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Global Consensus Statement on the Management of Pregnancy in Inflammatory Bowel Disease

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Abbreviations used in this paper: **5-ASA, 5-aminosalicylate; 6-mmpn, 6-methylmercaptopurine nucleosides; aIRR, adjusted incidence rate ratio; aHR, adjusted HR; AMH, anti-Müllerian hormone; anti-TNF, anti-tumor necrosis factor; APGAR, Appearance, Pulse, Grimace, Activity, and Respiration; aOR, adjusted odds ratio; ART, assisted reproductive technology; ASD, autism spectrum disorder; ASGE, American Society for Gastrointestinal Endoscopy; ASQ3, Ages and Stages Questionnaire 3; BCG, Bacille Calmette-Guérin; CAs, congenital abnormalities; CCP-KNOW, Crohn's and Colitis Pregnancy Knowledge Score; CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; CS, cesarean delivery; CT, computed tomography; DBP, dibutyl phthalate; DI, disagreement index; ECCO, European Crohn's Colitis Organization; FA, food additive; FC, fecal calprotectin; GBS, group B Streptococcus; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; GWG, gestational weight gain; HBV, hepatitis B virus; HR, hazard ratio; IBD, inflammatory bowel disease; IBD-U, IBD unclassified; IgG, immunoglobulin; IL, interleukin; IPAA, ileal pouch–anal anastomosis; IQR, interquartile range; IRR, incidence rate ratio; IUS, intestinal ultrasound; JAKi, Janus kinase inhibitor; LARC, long-acting reversible contraceptive; LBW, low birth weight; MELODY, Modulating Early Life Microbiome through Dietary Intervention in Pregnancy; MHRA, Medicines and Health Products Regulatory Agency; MoBa, Mother and Child Cohort Study; MoMMY-IBD, Mother-to-Infant Transfer of Bacteriome, Virome, Fungome, and Metabolome in Health; MTX, methotrexate; NICU, neonatal intensive care unit; NSAIDS, non-steroidal anti-inflammatory agents; PIANO, Pregnancy IBD Inflammatory Bowel Disease and Neonatal Outcomes; PICO, population, intervention, comparison, outcome; PY, person-year; OR, odds ratio; RA, rheumatoid arthritis; RAND, Research and Development; RID, relative infant dose; RR, relative risk; RVF, rectovaginal fistula; SGA, small for gestational age; S1P, sphingosine-1-phosphate; UC, ulcerative colitis; VD, vaginal delivery; VTE, venous thromboembolism.**

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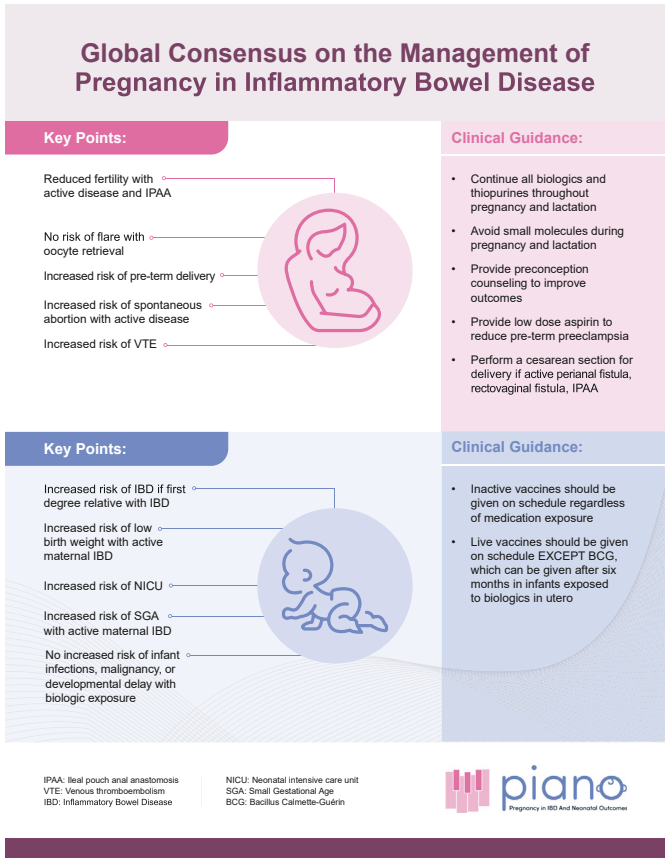

BACKGROUND & AIMS: **Pregnancy can be a complex and risk-filled event for women with inflammatory bowel disease (IBD). High-quality studies in this population are lacking, with limited data on medications approved to treat IBD during pregnancy. For patients, limited knowledge surrounding pregnancy impacts pregnancy rates, medication adherence, and outcomes. Limited provider knowledge leads to highly varied practices in care affected by local dogma, available resources, individual interpretation of the literature, and fear of harming the fetus. The variations in guidelines by different societies and countries reflect this and lead to confusion for physicians and patients alike. The Global Consensus Consortium is a group of 39 IBD and content experts and 7 patient advocates from 6 continents who convened to review and assess current data and come to an agreement on best practices based on these data.**

METHODS: **The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) process was used when sufficient published data were available and the RAND (Research and Development) process in those instances where expert opinion was needed to guide consistent practice. Recommendations were informed by the guiding principle that maternal health best supports infant health.**

RESULTS: **The topics were divided into ten categories with 34 GRADE recommendations and 35 consensus statements.**

CONCLUSIONS: **Overall, the goal of the group was to provide data-driven and practical guidance to improve the care of women with IBD around the globe based on the best available research.**

Keywords: Biologics; Crohn's Disease; Inflammatory Bowel Disease; JAK Inhibitors; Pregnancy; Ulcerative Colitis.

As a matter of policy, pregnant women are excluded from clinical trials of experimental agents not primarily directed at pregnancy.[1] When a new therapy achieves regulatory approval, there are animal reprotoxicity data but no human pregnancy safety data. Human data are cobbled together with mandatory

postmarketing registries (which often require years to be published), case reports (which are quick but very limited), population representative data from insurance databases and European countries (many years after drug is approved), and, rarely, preexisting national prospective disease state registries like PIANO (Pregnancy in IBD [Inflammatory Bowel Disease] and Neonatal Outcomes).[2] This results in the default of not prescribing a medication to women of childbearing age or stopping it if they become pregnant. For patients with IBD, medication cessation leads to an increase in disease activity, which then is associated with an increase in maternal and fetal adverse outcomes.[2] The piecemeal data also result in varied interpretations and recommendations by global experts for the management of this vulnerable population.

Patients with IBD do not receive appropriate counseling and education surrounding pregnancy-related concerns. In 2 separate studies utilizing an instrument measuring pregnancy-related knowledge (Crohn's Colitis Pregnancy Knowledge Score [CCP-KNOW]), nearly one-half had poor knowledge.[3,4] Other survey-based studies demonstrate a higher rate of "voluntary childlessness" in women with IBD as compared with the general population (18% vs 6%). This may be explained by concerns from patients surrounding the impact of their disease on pregnancy, the impact of pregnancy on their disease, fertility concerns, and infant outcomes including the risk of passing the disease on to their offspring.[5] Patients often have concerns surrounding potential harms of medications; in one study, more than 80% expressed these concerns.[6] Therefore, evidence-based education is needed to appropriately inform patients, requiring assessment of the evidence associated with factual statements to be utilized in counseling.

