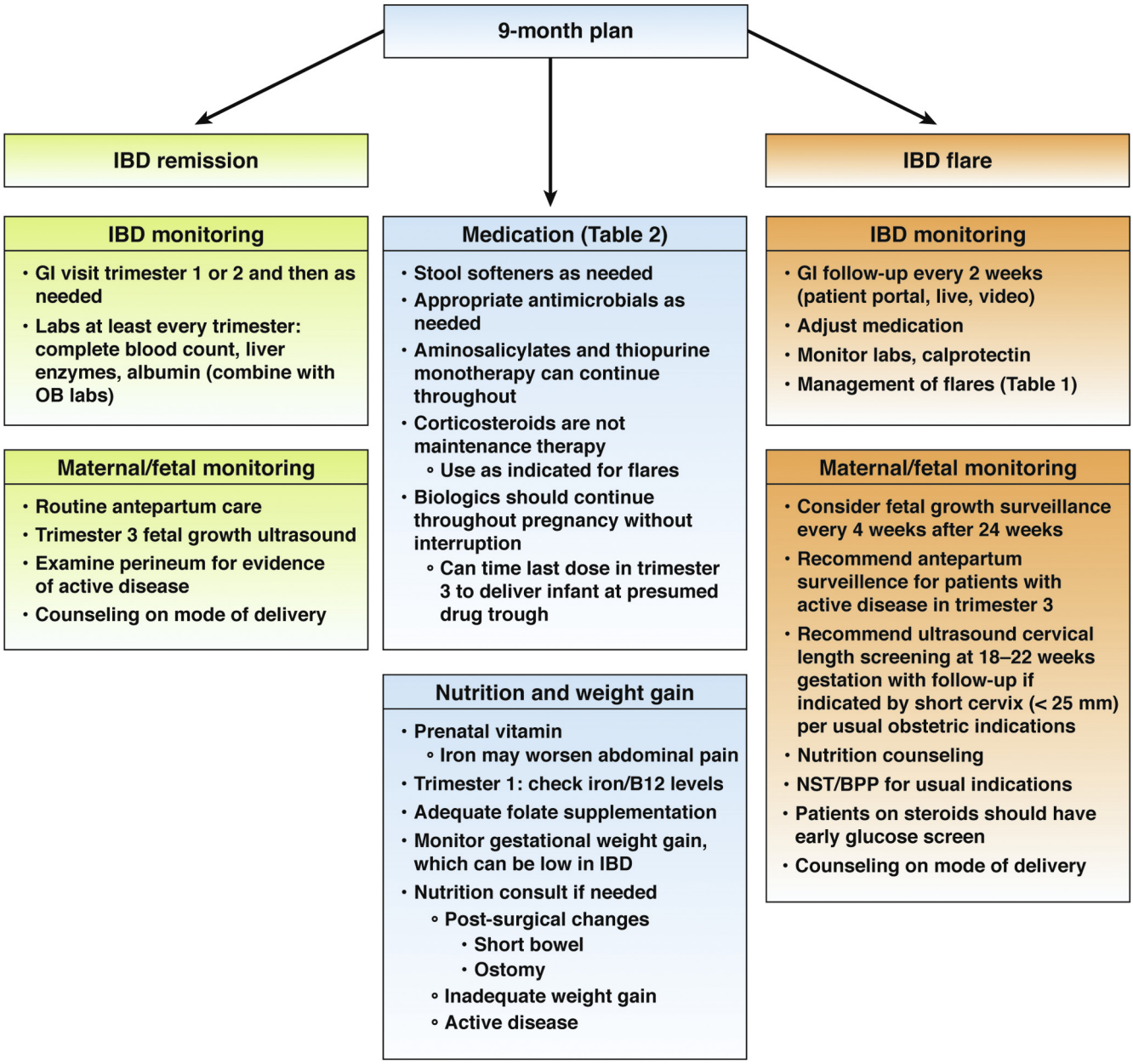
One area of concern for pregnant women with IBD is not achieving the targeted gestational weight gain for their body mass index category. The Norwegian Mother and Child Cohort Study (MoBa) found that mothers with CD and UC had a 2-fold and a 1.5-fold, respectively, increased risk of inadequate gestational weight gain based on the Institute of Medicine recommendations. Mothers with IBD with inadequate gestational weight gain had a 2-fold risk of small-for-gestational-age infants compared with exposed non-IBD mothers. The MoBa investigators also found a correlation with disease activity and reduced gestational weight gain.[57] In a prospective cohort study, women with IBD and inadequate gestational weight gain also had a 2.5-fold increased risk of preterm birth.[58]