Management of pregnancy in women with IBD is complex and has evolved as data from multiple large cohort studies in the past decade have become available. In addition, international considerations to recommendations must be considered, including background rates of infectious disease and resource availability that can affect practice patterns. The goal of the Helmsley PIANO Expert Global Consensus (utilizing GRADE [Grading of Recommendations Assessment, Development, and Evaluation] when appropriate)[7] is to provide standardized evidence-based recommendations to providers caring for women with IBD throughout the world. Specific considerations range from fertility to medical management during pregnancy, delivery, and care of the offspring in the first year of life. The GRADE statements are listed in Table 1. Although objective comparative observational data are available for many aspects of management and amenable to the GRADE process, for those areas without data amenable to GRADE (often only limited case series or animal data are available), a RAND (Research and Development)[8] panel was convened to provide expert consensus based on the available literature. Importantly, animal data do not necessarily correlate with human outcomes, and therefore, expert consensus is needed in these areas. Consensus statements are listed in Table 2. Additional questions were explored with commentary below but were not included as statements due to lack of adequate data among pregnant women with IBD.

Methods

Where possible, the GRADE process was utilized to evaluate the quality of supporting evidence (Table 3). A strong recommendation is made when the benefits or desirable effects of an intervention clearly outweigh the negatives or undesirable effects and/or the result of no action. The term "conditional" is used when some uncertainty remains regarding the balance of benefits and potential harms, either because of low-quality evidence or because of a suggested balance between desirable and undesirable effects. The quality of the evidence is graded from high to low, where high-quality evidence indicates that the authors are very confident that the true effect lies close to that of the estimate of the effect. Moderate-quality evidence is associated with moderate confidence in the effect estimate, although further research would be likely to have an impact on the confidence of the estimate. Low-quality evidence indicates limited confidence in the estimate, and thus, the true effect could differ from the estimate of the effect. Very-low-quality evidence indicates very little confidence in the effect estimate and that the true effect may be substantially different than the estimate of the effect.[9–11] In specific scenarios, recommendations can be upgraded to strong even when only low evidence is available. These scenarios include (1) life-threatening or catastrophic situation; (2) potential equivalence, one option less risky or costly through high-quality evidence; (3) uncertain benefit, certain harm; (4) high certainty in similar benefits, one option potentially more risky or costly; or (5) potential catastrophic harm (very-low-quality or low-quality evidence suggests the possibility of catastrophic harm). In this document, there are scenarios when recommendation was upgraded, specifically due to the potential for catastrophic harm to the infant or mother.

The RAND/University of California, Los Angeles Appropriateness Method[8] is a widely used, iterative, evidence-based process that combines the best available evidence with the expert opinion of the available literature to determine the appropriateness of processes of care in medicine. In this consensus, the RAND panel was applied to provide clinically relevant guidance. Although this approach can be seen as methodologically less rigorous than GRADE, it allows for practical expert-driven advice in areas where robust evidence is lacking.

Clinical Scenarios

The literature review and subsequent surveys were divided into 10 sections broadly related to aspects of

Table 1. GRADE Statements

	GRADE statement	Recommendation	Level of evidence
Maternal factors impacting pregnancy to be addressed in counseling			
1	We suggest counseling that children with first-degree relatives with inflammatory bowel disease, as compared with those without, have an increased risk of the development of inflammatory bowel disease.	Conditional	Low
Fertility			
2	We suggest counseling that women with inflammatory bowel disease may have decreased fertility compared with women without inflammatory bowel disease.	Conditional	Very low
3	In women with ulcerative colitis, we suggest counseling that prior ileal pouch–anal anastomosis is associated with decreased fertility when compared with women with ulcerative colitis who have not had ileal pouch–anal anastomosis.	Conditional	Very low
4	In women with inflammatory bowel disease, we recommend counseling that active disease increases the risk of infertility as compared with inactive disease.	Strong	Very low
5	We suggest counseling that women with inflammatory bowel disease may have comparable effectiveness of assisted reproductive technology when compared with women without inflammatory bowel disease, as measured by live birth.	Conditional	Very low
6	We suggest counseling that women with inflammatory bowel disease who have undergone pelvic surgery with inflammatory bowel disease have similar effectiveness of in vitro fertilization when compared with women without inflammatory bowel disease, as measured by live birth.	Conditional	Very low
Preconception counseling and optimization			
7	We recommend that women with inflammatory bowel disease undergo Preconception counseling.	Strong	Low
Management of disease activity during pregnancy			
8	We suggest that urgent and emergent inflammatory bowel disease surgery during pregnancy be completed when required and not based on trimester.	Conditional	Very low
Management of pregnancy			
9	We suggest that pregnant women with inflammatory bowel disease take low-dose aspirin by 12 to 16 weeks' gestation to prevent preterm preeclampsia.	Conditional	Low
10	We suggest that pregnant women with Crohn's disease and active perianal disease undergo cesarean delivery.	Conditional	Very low
11	We suggest that pregnant women with inflammatory bowel disease and prior ileal pouch–anal anastomosis consider cesarean delivery.	Conditional	Very low
Medications in pregnancy			
12	For women with inflammatory bowel disease who are pregnant or attempting conception, we recommend continuing maintenance 5-aminosalicylate therapy.	Strong	Low
13	In women with inflammatory bowel disease who are pregnant or attempting conception, we suggest continuing maintenance sulfasalazine therapy.	Conditional	Very low
14	In women with inflammatory bowel disease who are pregnant, we suggest the use of corticosteroid therapy when clinically necessary with appropriate monitoring.	Conditional	Low
15	In women with inflammatory bowel disease, we recommend discontinuing maintenance methotrexate therapy prior to conception.	Strong	Very low
16	In women with inflammatory bowel disease who are pregnant or attempting conception, we suggest continuing maintenance thiopurine therapy as data do not demonstrate an increased risk of congenital malformations or infant infections.	Conditional	Very low
17	In women with inflammatory bowel disease who are pregnant or attempting conception, we recommend continuing maintenance anti-tumor necrosis factor therapy throughout pregnancy.	Strong	Low
18	In women with inflammatory bowel disease who are pregnant or attempting conception, we suggest continuing maintenance combination therapy with an anti-tumor necrosis factor and thiopurine therapy throughout pregnancy.	Conditional	Very low
19	In women with inflammatory bowel disease who are pregnant or attempting conception, we suggest continuing maintenance vedolizumab therapy throughout pregnancy.	Conditional	Low
20	In women with inflammatory bowel disease who are pregnant or attempting conception, we suggest continuing maintenance ustekinumab therapy throughout pregnancy.	Conditional	Low

Table 1. Continued

GRADE statement		Recommendation	Level of evidence
Medications during lactation			
21	We recommend breastfeeding as it is NOT associated with an increased risk of disease exacerbation in women with inflammatory bowel disease.	Strong	Very low
22	We suggest counseling that infants born to mothers on anti-tumor necrosis factor therapy who breastfeed have no increased risk of infection in the first 12 months of life.	Conditional	Very low
Pregnancy adverse events			
23	We suggest counseling that women with inflammatory bowel disease as compared with women without inflammatory bowel disease have an increased risk of adverse pregnancy outcomes including low birth weight and preterm delivery.	Conditional	Very low
24	We suggest counseling that women with inflammatory bowel disease with moderate to severe disease activity have an increased risk of spontaneous abortion as compared with women without inflammatory bowel disease or women with mild inflammatory bowel disease.	Conditional	Very low
25	We suggest counseling that pregnant women with inflammatory bowel disease have an increased risk of venous thromboembolism during pregnancy as compared with pregnant women without inflammatory bowel disease.	Conditional	Low
26	We suggest counseling that pregnant women with inflammatory bowel disease have an increased risk of venous thromboembolism during the postpartum as compared with pregnant women without inflammatory bowel disease.	Conditional	Low
Fetal and neonatal adverse events			
27	We suggest counseling that children born to women with inflammatory bowel disease have an increased rate of neonatal intensive care unit admissions and hospitalizations in the first year of life compared with children born to women without inflammatory bowel disease.	Conditional	Very low
28	We suggest counseling that children born to women with active inflammatory bowel disease have an increased rate of small for gestational age and low birth weight compared with children born to women with inactive inflammatory bowel disease.	Conditional	Very low
29	We suggest counseling that children born to women treated with anti-tumor necrosis factor therapy, ustekinumab, or vedolizumab during pregnancy have no increased risk of early childhood malignancy.	Conditional	Very low
30	We suggest counseling that children born to women treated with anti-tumor necrosis factor therapy, ustekinumab, or vedolizumab during pregnancy have no increased risk of early childhood developmental delay.	Conditional	Very low
31	We suggest counseling that children born to women treated with thiopurine therapy during pregnancy have no increased risk of early childhood developmental delay.	Conditional	Very low
Vaccines			
32	We recommend that inactive vaccines be provided to children born to mothers with inflammatory bowel disease on anti-tumor necrosis factor agents	Strong	Very low
33	We suggest that live rotavirus vaccine may be provided in children with in utero exposure to biologics.	Conditional	Very low
34	We recommend that live Bacillus Calmette-Guérin vaccine be avoided in the first 6 months[a] of life in children with in utero exposure to anti-tumor necrosis factor therapy due to risk of disseminated tuberculosis and associated mortality.	Strong	Very low

[a]Regional risk should be considered.

pregnancy and neonatal outcomes. These sections include (1) Maternal Factors Impacting Pregnancy, (2) Fertility, (3) Preconception Counseling and Optimization, (4) Management of Active Disease during Pregnancy, (5) Management of Pregnancy, (6) Use of IBD Medications During Pregnancy, (7) Use of IBD Medications During Lactation, (8) Pregnancy Adverse Events, (9) Fetal and Neonatal Adverse Events, and (10) Vaccines.

Table 2. Consensus Statements

Maternal factors impacting pregnancy	
1.	Children born to a parent with Crohn's disease may have a higher risk of developing inflammatory bowel disease than children born to a parent with ulcerative colitis.
Fertility	
2	Women with inflammatory bowel disease may have reduced fertility compared with women without inflammatory bowel disease due to reduced ovarian reserve.
3	Women with inflammatory bowel disease may undergo oocyte retrieval without an increased risk of flare.
Preconception counseling and optimization	
4	Women with inflammatory bowel disease desiring contraception should use long-acting reversible contraception over estrogen-containing contraceptives.
5	Women with inflammatory bowel disease should be in documented remission and medically optimized prior to elective conception.
Management of disease activity during pregnancy	
6.	Endoscopy during pregnancy among women with inflammatory bowel disease is low risk but should only be performed if it may change management.
7.	If cross-sectional imaging is needed during pregnancy, intestinal ultrasound and magnetic resonance imaging without gadolinium are preferred to computed tomography.
8.	Fecal calprotectin is useful for monitoring disease activity in pregnant women with inflammatory bowel disease.
Management of pregnancy	
9.	Pregnancies for women with inflammatory bowel disease should be considered as high risk for complications.
10.	Women with current or past history of rectovaginal fistulas should deliver by cesarean delivery.
11.	Women with inflammatory bowel disease should be assessed early in pregnancy or preconception for nutritional status, weight gain, and micronutrient deficiency.
Medications during pregnancy	
12	Women with inflammatory bowel disease who are pregnant and with active disease should start or optimize the same appropriate therapies as in nonpregnant patients, except for thiopurines, methotrexate, Janus kinase inhibitors, and sphingosine 1 receptor modulators.
13	In women with inflammatory bowel disease who continue thiopurines during pregnancy, precaution should be taken for intrahepatic cholestasis by measurement of liver enzymes, metabolite levels, and consideration of split dosing.
14	Women with inflammatory bowel disease who are pregnant and have infections, fistula, or pouchitis that require antibiotics may take an appropriate course of a low-risk antibiotic.
15	Women with inflammatory bowel disease may initiate or continue calcineurin inhibitors (cyclosporine and tacrolimus) during pregnancy with careful monitoring if there are no viable alternate treatment options available.
16	Women with inflammatory bowel disease who are pregnant or attempting conception should continue biosimilars to existing biologics.
17	Women with inflammatory bowel disease who are pregnant or attempting conception should continue anti-interleukin-23 therapy throughout pregnancy (mirikizumab, risankizumb, guselkumab).
18	Women with inflammatory bowel disease should discontinue ozanimod at least 3 months prior to conception unless there is no effective alternative therapy to maintain maternal health.
19	Women with inflammatory bowel disease should discontinue etrasimod at least 1 to 2 weeks prior to conception unless there is no effective alternative therapy to maintain maternal health.
20	Women with inflammatory bowel disease should discontinue tofacitinib at least 4 weeks prior to conception unless there is no effective alternative therapy to maintain maternal health.
21	Women with inflammatory bowel disease should discontinue upadacitinib at least 4 weeks prior to conception unless there is no effective alternative therapy to maintain maternal health.
22	Women with inflammatory bowel disease should discontinue filgotinib at least 4 weeks prior to conception unless there is no effective alternative therapy to maintain maternal health.
Medications during lactation	
23	Mothers with inflammatory bowel disease currently on 5-aminosalicylates/sulfasalazine may breastfeed.
24	Mothers with inflammatory bowel disease currently on thiopurines may breastfeed.

Table 2. Continued

25	Mothers with inflammatory bowel disease currently on corticosteroids may breastfeed.
26	Mothers with inflammatory bowel disease currently on anti-tumor necrosis factor agents (infliximab, adalimumab, golimumab, certolizumab) may breastfeed.
27	Mothers with inflammatory bowel disease currently on anti-integrins (vedolizumab, natalizumab) may breastfeed.
28	Mothers with inflammatory bowel disease currently on anti-interleukin-12/23 and anti-interluekin-23 agents may breastfeed (ustekinumab, risankizumab, mirikizumab, guselkumab).
29	Mothers with inflammatory bowel disease currently on biosimilars may breastfeed.
30	Mothers with inflammatory bowel disease currently on sphingosine 1 receptor modulators (etrasimod or ozanimod) should not breastfeed.
31	Mothers with inflammatory bowel disease currently on Janus kinase inhibitors (tofacitinib, upadacitinib, filgotinib) should not breastfeed.
Pregnancy adverse events	
32	Controlling disease activity during pregnancy among women with inflammatory bowel disease is critical to reduce adverse outcomes.
Vaccines	
33	Inactive vaccines should be given on schedule to infants of women with inflammatory bowel disease regardless of in utero inflammatory bowel disease medication exposure.
34	Children exposed to Janus kinase inhibitors or sphingosine 1 receptor modulators in utero may receive live vaccines after 1 month of age.
35	Live vaccines can be given to infants of mothers breastfeeding while on biologics.

Table 3. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Strength of Recommendations, Quality of Evidence, and Implications for the Patients and Clinicians[3]

Strength of recommendation	Criteria
Factors influencing the strength of the recommendation include the quality of the evidence, clinical and patient-reported outcomes, risk of harm, and costs/health care resource utilization.	
Strong	Strong recommendations are offered when the desirable effects of an intervention clearly outweigh the undesirable effects. Implications from a patient and clinician perspective: **Patients:** Most individuals in this situation would prefer the recommended course of action and only a small proportion would choose an alternative. **Clinicians:** Most patients should receive the recommended course of action or an alternative with similar strength of recommendation.
Conditional	Conditional recommendations are offered when trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced. Implications from a patient and clinician perspective: **Patients:** Some individuals would want the suggested course of action, whereas others may not. A discussion regarding pros, cons, and available alternatives is appropriate to reach an individualized patient-specific decision. **Clinicians:** A shared decision-making model through a discussion regarding the available evidence and alternative options is appropriate, taking into consideration the values and preferences of the patient.