Inflammatory Bowel Disease Concerns

Disease activity. Figure 3 outlines some of the key concerns relating to IBD disease activity and its impact on maternal and fetal outcomes. One such concern is flares of CD or UC, which complicate 30%–35% of pregnancies.[59] A meta-analysis of 14 studies found a significantly higher risk ratio of active disease during pregnancy in patients with UC who commenced pregnancy with active disease (55%) compared with those whose disease was in remission at conception (36%) (risk ratio, 2.0; 95% confidence interval, 1.5–3; $P < .001$); this risk was also higher in patients with CD (risk ratio, 2.0, 95% confidence interval, 1.2–3.4; $P = .006$).[60] Those results are consistent with a recent European multicenter cohort: overall, 14% of patients in remission at conception relapsed during pregnancy, whereas 26% of those with active disease remained so until delivery.[61] Having active disease is associated with a significant increase in the rate of preterm birth. In a Danish cohort study examining the impact of CD activity on birth outcomes, 55% of mothers had inactive disease during pregnancy and 45% had low or moderate-high disease activity. The relative risk of preterm birth was 2-fold higher in women with low or moderate-high disease activity during pregnancy compared with women without activity.[62]

Perianal disease. Active perineal disease may present as anorectal fistula/abscess, rectovaginal fistula, anal fissure, or anal stenosis. When active disease is present (usually CD), there is up to a 10-fold increased risk for fourth-degree laceration.[63] During routine pregnancy care, group B streptococcus screening culture collection (at 35–37 weeks' gestation) provides an excellent opportunity to examine the perineal area for active disease and revise counseling as indicated, particularly if the patient presents with new symptoms or has a history of perianal disease.

Assessing disease activity. Pregnant women who have new symptoms suggestive of IBD, or those experiencing a flare, may be considered for diagnostic imaging, endoscopy, or surgery if the results would alter management[15,64–67] (Table 1). For endoscopy and surgery,



Abbreviations used: NST, Nonstress test; BPP, Biophysical profile

Figure 3. Nine-month plan.

considerations such as the type of anesthesia, use of sedative medications for procedures, and gestational age at the time of the procedure, should be undertaken in consultation with an OB/GYN or MFM specialist, as well as an anesthesiologist. In general, a flexible sigmoidoscopy may be performed without sedation or preparation throughout gestation. Full colonoscopy, as well as any sedated procedure performed after 24 weeks (around the time of viability), requires a documented discussion with the patient about fetal monitoring and possible need for emergent cesarean section. Additionally, one should carefully position the patient in the left lateral tilt position to avoid compression of the inferior vena cava and aorta, which may lead to maternal hypotension and reduced placental perfusion.

Medications. All discussion of medication during pregnancy is based on best available data, taking into account the risk of maternal disease flare and the understanding that long-term follow-up on these children is not available.

Aminosalicylates, biologics, or immunomodulator therapies may be continued during pregnancy and through delivery (Table 2).[68–71] Corticosteroids can also be utilized as

Table 1. Options for Flare Management[61–64,115–120]

Laboratory values	Endoscopy	Radiologic imaging	Surgery	Medication
Standard IBD laboratory values checked Trends for CRP and ESR may be helpful Fecal calprotectin Serum drug concentrations Possibly elevated in pregnancy: ESR CRP Alkaline phosphatase (also elevated in lactation) Reduced in pregnancy: Hemoglobin Albumin	Perform for strong indications: Determining IBD disease activity When result will change management Flexible sigmoidoscopy is preferred over pan-colonoscopy when possible; can be performed unsedated, unprepped, and in any trimester	MRI and CT have similar diagnostic accuracy for assessing IBD Gadolinium should be avoided in pregnancy The cumulative radiation exposure of a single CT scan (about 50 mGy) is below the level of concern Ultrasound, where available is appropriate for terminal ileal disease	Surgical intervention may be needed for: Acute refractory colitis Perforation Abscess Severe hemorrhage Bowel obstruction	Manage similar to nonpregnant IBD patients Exceptions: Thiopurine-naïve patients: avoid first start in pregnancy due to concerns for distinctive rare adverse reactions Methotrexate contraindicated Tofacitinib: avoid due to limited human data

CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging.