Quality of evidence	Criteria
High	We are very confident that the true effect closely aligns with that of the estimate of the effect.
Moderate	We have a moderate level of confidence in the estimate of effect. It is likely that the true effect is close to the estimate of the effect.
Low	Our confidence in the effect estimate is limited. The true effect could differ from the estimate of effect.
Very low	We have very little confidence in the effect estimate. The true effect may be substantially different from the estimate of effect.

Definitions

RAND panels require specific definitions and assumptions to manage the impractical number of scenarios if we tried to address every possible combination of variables. These definitions and assumptions were made clear to the panel before any voting took place. For example, we defined medication use during pregnancy as use in the 3 months prior to pregnancy and/or at any point during pregnancy (at any dose) prior to delivery.

Literature Review

We conducted literature searches under each section using MEDLINE from inception to December 2023 using keywords for each content subgroup. The literature review, including summaries for each subgroup, was distributed to all the panelists prior to the first round of ratings.

Appropriateness Panel. The panel consists of the 39 members of the PIANO global consensus consortium, composed of gastroenterologists and specialists in teratology, colorectal surgery, lactation, and maternal–fetal medicine. These specialists represent each continent and are all engaged in the care and study of women with IBD. These members were selected based on publication records, clinical experience in care of IBD patients during pregnancy, geographic location, leadership in major gastroenterology societies, and representatives from nongastrointestinal collaborating societies including the Society for Maternal–Fetal Medicine and Organization of Teratology Information Specialists. Seven global patient advocates also took part in the process with review of statements and voting.[12] The goal of the panel was to rate the level of appropriateness for each statement.

Concepts of importance for each subgroup were identified in the population, intervention, comparison, outcome (PICO) format when possible. Literature searches were performed for each question from PubMed (MEDLINE) utilizing MeSH headings and keywords specific to the PICO. Group participants then reviewed output and provided literature in a hierarchical format for each statement (as there are no randomized controlled trials in pregnant patients with IBD, and systematic reviews and large cohort studies were prioritized). A literature summary including the full-text articles was made available to all PIANO global consensus participants. After receiving the literature summary, panelists confidentially rated the proposed elements for appropriateness on a 1 to 9 scale (1–3: inappropriate, 4–6: uncertain, 7–9: appropriate). Median scores were calculated and rounded up, so that a median score of 3.5 was rated as uncertain, whereas a median score of 6.5 was rated as appropriate. To quantify the level of agreement, a RAND disagreement index (DI) was calculated for each statement using a standard published equation.[8] A DI greater than or equal to 1.0 indicates extreme variation, whereas DI values less than 1.0 reflect general agreement. The DI expresses the spread of responses and is calculated using a previously described approach and the following formula:

$$DI = \frac{66\ \%ile - 33\ \%ile}{2.35 + \left(1.5^{*}\left(\frac{66\ \%ile + 33\ \%ile}{2}\right)\right)}$$

Statements in which ratings met criteria for disagreement were rated "uncertain" regardless of the median appropriateness score. Panelists convened 4 weeks after the initial voting at a moderated, in-person, 2-day meeting. During this meeting, highly rated and controversial elements were discussed in detail, and primary literature was reviewed again, after which time panelists confidentially rerated each proposed element. When there was inadequate data to make a formal statement but the authors felt the question was common and of importance, a discussion and participants' shared clinical experience were noted.

Maternal Factors Impacting Pregnancy Outcomes to Be Addressed in Counseling

GRADE statement	Recommendation	Level of evidence
1. We suggest counseling that children with first-degree relatives with IBD, as compared with those without, have an increased risk of IBD development	Conditional	Low

Consensus statement
1. Children born to a parent with Crohn's disease may have a higher risk of developing IBD than children born to a parent with ulcerative colitis

There are multiple, often interacting, maternal factors that can impact pregnancy outcomes. For many of them, data are only now emerging. Table 4 lists factors discussed subsequently.

Table 4. Maternal Factors Impacting Pregnancy Outcomes

Maternal risk factors
Familial risk
Impact of inflammation on placenta
Maternal smoking
Prenatal antibiotics use
Western diet
Maternal microbiome

Familial Risk

Genetics plays an important part in the pathophysiology of IBD, and hence, a family history is an important risk factor for developing IBD.[13] Most data on familial risk of IBD stem from population-based Scandinavian studies. A Danish cohort of 9238 children born to women with IBD and 1,371,407 born to women without IBD showed that exposure to maternal ulcerative colitis (UC) was associated with a hazard ratio (HR) of 4.6 (95% confidence interval [CI], 3.5–6.2) of developing IBD in the offspring, whereas exposure to maternal Crohn's disease (CD) was associated with an HR of 7.7 (95% CI, 5.7–10.5) of developing IBD in the offspring.[14] An earlier Danish study showed that offspring had a higher chance of developing the same type of IBD as their parents.[15] Prevalence proportion ratios (defined as the observed number of offspring with UC and CD, respectively, divided by the expected numbers) were higher for the offspring of parents with CD compared with UC.[15] The risk of developing IBD in offspring was 6.26% (95% CI, 4.9%–7.9%) if the parents had UC and 9.2% (95% CI, 6.3%–13.0%) if the parents had CD.[15] Data from Sweden reported familial IBD in 5.4% of patients with UC and 6.5% of patients with CD.[16] The relative risk of UC was 3.9 (95% CI, 3.5–4.3) and that of CD was 6.0 (95% CI, 5.4–6.7) in offspring of affected parents.[16] A Korean study also found a higher risk of developing IBD in offspring born to parents with CD rather than UC.[17] In contrast to most studies reporting a higher risk for children born to a mother with CD, in a Swedish analysis, the risk of developing IBD in offspring appeared similar between CD vs UC and maternal vs paternal exposure.[18]

Population studies from multiple countries have shown an increased adjusted incidence rate ratio (aIRR) of IBD in first-degree relatives, with the aIRR for relatives of patients with CD to be 7 to 22 and patients with UC to be 4 to 10 compared with those without a family history.[13,17] The occurrence of any IBD in offspring of patients with UC was approximately 6%, compared with 9% of patients with CD in an early Danish population study.[15] The strength of the association of IBD in offspring is greater with an increasing number of first-degree relatives, a younger age at diagnosis, and a diagnosis of CD.[18] In addition, the risk within generations (siblings) is higher than that of between generations (parent to offspring).[13,17]

Older cohort studies suggested an increased risk of maternal transmission of susceptibility; however, subsequent population studies showed an equivalent risk between parents. In a small 1997 study of multiplex families, the risk of transmission of susceptibility was higher from mother to child than from father to child, with the effect seen only in non-Jewish pairs with CD.[19] In a large Korean population study of 21 million persons, the incidence rate ratio (IRR) of CD among offspring of CD-affected fathers was 9.4 (95% CI, 6.8–13.0), compared with 6.5 (95% CI, 4.2–10.3) among offspring of affected mothers. The risk of UC among offspring of parents with UC was lower than that for CD but still not statistically different between parents, with an IRR of 7.1 (95% CI, 6.1–8.3) among offspring of affected fathers and of IRR 8.8 (95% CI, 7.5–10.3) for those with affected mothers ($P = .81$).[17]

In a Danish population study of concordant parent–offspring pairs, it was found that an aIRR of UC for offspring of fathers with UC was 4.3 (95% CI, 3.7–4.9), compared with mothers with UC (3.7; 95% CI, 3.2–4.3). The IRR of CD in offspring of fathers with CD was 7.5 (95% CI, 6.4–8.9), not significantly different from mothers with CD (6.4; 95% CI, 5.1–8.0).[13]

Cesarean delivery (CS) has been inconsistently associated with an increased risk of IBD in the offspring of mothers without IBD.[20] However, there are no data to support the mode of delivery as a risk factor for the development of IBD among the offspring of mothers with IBD themselves.[21]

Placental Function and Inflammation

The placenta is the most unusual human organ.[22] It is the first organ to become fully functional but ages rapidly as its lifespan is matched to the 9-month length of pregnancy. Given its rapid growth, steep decline near birth, and many unusual functions, it is not surprising that abnormal placentation is associated with major obstetrical syndromes. Preterm preeclampsia, the sudden and new onset of hypertension, and other signs of maternal vascular damage, is associated with shallow placentation and a failure of cytotrophoblasts to adequately remodel spiral arteries, restricting blood flow to the placenta and impairing fetal growth.[23]

Accordingly, the impact of preexisting maternal inflammatory conditions like IBD on pregnancy outcomes is under investigation. Given the placenta's critical role in normal pregnancy and pregnancy complications, it seems likely that IBD is negatively impacting its development and/or function. Whether the mechanisms include chronic inflammation remains to be determined. A small study of placentas from 14 patients failed to detect inflammation,[24] but much more extensive analyses are needed to reach a firm conclusion. Likewise, investigations at RNA and protein levels will give important information about the placental pathways that could contribute to poor pregnancy outcome among these patients.