an adjunctive therapy for disease flares, but are avoided for maintenance therapy, owing to increased risks for preterm birth, low birthweight, or gestational diabetes.[72,73] Antimicrobials are reserved as an acute intervention for patients with pouchitis or perianal disease.[74] Loperamide (limited human data, question of cardiovascular defects) and diphenoxylate (limited human data, no associated risk) are common antidiarrheals used for IBD and should be discontinued when possible.[75] When considering maintenance therapy in pregnancy, monotherapy is preferred. Continuation of biologic therapy in pregnancy has been associated with reduced flares, decreased disease activity, and fewer postpartum flares, with a lower incidence of adverse pregnancy outcomes. While most biologics, aside from certolizumab, actively cross the placenta, safety data from prospective trials and large nationwide cohorts of women who continued taking biologics in pregnancy have not shown an increase in adverse fetal outcomes.[68,76,77] The greatest amount of safety data are for infliximab and adalimumab, which have shown no increased rates of congenital anomalies or infections among infants up to 1 year of age who were exposed to these agents in utero.[68,76,78,79] Generally, combination therapy utilizing biologics and immunomodulatory thiopurines is discouraged due to increased risk of infection in the infant, though this has not been consistently shown.[80,81] Stopping the thiopurine is an individualized decision based on indication for combination therapy and severity of patient's disease. Starting thiopurine therapy for the first time in pregnancy is not recommended due to the risk of pancreatitis, leukopenia, and the delayed time to effect. In the final trimester of pregnancy, appropriate IBD medications, including biologic therapy, should be continued without interruption. However, to minimize transplacental transfer near the time of delivery, biologic dosing can be adjusted (but not interrupted) to achieve trough or lowest serum drug concentrations at the estimated date of confinement (Table 2).[36] The benefits of maintaining disease remission and allowing vaginal delivery may outweigh any risks associated with biologic monotherapy for maintenance.[36,68,76]

Delivery Plan

In pregnancy complicated by IBD, the mode of delivery—cesarean vs vaginal delivery—should focus on usual obstetric indications (Figure 4).[15,82,83] A patient may undergo vaginal delivery in most presentations of IBD, unless there is active perineal disease present around the time of delivery or unique patient circumstances present.[83,84] Vaginal delivery has not been demonstrated to influence risk for development of IBD in the offspring. For those undergoing labor and planned vaginal delivery, care should include adequate anesthesia and reservation of vacuum or forceps operative delivery based on usual obstetric indications.

Examination near term (from 37 weeks until labor) and before delivery allows for modification of delivery planning according to disease state. We recommend cesarean delivery for women with prior rectovaginal fistulas, owing to

Table 2. Inflammatory Bowel Disease Maintenance Therapies During Pregnancy and Lactation

Medication	Maintenance dosing recommendation	Breastfeeding considerations
Aminosalicylates	Maintain prepregnancy dosing	
Mesalamine	All preparations are now phthalate-free	Compatible with breastfeeding No preparation preference Monitor infant for diarrhea
Sulfasalazine	Consider 2-mg folate supplement in pregnancy Azulfidine EN contains phthalate	Compatible with breastfeeding Mesalamine preferred
Immunomodulators	Dosing may be altered due to increased renal clearance with pregnancy. Therapeutic drug monitoring recommended	Routine infant monitoring not necessary
Cyclosporine (calcineurin inhibitor)	Limited data in pregnancy suggest associations with hypertension, gestational diabetes, preterm birth, low birthweight/SGA. Used as a salvage therapy.	Compatible with breastfeeding Minimal infant exposure, no reports of harm from breastfeeding
Methotrexate	Contraindicated in pregnancy. Stop 3 months before conception.	Limited human data. Not advised.
Thiopurines (azathioprine, 6-mercaptopurine)	Continue as monotherapy In appropriate patients, consider cessation of thiopurine as combination therapy, given possible association with increased infant infections. Use with caution in combination with allopurinol, which carries potential embryo toxic effects	Compatible with breastfeeding Minimal infant exposure, no reports of harm from breastfeeding
Small molecules		
Tofacitinib	Limited human data. Consider other options, particularly in first trimester	Limited human data. Not advised.
Biologics	Maintain prepregnancy dosing Continue dosing throughout all 3 trimesters If possible, plan final dose according to drug half-life to minimize transfer	Compatible with breastfeeding Encourage participation in pregnancy registries if not already done during pregnancy.
Adalimumab	Plan final pregnancy injection 2–3 wk before EDC and resume postpartum[a] (1–2 wk if weekly dosing)	
Certolizumab pegol	May continue scheduled dosing throughout pregnancy.	
Golimumab	Plan final pregnancy injection 4–6 wk before EDC and resume postpartum[a]	
Infliximab	Plan final pregnancy infusion 6–10 wk before EDC and resume postpartum[a] (If every-4-wk dosing, then 4–5 wk before EDC) Base dosing on prepregnancy weight during pregnancy and immediate postpartum	
Natalizumab	Plan final pregnancy infusion 4–6 wk before EDC and resume postpartum[a]	
Ustekinumab[b]/ Vedolizumab[b]	Plan final pregnancy dose 6–10 wk before EDC and resume postpartum[a] (If every-4-week dosing, then 4–5 wk before EDC)	
Corticosteroids	Reserved for active flares in pregnancy. Not recommended for planned maintenance therapy during pregnancy.	Compatible with breastfeeding Subtherapeutic infant exposure expected, even with flare dosing Avoiding feeding 1–2 h post-dose (non-enteric coated forms) can further minimize exposure but is not necessary
Antibiotics	Reserved for perianal disease and pouchitis and not recommended for planned maintenance therapy (amoxicillin/metronidazole preferred over ciprofloxacin)	Amoxicillin/clavulanic acid compatible with breastfeeding Ciprofloxacin preferred over metronidazole