Maternal Smoking and Risk of IBD in Offspring

A meta-analysis, including 9 studies, has reported an association between tobacco smoke during pregnancy and diagnosis of IBD in the offspring (odds ratio [OR], 1.5; 95% CI, 1.2–1.9).[25] However, there was no significant association after considering the IBD subtype (CD: prevalence OR [pOR], 1.2; 95% CI, 0.8–1.9; $I^2 = 83.55\%$, based on 6 studies, and UC: pOR, 1.5; 95% CI, 1.0–2.3; $I^2 = 68.05\%$, based on 4 studies).[25] In a later population-based cohort study, offspring of smoking mothers were found to have an increased risk of IBD than those born to nonsmoking mothers (OR, 1.5; 95% CI, 1.2–1.8; $P < .01$).[26]

Prenatal Antibiotic Use on IBD Risk in Offspring

Preclinical studies have also shown that prenatal antibiotic use can lead to an increased risk of IBD in offspring.[27–29] Murine studies demonstrate that administering antibiotics during pregnancy had significant effects on the offspring's microbiome, leading to reduced bacterial diversity[28] and gut dysbiosis.[27] This may influence the immune response of the offspring and increase their susceptibility to developing colonic inflammation in either a chemical-induced murine model of colitis[28] or a genetically prone murine model.[27] Moreover, a study in mice showed that an increased risk of IBD in offspring following prenatal antibiotics may be attributed to the transmission of an antibiotic-perturbed microbiota from mothers to their children.[29]

Epidemiological data have consistently shown that prenatal antibiotic use is associated with an increased risk of IBD.[30] A meta-analysis of cohort and case–control studies demonstrated an association between antibiotic exposure during pregnancy and subsequent diagnosis of IBD in the offspring (OR, 1.75; 95% CI, 1.2–2.5; $I^2 = 0$).[25,31] In a population-based study, intrauterine antibiotic exposure was associated with an increased risk of very-early-onset IBD (adjusted HR [aHR], 1.93; 95% CI, 1.1–3.5). This risk is increased for CD (aHR, 2.5; 95% CI, 1.0–6.1) but not for UC (aHR, 1.3; 95% CI, 0.5–3.3).[31] The highest risk of very-early-onset IBD was seen in mothers exposed to antibiotics in the third trimester of pregnancy (aHR, 2.6; 95% CI, 1.1–6.0).[31] In a recent population-based study, exposure to $\geq$3 courses of antibiotics was associated with an increased risk of IBD (aHR, 1.3; 95% CI, 1.0–1.6).[32] This was driven by UC (aHR, 1.5; 95% CI, 1.1–2.0) but not CD (aHR, 1.2; 95% CI, 0.8–1.6) risk.[32] Although a population study showed maternal antibiotic exposure during pregnancy was not associated with IBD onset in the offspring,[33] the cohort focused on an at-risk population (with a family history of IBD), which may have overshadowed the effects of prenatal antibiotics.

To date, most studies related to intrauterine antibiotic exposure and risk of IBD in offspring have been limited to studies in non-IBD mothers, but there are some plausible biological explanations highlighting the natural diminution of both the resilience and range of microbes in the gut microbiome, which antibiotic use is likely to compound. Limiting prescriptions for antibiotics may help lower the risk of IBD. However, it is important to note that antibiotics for appropriate indications, such as group B Streptococcus (GBS), should be given to pregnant mothers with IBD.[34] Most early-onset GBS infections (in infants aged 0–6 days) could be prevented by giving intravenous antibiotics during labor to women whose infants are at an increased risk of developing GBS infection.

Western Diet in Mothers With IBD and IBD Risk in Offspring

The notion that maternal diet may shape the risk of disease in offspring has been examined in intervention studies of allergic conditions. Probiotic intake in late pregnancy and during lactation has been shown to reduce the risk of eczema in children.[35] Women with IBD may be more likely to have children with IBD than fathers with IBD, with the highest risk if the mother already has IBD at the time of birth.[36] These findings suggest that there are early environmental triggers for the development of IBD, such as maternal diet during pregnancy, which may shape the acquisition of the microbiome and alter the risk. In the GEM (Genetics, Environmental, Microbial) cohort,[36] mothers were not asked about diet during pregnancy; thus, we do not know whether specific diets influence the risk of developing IBD in offspring.

Longitudinal studies have been performed to examine the risk factors for childhood IBD. In North America, mothers of patients with UC and CD took vitamin, mineral, and iron preparations during pregnancy significantly less frequently than mothers of controls.[37] The Norwegian Mother and Child Cohort Study (MoBa) study includes about 95,000 pregnant women recruited

throughout Norway from 1999 to 2008 and included a subset of women with IBD. The same study found that women with IBD consumed less dairy protein during pregnancy; compared with those who consumed higher levels, their children were less likely to be small for gestational age (SGA).[38]

The MOMMY-IBD (Mother-to-Infant Transfer of Bacteriome, Virome, Fungome, and Metabolome in Health) study, from 3 sites in Hong Kong and Mainland China, is a prospective longitudinal birth cohort aiming to explore the role of maternal diet and gut microbiota in IBD mothers and their impact on infants' health. The study found that IBD mothers had higher food additive (FA: substances added to food to preserve flavor or enhance taste, appearance, or longevity) intake than non-IBD mothers, and FA intake was associated with depletion in gut Bacteroides species and enrichment in Streptococcus species in mothers with IBD. In addition, fecal calprotectin (FC) levels were significantly higher in the gut of infants born to mothers with higher FA intake in IBD and non-IBD groups.[39] For now, most of the data that suggest altering diet in the mother affects the risk of IBD in offspring come from mouse models and thus are difficult to extrapolate.

Diet may have an impact on the microbiome or on breast milk, and the microbiome itself can also impact breast milk composition.[40] For example, maternal consumption of probiotics and lactation protected against eczema, and fish oil supplementation during pregnancy and lactation may reduce the risk of egg allergies in offspring. These data support the idea that diet during pregnancy of a mother with IBD may change the risk of these conditions in their offspring.[35]

Maternal Microbiome Impact on Pregnancy and/or Risk of IBD in Offspring

Alterations in the maternal microbiome during pregnancy may be associated with an increased risk of adverse pregnancy outcomes.[41] Disruptions in the microbiome can lead to inflammation and immune dysregulation,[42] which are believed to be involved in the development of pregnancy complications. However, data are limited as to how maternal microbiome may impact the risk of IBD in offspring. The best evidence to date is based on one human study, which showed that abnormal gut microbiota composition persisted in mothers with IBD during pregnancy and was associated with changes in bacterial diversity and abundance of bacteria species in the infant's stool.[43] In germ-free mice, a dysbiotic microbiota triggered abnormal imprinting of the intestinal immune system.[43] Additionally, a preclinical study reported that an antibiotic-perturbed maternal microbiota could be transferred to their offspring and resulted in worsened colitis in susceptible mice.[29] In addition, in the MOMMY-IBD study, altered gut bacteria and virome persisted in IBD mothers during pregnancy and up to 18 months postpartum and were associated with reduced "commensal" bacteria strain sharing in IBD mothers and their infants. The authors found that CS and maternal antibiotic exposure led to decreased vertical transmission of beneficial bacterial communities in infants.[44] Fecalibacterium species, *Alistipes onderdonkii* and *Gemmiger formicillus*, were depleted in mothers with IBD from pregnancy until 6 months postpartum. CD and maternal antibiotics were associated with reduced transfer of bacterial communities from mothers to infants, and this observation was more pronounced in mothers with IBD.

Some prevention studies have been reported that targeted the maternal microbiome to alleviate intestinal inflammation in offspring. A preclinical animal study found that maternal *Lactobacillus reuteri* supplementation altered the gut microbiome in offspring mice and further prevented female offspring from experimental colitis.[45] There is an ongoing clinical trial, MELODY (Modulating Early Life Microbiome through Dietary Intervention in Pregnancy), which aims to improve the microbiome composition of pregnant women with CD to determine the effectiveness of anti-inflammatory dietary intervention in restoring the microbiome during early life in the offspring, thereby promoting priming of a healthy immune system.[46] Such an approach is promising, but long-term follow-up will be needed to confirm if dietary intervention in early life can reduce the risk of colitis.

Fertility

GRADE statement	GRADE recommendation	Level of evidence
2 We suggest counseling that women with IBD may have decreased fertility compared with women without IBD.	Conditional	Very low
3 In women with UC, we suggest counseling that prior ileal pouch–anal anastomosis is associated with decreased Fertility when compared with women with UC who have not had ileal pouch–anal anastomosis	Conditional	Very low
4 In women with IBD, we recommend counseling that active disease increases the risk of infertility as compared with inactive disease	Strong	Very low
5 We suggest counseling that women with IBD may have comparable effectiveness of	Conditional	Very low

Continued

GRADE statement	GRADE recommendation	Level of evidence
assisted reproductive therapy when compared with women without IBD, as measured by live birth		
6 We suggest counseling that women with IBD who have undergone pelvic surgery for IBD have similar effectiveness of in vitro fertilization when compared with women without IBD, as measured by live birth.	Conditional	Very low

Consensus statement	
2	Women with IBD may have reduced fertility compared with women without IBD due to reduced ovarian reserve
3	Women with IBD may undergo oocyte retrieval without an increased risk of flare

Fertility Among Women With IBD

In an epidemiologic context, *fertility* refers to the actual production of offspring, rather than the physical capability to reproduce, which is termed *fecundity*. The terminology in the field of epidemiology is influenced by the fact that data are collected from registers, where parameters such as birth and death are mostly used. Live birth is not necessarily the best way to define fertility, as studies concerning fertility in patients who undergo assisted reproduction also examine biochemical and clinical pregnancy. These varied definitions can be confusing and make the overall data of lower quality as there is no singular definition of fertility.

While fertility can be measured, fecundity cannot. *Fecundability* measures the degree of fecundity and is the probability of a pregnancy, during a single menstrual cycle, in a woman with adequate exposure to sperm and no contraception, culminating in a live birth. Fecundability depends on the timing and frequency of coitus, as well as on other biological parameters. Similarly, the definition of infertility relies on a restricted time period in population-based studies, whereas *sterility* is a permanent state of infertility. From an epidemiologic point of view, fecundity is limited to the biological ability to reproduce, whereas fertility beyond fecundity is dependent on several demographic, socioeconomic, and anthropometric factors. Such factors are stress, emotional and reproductive health, willingness, availability of a potential mating partner, and preventive measures being taken.[47]

A recent systematic review on fertility in IBD, which included 14 studies of different design and quality (large unselected cohorts, single-center cohort studies, multicenter case–control studies), suggested similar infertility rates in women with UC and somewhat reduced fertility in women with CD compared with the general population.[48] The authors also concluded that voluntary childlessness might have played a role. The findings of the most recent large population-based cohorts demonstrate similar results, with slightly decreased fertility in women with IBD, mainly in those with CD and less so or only marginally in females with UC.[48–50] Furthermore, potential impact of voluntary childlessness and overall improvement in fertility over time have been demonstrated in these studies.

A national cohort study from Sweden including over 20,000 females with IBD demonstrated slightly decreased fertility rates in women with IBD compared with age-matched controls from the general population.[49] Fertility was impaired in all IBD subtypes, but mostly in women with CD (HR, 0.88; 95% CI, 0.85–0.91) and IBD unclassified (IBD-U) (HR, 0.86; 95% CI, 0.83–0.89) and only marginally decreased in women with UC (HR, 0.96; 95% CI, 0.93–0.98). During the study period from 1964 to 2014, fertility rates improved in women with UC and IBD-U compared with population norms in the last decade but remained lower in those with CD. An increasing number of bowel resections (all IBD subtypes) and perianal disease in CD were associated with reduced fertility. Of note, women with IBD used contraception more often than their matched controls.[49]

Fertility After Surgery

The quality of evidence on the effect of surgery on fertility in women with UC is very low, making firm conclusions difficult as existing data are primarily observational. Furthermore, data on the impact of specific surgical interventions on fertility in UC are limited. The most recent meta-analysis by Sriranganathan et al assessed the impact of ileal pouch–anal anastomosis (IPAA) surgery on female fertility in UC and included 13 studies with 793 patients pre-IPAA and 802 post-IPAA. The relative risk of infertility in the IPAA group was 4.17 (95% CI, 1.99–8.74), with the mean rate of infertility in the pre-IPAA and post-IPAA groups of 13.26% and 42.97%, respectively.[51] A subsequent sensitivity analysis with omission of 4 studies due to heterogeneity ($I^2 = 26\%$; $P = .21$) found the relative risk of infertility in the IPAA group was attenuated but remained elevated at 2.96 (95% CI, 1.95–4.50).[51] The findings are consistent with 2 previous meta-analyses.[52,53] However, these data were not replicated in a recent systematic review by Lee et al, which suggested that the fertility rate after IPAA was no lower than that of women with medically treated UC.[54] Although the authors reported a nonsignificantly

increased relative risk of infertility of 5.45 (95% CI, 0.41–72.57), only 2 studies were included due to strict inclusion criteria, making it difficult to draw any firm conclusions due to the small sample size and lack of precision. In a Swedish population-based study by Druvefors et al including 1191 patients with UC, the impact of reconstruction and proctectomy in UC on fertility was compared with the fertility of women with ileostomy and the rectum remaining intact. The authors adjusted for age at disease onset, year of colectomy, and parity at colectomy.[55] Compared with colectomy only, fertility remained unaffected after IRAA (HR, 0.86; 95% CI, 0.63–1.17) but was impaired after IPAA (HR, 0.67; 95% CI, 0.50–0.88) and after completion of proctectomy (HR, 0.65; 95% CI, 0.49–0.85).

Although a laparoscopic approach may be of less risk to fertility, data are sparse. Two cross-sectional studies have investigated the role of laparoscopic vs open IPAA on fertility in UC. Bartels et al surveyed 37 patients with UC and found that those with a laparoscopic IPAA had a significantly shorter time to spontaneous pregnancy ($P = .033$).[56] In the laparoscopic group, 11 (55%) became pregnant within 12 months of attempting in comparison with 6 (35%) in the open group. Gorgun et al reported no difference in infertility rates between laparoscopic and open groups but a significant reduction in time to pregnancy in the laparoscopic group.[57] As the mechanism behind fertility loss after surgery is thought to be adhesions, there are no data to support ovarian cryopreservation prior to surgery at this time.