EDC, estimated date of confinement; SGA, small for gestational age.
[a]48 hours post-delivery
[b]Limited pregnancy data

its protective effects on the prior surgical repair site, as well as higher rates of recurrent involvement of the tissue with possible incontinence in complex cases.[63,85] Avoiding perineal trauma in cases of perineal involvement or prior perineal surgery may prevent recurrent damage or incontinence.[36,86,87] Avoiding obstetrical laceration or episiotomy through cesarean delivery also protects the perineum and anal sphincter function. Long-term protections are less certain given the lack of extended outcome studies.[36]

Special consideration is given to women who have had IPAA surgery, which does not appear to independently affect pregnancy outcomes; nor does mode of delivery appear to independently affect pouch function.[88] However, cesarean delivery is thought to prevent anal sphincter injury—an important consideration due to the increased risk of incontinence.[87] At the time of delivery, one should consider a preoperative consultation with a surgeon familiar with the physiology of an IPAA, as cesarean delivery may involve adhesions or require mobilization of the bowel to achieve delivery. Additional considerations for cesarean delivery in women with IPAA include availability of surgical backup and surgical instruments for bowel surgery at the time of delivery.

Models of shared decision-making should be employed when counseling patients regarding mode of delivery. The care coordination team should work to ensure adequate communication regarding counseling and planning for mode of delivery, as this will alleviate patient confusion and anxiety regarding delivery.

In order to ensure adequate ongoing disease control through the postpartum period, it is important to begin planning the postpartum dosing of biologic therapy before delivery. This may involve insurance preauthorization and locating the appropriate site for administering the infusion. Appropriate follow-up with both the OB and gastroenterologist should be arranged for post-delivery disease monitoring and therapy as needed.[36]

Anticoagulation Prophylaxis

Pregnant women hospitalized for IBD are candidates for anticoagulation prophylaxis, given the higher risks of venous thromboembolic disease in patients with IBD, as well as the immobilization that often accompanies hospitalization. This advisory includes patients admitted for an IBD flare, as well as those patients undergoing cesarean delivery.[15] For the latter, a postoperative course of prophylactic anticoagulation should be considered after delivery, along with mechanical prophylaxis with sequential compressive devices and early ambulation.[89] Anticoagulant thromboprophylaxis may be extended up to 3–6 weeks postpartum, corresponding to the time period of greatest risk for pregnancy-associated venous thromboembolic disease, in patients with a history of venous thromboembolic disease event or other risk factors.[89–91] Unfractionated heparin, low-molecular-weight heparin, and warfarin are appropriate to prescribe to breastfeeding women, while oral direct thrombin and factor Xa inhibitors should be avoided.[91]

Post-Delivery Care for Mother

Medications

If there is no evidence of infection and the dosing interval is appropriate, biologics may be resumed 24 hours after vaginal delivery and 48 hours after cesarean delivery.[37] When using weight-based dosing for biologics and thiopurines during pregnancy and the immediate postpartum, we recommend using prepregnancy weight to calculate the appropriate dose. Dosing can be adjusted as needed based on disease activity, serum drug concentrations, and persistent postpartum weight gain as appropriate. Other IBD-specific medications should be continued in the postpartum period, with the exception of methotrexate (Figure 5).

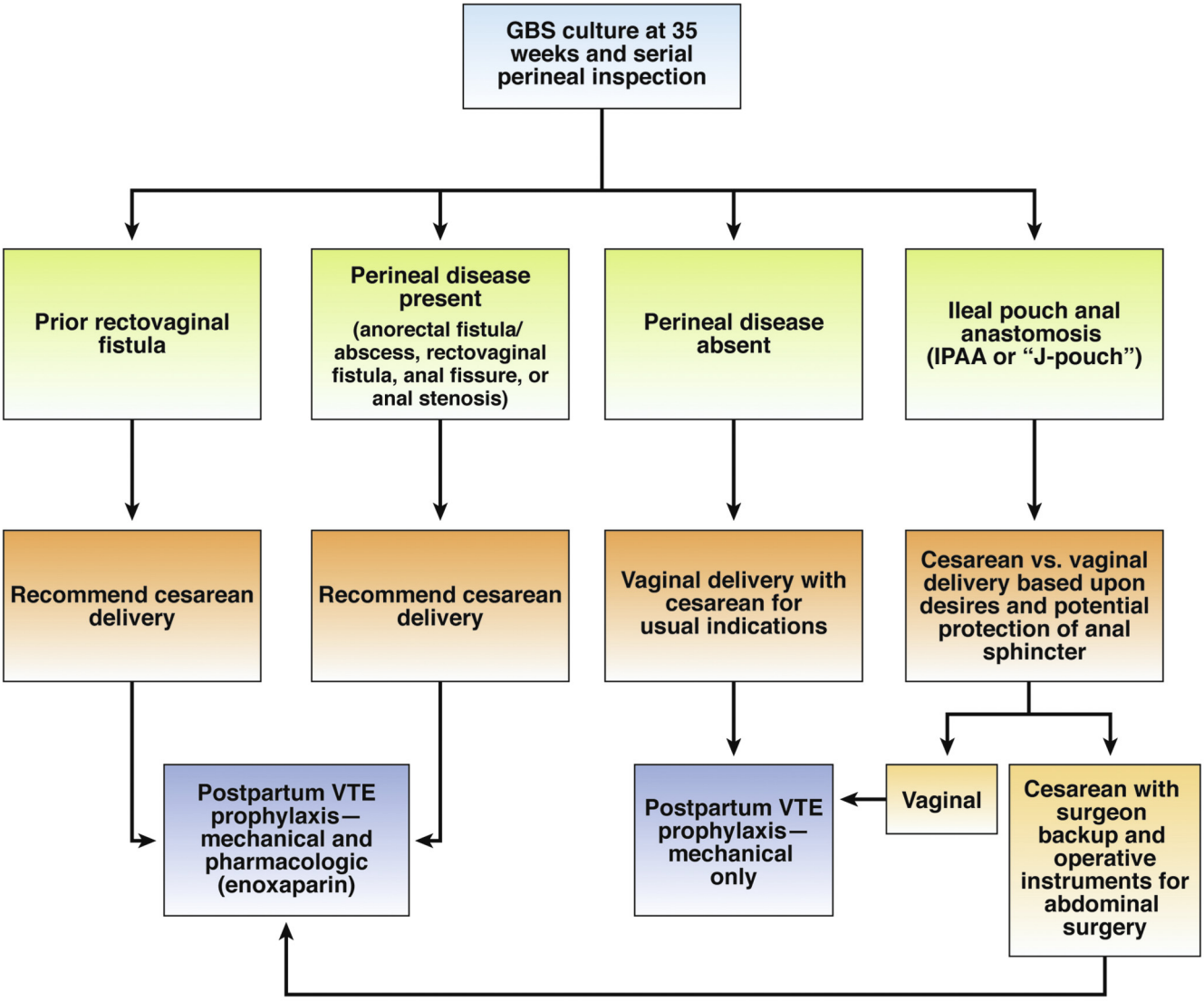
After delivery, women with IBD should receive adequate monitoring and management of pain. Short courses of opioids can be used for postpartum management of pain in concert with OB/GYN and pediatrician review. Codeine and tramadol are the least preferred agents.[92–94] Some opioids should be avoided during lactation due to the increased risk of infant sedation or respiratory depression.[94] As opioids may induce constipation, concomitant therapy for maintaining physiologic stool consistency (eg, with osmotic agents) should be considered. Nonsteroidal anti-inflammatory drugs may be used for a short course (1–2 weeks)[95]; however, extended nonsteroidal anti-inflammatory drugs therapy has been linked to IBD flares and should be avoided.[96,97] A more detailed discussion of transfer of medications during lactation is discussed in the section on Post-Delivery Care for Baby. Finally, before discharge, there should be a discussion regarding contraception plan to avoid unintended pregnancy and short inter-pregnancy interval, as appropriate.