Effect of Disease Activity on Fertility

Disease activity in women with IBD has been consistently demonstrated to have a negative impact on several aspects of reproductive health, including fertility. In a recent systematic review of cohort and case–control studies on fertility of women with nonsurgically managed IBD, 2 of the 13 included studies looked at the impact of disease activity on fertility.[48] A population-based cohort study from the United Kingdom, which used corticosteroid prescriptions as a surrogate marker of disease activity, demonstrated decreased fertility in women with disease flare compared with those with disease in remission or females without IBD.[58] Adjustment for contraception use in women with disease flare, calculation of age-specific fertility rate ratios, and separate analyses for CD and UC revealed consistent results with decreased fertility in periods following flares.[58] The national cohort study from Sweden includes over 20,000 females with IBD and compared their fertility with that of the general population. Using hospital admissions due to IBD as a proxy measure of disease activity, there was an association between hospital admissions and a lower chance of giving birth in women with IBD, mainly in those with UC and IBD-U.[49]

Longitudinal trends in pregnancy rates in women with IBD were studied in a population-based study from Canada.[50] In that study, the authors defined disease severity as any hospitalization or corticosteroid or biologic dispensation within 180 days prior to the estimated date of conception. Compared with women with CD in remission, those with severe disease were less likely to become pregnant in the subsequent 9 months and have a child (aIRR, 0.68; 95% CI, 0.47–0.99 for pregnancy and aIRR, 0.57; 95% CI, 0.35–0.93 for live births). No significant difference was observed for women with UC.[50] Another nationwide population-based cohort study from Korea investigated the impact of disease severity on pregnancy outcomes.[59] Women with moderate to severe disease, defined as those utilizing steroids or anti-tumor necrosis factor (anti-TNF) agents for a specified time period or previous intestinal resection, had lower live birth rates compared with a control group of randomly selected pregnant women without IBD.[59]

A recently published population-based Swedish study examined fertility as calculated by fertility rate (live births per 100 person-years [PYs] of follow-up) and fertility rate ratio where a result of <1.00 indicated reduced fertility. The authors examined histologic inflammation and clinical disease activity as measured by IBD-related surgery, hospitalization, corticosteroid dispensing (either systemic or locally acting), or initiation of an immunomodulator (eg, thiopurine) or advanced therapies, including biologics, within the past 6 months. Additionally, the authors excluded voluntary childlessness by identifying patients who used contraception. The authors found a reduction of fertility with histologic inflammation in IBD as compared with histologic remission, even in the absence of clinically defined disease activity.[60] Finally, a systematic review on ovarian reserve in women with IBD reported that although patients with IBD in remission have a similar ovarian reserve to the general population, those in active stage have a significantly impaired ovarian reserve.[61]

Assisted Reproductive Technology Success in IBD

Data on the efficacy of assisted reproductive technology (ART) in women with IBD are conflicting. Several cohort studies investigating the success rates of ART in IBD have been performed; 3 found no significant difference in live birth rates between women with UC, CD, or controls.[62–64] In a large Danish registry study, Friedman et al compared 381 women with UC, 158 women with CD, and 50,321 women without IBD receiving first-time ART with a follow-up time of 18 months.[63] In women with either CD or UC, there was a notable reduction in live birth rates when compared with the general population, but this did not reach statistical significance. However, in women with CD with prior CD-related surgery, the adjusted odds ratio (aOR) of a live birth was

significantly decreased when compared with women who had not undergone CD-related surgery (aOR, 0.29; 95% CI, 0.13–0.65). In contrast, previous UC surgery did not impact live birth rates.[63]

There are data to suggest that ART may be less effective in women with IBD. Nørgård et al performed a nationwide Danish health registry study including 432 patients with UC, 182 with CD, and 52,489 women without IBD.[65] For each embryo transfer, the chance of a live birth was significantly reduced following ART in women with UC (OR, 0.73; 95% CI, 0.58–0.92). In an analysis of patients with CD, combining medically treated and surgically treated subjects, a reduction in live birth rates was not significant in women with CD as compared with controls (OR, 0.77; 95% CI, 0.52– 1.14). However, surgery for CD before ART treatment significantly reduced the chance of a live birth for each embryo transfer (OR, 0.51; 95% CI, 0.29–0.91).

In a systematic review of 11 studies, which included a meta-analysis of 4 studies,[66] women with CD (with and without prior surgery), compared with the general population, had reduced odds of live births (OR, 0.67; 95% CI, 0.53–0.85) per cycle of ART. Rates of live births were further impacted following CD-related surgery (49%–71% lower after surgery). In contrast, ART live birth rates were not reduced in women with medically managed CD. Women with UC had no difference in live birth rates (OR, 0.88; 95% CI, 0.67–1.17). For women with UC, the chance of a live birth seems to be reduced only in women with a failed IPAA surgery (defined as the need for removal or replacement). Laube et al reported on 5 cohort studies that have examined the effect of UC surgery on the efficacy of ART, and only 3 of these studies specify the surgery as an IPAA.[63,65–68] Three cohort studies demonstrated no difference in ART live birth rates in women with previous UC-related surgery, including IPAA, compared with women with medically managed UC.[63,65,69] Nørgård et al compared women with UC and prior surgery to women with IBD and no prior surgery and found no decreased chance of a live birth (aOR, 0.91; 95% CI, 0.61–1.36).[65] Friedman et al compared women with UC and prior UC surgery to women with UC and no prior surgery and found no decreased chance of a live birth (aOR, 0.81; 95% CI, 0.47–1.40).[63] Pachler et al compared women with UC with an IPAA with women with UC and no surgery and found no decreased chance of a live birth (aOR, 0.8; 95% CI, 0.6–1.1).[69] However, Pachler et al found that women with a failed IPAA had a significantly lower live birth rate after in vitro fertilization compared with women with medically managed UC (aOR, 0.36; 95% CI, 0.4–0.92), whereas women with a functional RPC had comparable in vitro fertilization success (aOR, 0.43; 95% CI, 0.16–1.14).[68]

It should be noted that the efficacy of ART was measured in different ways in these studies. Nørgård et al measured the chance of a live birth per ART treatment cycle.[65] Friedman et al measured the chance of a live birth after the first ART treatment per woman rather than per ART cycle.[63] The outcome was at least 1 live birth within the period of 18 months. Pabby et al measured the cumulative chance of a live birth after 6 cycles.[67] Additionally, these studies measured live births and not pregnancies and do not examine where in the process the risk of delivering a live-born child decreased. Friedman et al examined the chance of a confirmed pregnancy (positive human chorionic gonadotropin or ultrasound) in women with CD or UC undergoing ART.[70] They found that women with CD and UC have a reduced chance of conceiving per ART cycle (CD: aOR, 0.75; 95% CI, 0.51–1.10; UC: aOR, 0.67; 95% CI, 0.53–0.84). However, women with CD or UC did not have a reduced chance of carrying the pregnancy to term. Thus, a reduced chance of a live birth after ART in women with UC and CD might be due to a failure to achieve a pregnancy rather than a failure of carrying the pregnancy to term.