Postoperative Care

In the non-IBD patient undergoing cesarean delivery, ileus and wound infection are the leading causes of increased length of hospital stay.[98] Routine supportive measures and early feeding may minimize the risk of ileus.[99] The risk of ileus may also be increased in patients with an IPAA if the pouch was manipulated during cesarean delivery. Small bowel obstruction is a rare complication in women with an IPAA after cesarean delivery.[86,100,101]

Ostomy Management

In patients who have an ostomy, stomal problems, such as displacement, enlargement, retraction, stenosis, and prolapse, may occur with stretching of the abdominal wall in the region of the linea alba. Patients should work with a nutritionist, if needed, to avoid excessive weight gain during pregnancy. Postpartum care may require coordination with a colorectal surgeon and an ostomy/wound nurse. If a cesarean section is required, simply covering the ostomy with gauze is adequate to protect the operative field.[102–104]



Abbreviations used: GBS, Group B streptococcus; VTE, Venous thromboembolic disease

Figure 4. Decision algorithm for mode of delivery. GBS, group B streptococcus; VTE, venous thromboembolism.

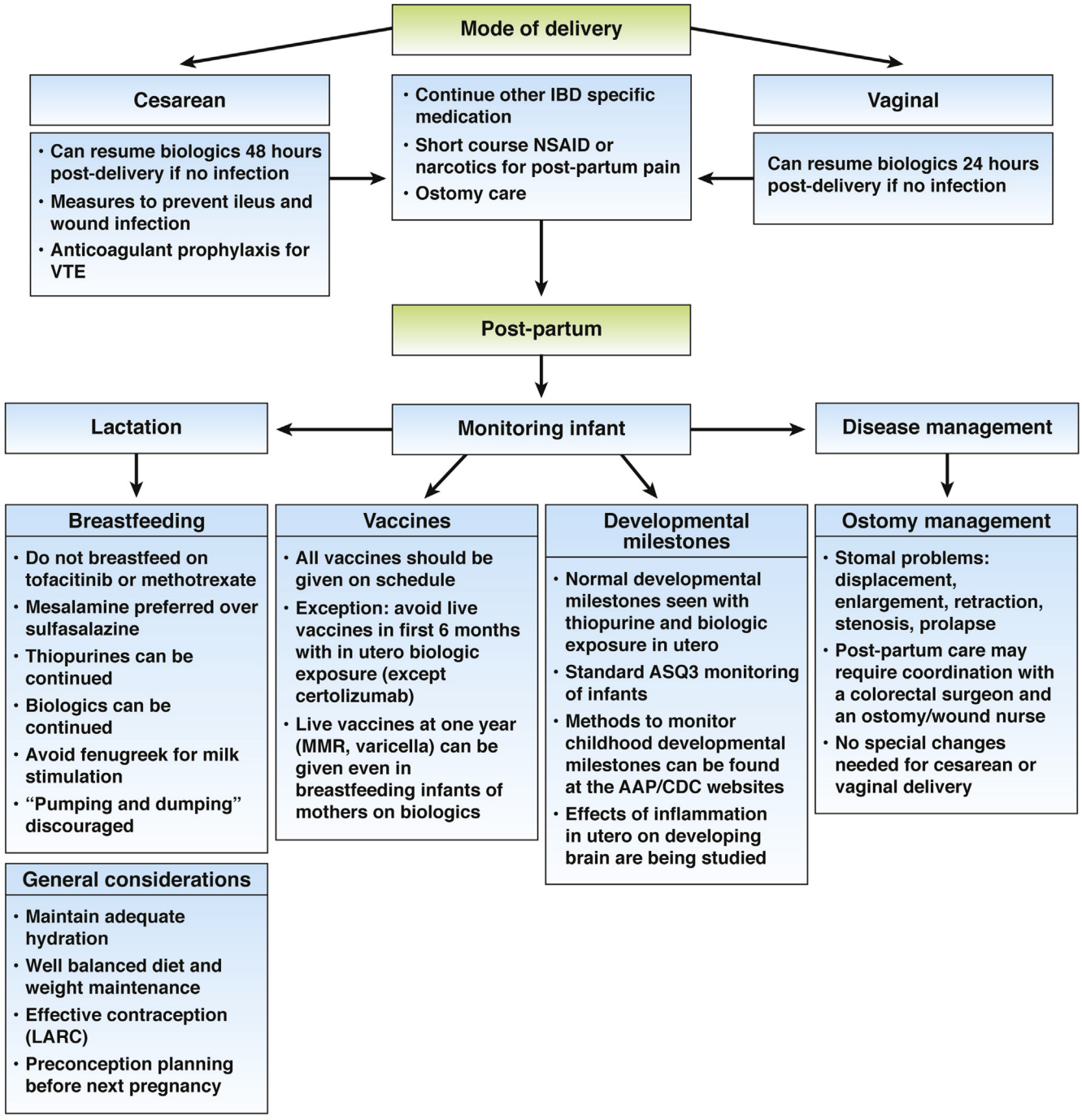
Post-Delivery Care for Baby

Breastfeeding—General Considerations

Mothers with IBD who are breastfeeding should follow standard nutritional recommendations. This means increasing their caloric intake by 450–500 kcal/d and adding 200–300 mg/d omega-3 fatty acids from dietary or medicinal sources.[105] However, staying hydrated and well-nourished may be difficult for mothers with IBD, particularly those with an ostomy or those with active disease who are losing weight. In such cases, the mother should be provided with nutritional counseling. If the mother perceives a need to increase her milk supply, the galactogogue fenugreek should be avoided because diarrhea is a common side effect and bleeding can occur.[106] Parenteral corticosteroids have been reported to cause self-resolved, temporary suppression of milk production in non-IBD mothers. However, no IBD treatments, including standard-dose oral or rectal corticosteroids, are known to or would be expected to suppress lactation.[107]

Inflammatory Bowel Disease Medication Safety in Lactation

The US National Library of Medicine LactMed database[108] is the recommended resource for clinicians to obtain the most current data on individual medications during lactation.[109] Upon reviewing the scientific literature cited in LactMed, we conclude that the majority of the medications prescribed for IBD are either undetectable in breast milk or are present in such low concentrations that they would not be expected to cause harm to the breastfeeding infant. Safety outcomes from



Abbreviations used: IBD, inflammatory bowel disease; NSAID, nonsteroidal anti-inflammatory drugs; MMR, measles, mumps, rubella; AAP, American Academy of Pediatrics; CDC, Centers for Disease Control and Prevention

Figure 5. Post-delivery care for mother and baby. AAP, American Academy of Pediatrics; ASQ, Ages and Stages Questionnaire; CDC, Centers for Disease Control and Prevention; LARC, long-acting, reversible contraception; MMR, measles, mumps, rubella; NSAID, nonsteroidal anti-inflammatory drug; VTE, venous thromboembolism.

the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry provide further reassurance that breastfeeding during IBD treatment is not harmful for the infant. Breastfed infants exposed to immunomodulators, biologics, or combination therapy in PIANO had similar milestone achievement and were not more likely to have an infection in the first 12 months of life compared to infants who were not breastfed.[110]

Key caveats to the general acceptability of IBD medication use during breastfeeding include:

1. Among the 5-ASA agents, mesalamine, balsalazide, and olsalazine are preferred to sulfasalazine due to the unknown side effects of sulfasalzine's sulfapyridine metabolite, which is excreted into milk at higher concentrations than the parent drug and has hemolytic and antimicrobial properties.[108]
2. The majority of women studied have undetectable or very low concentrations of biologic agents in their milk (<1% of serum concentration) with no negative impact of breastfeeding on infant health outcomes. While further studies are needed on the impact of uncontrolled inflammation on milk concentrations, and on the intraluminal activity of the small quantities ingested by the infant, at this time, there is no indication of harm from breastfeeding on biologic therapies.[110]
3. The practice of "pumping and dumping" is neither necessary nor likely to be effective for most IBD drugs and should be discouraged.
4. Methotrexate concentrations in milk after anti-inflammatory dosing appear to be clinically insignificant; however, too few women have been studied thus far to permit an endorsement at this time.
5. We recommend clinicians follow the Food and Drug Administration–approved labeling for tofacitinib and advise mothers receiving this agent not to breastfeed.

These and other recommendations are summarized in Figure 5.

We recommend that mothers and pediatricians be vigilant about infections as they would with any child. However, consideration should be given to minimizing unnecessary antibiotic exposure, as that may increase the risk of developing CD later in childhood.[111]

There are no specific recommendations for weaning from breast milk to complementary foods other than what the American Academy of Pediatrics recommends for all mothers: exclusive breastfeeding for 6 months, with continuation of breastfeeding for 1 year or longer as mutually desired by mother and infant.[105]

Vaccination Recommendations for the Newborn

All vaccines should be given on schedule according to the accepted Centers for Disease Control and Prevention guidelines.[112] However, if the mother is exposed to any biologic therapy, other than certolizumab, during the third trimester of pregnancy (ie, after 27 weeks gestation) avoidance of live vaccines is recommended for the first 6 months of life. The orally administered rotavirus vaccine is the only live vaccine that is administered before 6 months in the United States. Rotarix is given in 2 doses at ages 2 and 4 months. To be most effective, the first dose should be administered before an infant turns 15 weeks of age, which falls within the 6-month time window. The varicella and measles, mumps, rubella live vaccines, which are given at 1 year of age, are acceptable to administer while the infant is actively breastfeeding. It remains unknown whether a mother who is taking tofacitinib and breastfeeding at the time the varicella and measles, mumps, rubella vaccines are due should hold the medication for a short period of time to minimize any immunosuppressant effect on the child who is receiving the vaccine. More data are needed before any recommendation can be made with regard to tofacitinib.

Developmental Milestones

There is no evidence to suggest that babies born to mothers with IBD regardless of medication exposure have any developmental delays. Recommendations on monitoring childhood developmental milestones can be found at the American Academy of Pediatrics and Centers for Disease Control and Prevention websites. The PIANO data on developmental milestones support the lack of negative effect of IBD medications on development.[58,113] The effects of inflammation in utero on the developing brain is an area of research that is quickly gaining momentum. It has been shown that pro-inflammatory mediators negatively influence both hippocampal neurogenesis and neuronal cytoarchitecture during brain development.[114] The importance of good inflammatory control during pregnancy should therefore be emphasized when counseling women with IBD.

Summary

The explosion of therapeutic options in the last 15 years has provided hope to women with IBD who wish to be healthy enough to conceive a child. However, a lack of adequate information and poor communication among providers has left the patient with limited and often contradictory advice. This Consensus Clinical Care Pathway has gathered all available data and tasked an expert multidisciplinary team representing multiple societies to put it all together in a format that is easily digestible and converts readily into everyday practice. While we understand that further studies are always needed and recommendations may change over time, we hope that every woman with IBD who is considering pregnancy or is pregnant will now have access to standardized, up-to-date, evidence-based recommendations that are agreed upon by her gastroenterology and obstetric provider, working in unison to ensure the healthiest possible pregnancy.

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Conflicts of interest
These authors disclose the following: Uma Mahadevan: Consulting for Janssen, AbbVie, Pfizer, Takeda, Celgene, Lilly, and Samsung. Christopher Robinson: Board of Directors, Society for Maternal Fetal Medicine; Associate Editor *American Journal of Perinatology*; Media Editor *American Journal of Obstetrics and Gynecology*. Nana Bernasko: Pfizer and Takeda Advisory Board. Brigid Boland: Consultant for AbbVie and Prometheus Labs. Christina Chambers: Research funding from AbbVie, Amgen Inc, Astra Zeneca, Apotex, Barr Laboratories, Inc, Bristol-Myers Squibb, Celgene, Gerber Foundation, GlaxoSmithKline, Janssen Pharmaceutical, Kali Laboratories Inc, Pfizer Inc, Hoffman La Roche-Genetech, Sandoz Pharmaceuticals, Genzyme Sanofi-Aventis, Regeneron, Sequirus, Takeda, Teva Pharmaceutical Industries, and UCB. Marla Dubinsky: Consultant for AbbVie, Boehringer Ingelheim, Celgene, Eli Lilly, Genentech, Janssen, Pfizer, Prometheus, Salix, Shire, Takeda, and UCB. Sunanda Kane: Consultant for AbbVie, Merck, Spherix Health, and Seres.

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