Ovarian Reserve Among Women With IBD

Ovarian reserve is defined by the number of primary follicles available in the ovarian cortex and can be used to provide information about female fertility. The level of anti-Müllerian hormone (AMH) is one of the most widely used modalities to evaluate ovarian reserve.[71] AMH levels cannot predict fertility and should be used only in the context of an evaluation for assisted reproduction. The impact of IBD on ovarian reserve is largely unknown and limited to small retrospective cohort or case–control studies in women with CD, with almost no data in UC. Although the results of these studies are conflicting, most do appear to show reduced ovarian reserve in women with IBD. The only factors that have consistently been associated with reduced ovarian reserve are age $\geq$30 years and active disease.[61,71–77] Recently, a systematic review and meta-analysis of 9 studies with data from 2386 IBD records and 149,742 matched controls was published.[76] Compared with women without IBD, women with IBD had significantly lower AMH levels. Patients below 30 years of age had comparable AMH levels when compared with the control group, whereas women over the age of 30 years had levels that were significantly lower. This study also suggested that active IBD is associated with reduced ovarian reserve.[61] Similar results were seen in another meta-analysis of 7 studies where ovarian reserve function was significantly lower in IBD women of reproductive age than in healthy women.[77]

Oocyte Retrieval in IBD

It has been hypothesized that exogenous sexual steroids may increase the risk of a flare in women with autoimmune diseases, including IBD. Although many infertile women with IBD undergo ART, there are no

published data on the chance of an IBD flare during egg harvesting. Nørgård et al examined the impact of treatment with gonadotropin-releasing hormone agonist vs antagonist in women with IBD undergoing ART.[78] The authors found no impact of hormone treatment protocol on the chance of a live birth. Flares of IBD at the time of egg harvesting were not examined.

Similarly, there are limited data evaluating the impact of IBD medications on the efficacy and safety of ovarian stimulation and egg harvesting, and data stem from the general medical literature.

The best data are for methotrexate (MTX), which is a known teratogen when given in the first trimester of pregnancy and should be discontinued at least 1 month before conception.[79] However, the impact of MTX on the success and safety of oocyte retrieval from studies of ART are conflicting. A retrospective cohort study reported a poor response to ovarian stimulation following MTX treatment for ectopic pregnancy.[80] In contrast, a large cohort study suggested that MTX had no adverse effects on ovarian reserve and outcomes in women undergoing ART.[81] Although there are no data in the setting of IBD, a prospective cohort study of 72 women with recent-onset rheumatoid arthritis (RA) demonstrated no significant difference in AMH values after 6 months of treatment comparing patients who did or did not receive MTX.[82]

Corticosteroids have been evaluated as an adjunctive therapy during oocyte stimulation in women undergoing ART, with conflicting results. Nørgård et al examined whether corticosteroids prior to embryo transfer cycles improved the rate of live birth in women with CD or UC. They examined the efficacy of ART in 2408 embryo transfers in women with CD or UC exposed to corticosteroids vs women with CD or UC not exposed to corticosteroids within 3 months of the date of embryo transfer. Results were adjusted for the use of IBD medications within 6 months prior to embryo transfer (azathioprine/mercaptopurine, 5-amino salicylic acid [5-ASA], and anti-TNF therapy). Corticosteroid prescriptions prior to transfer had no effect on the rates of biochemical pregnancy (positive human chorionic gonadotropin), clinical pregnancy (positive ultrasound), or live birth.[83]

A second study by Nørgård et al examined the impact of medical therapies in women with IBD or RA prior to ART cycles on live birth. The exposed cohort included 1824 embryo transfers in women with RA or IBD. Of these, 22.8% had CD, 40.1% had UC, and 38.4% had RA. There were a total of 97,191 embryo transfers in women without RA and IBD. The authors stratified results according to IBD vs RA and examined specific factors related to ART in each group. There was an increased chance of having a live birth in women with IBD treated with corticosteroids within 3 months prior to embryo transfer vs the general population (aOR, 1.20; 95% CI, 1.12≥1.30). Exposure to 5-ASA or azathioprine/mercaptopurine within 6 months of embryo transfer did not affect the chance of a live birth. Exposure to a biologic therapy was associated with a decreased chance of a live birth (aOR, 0.61; 95% CI, 0.39–0.96). Although these 2 papers examined the same groups of patients from the Danish health registries, the unexposed cohorts were different. In the first study, the exposed cohort included women with CD or UC, and in the second paper, the unexposed cohort included women in the general infertile population in Denmark.[78,83]

A recent meta-analysis that included 1391 infertile patients who underwent 1497 cycles of ART failed to show a significant effect of corticosteroids on live birth rate, abortion rate, and implantation rate when compared with controls.[84] Although corticosteroids were not effective, no safety signals were observed.

Prolongation of the QT interval, although uncommon, is a recognized side effect of gonadotropin-releasing hormone agonists, and it has been suggested that the concurrent use of sphingosine-1-phosphate (S1P) modulators (ozanimod, etrasimod) should be avoided due to the same risk from the S1P agents.[85]

There are no data evaluating the impact of 5-ASA, thiopurines, biologics, or Janus kinase inhibitors (JAKis) on the efficacy and safety of ovarian stimulation and egg harvesting in the literature regardless of whether there was a diagnosis of IBD. However, it is common clinical practice among the authors to continue these medications along with all biologics during egg harvesting with no anticipated flare.

Preconception Counseling and Optimization

GRADE statement	GRADE recommendation	Level of evidence
7 We recommend that women with IBD undergo preconception counseling	Strong	Low

Consensus statement
4 Women with IBD desiring contraception should use long-acting reversible contraceptives over estrogen-containing contraceptives
5 Women with IBD should be in documented remission and medically optimized prior to elective conception

Preconception Counseling Benefits and Recommendations

All women of childbearing age should be offered preconception counseling by their IBD care provider, ideally at least 6 months prior to attempting conception to confirm remission and optimize IBD maintenance medication use throughout pregnancy. Preconception

education should commence at the time of diagnosis for women of reproductive age or younger as well as with each new medication. Patients should know to advise their gastroenterologist of imminent conception plans and actual pregnancy. Dedicated individual pregnancy-related counseling for patients with IBD has the potential to improve patient knowledge, well-being, appropriate medication adherence, and disease activity perinatally and subsequently optimize pregnancy and infant outcomes.[86]

Women with IBD harbor unique fears and concerns relating to their disease and medications and the potential impact on their fertility, pregnancy, and offspring.[87] In this setting, higher rates of voluntary childlessness have been observed in women with IBD.[5] Voluntary childlessness has been linked to poor knowledge levels regarding IBD and pregnancy.[88,89] Women with IBD have commonly been found to have misconceptions surrounding pregnancy, such as overestimating concerns regarding fertility and perceived risks of continuing IBD medications while undervaluing the need to control inflammation.[88,90]

Questionnaire-based studies have identified that patients with IBD who had received counseling regarding medical treatment were less likely to be nonadherent during pregnancy.[91–93] One prospective study has specifically assessed the effect of preconception counseling in IBD. This single-center Dutch study compared patients with IBD who received preconception care in a dedicated IBD preconception clinic before they became pregnant (n = 155) with patients who were seen in the clinic after they were already pregnant (n = 162).[94] In this study, preconception care was associated with higher rates of IBD medication adherence during pregnancy (97.4% vs 86.4%; $P = .002$; aOR, 5.69; 95% CI, 1.88–17.27). Preconception care was also associated with reduced disease activity during pregnancy (18.5% vs 34.0%; $P = .05$; aOR, 0.51; 95% CI, 0.28–0.95). Additionally, the preconception care group had significantly higher rates of adequate folate intake and smoking cessation during pregnancy. In turn, those in the group who received preconception care were less likely to deliver low-birthweight infants (7.2% vs 12.6%; $P = .19$; aOR, 0.08; 95% CI, 0.01–0.48). There was no significant difference in other birth outcomes identified.

Even a single gastroenterologist-led consultation improves pregnancy-related knowledge,[86] as do online decision aids and educational portals.[95,96] Canadian data have shown that a dedicated IBD pregnancy clinic was associated with improved knowledge levels and infants with higher APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) scores.[97,98] Access to dedicated IBD-pregnancy clinics has also been associated with significantly reduced voluntary childlessness in women with IBD.[89] However, it is difficult to ascertain if multidisciplinary IBD pregnancy clinics yield improved maternofetal outcomes, particularly as patients may have higher rates of active disease when attending these services.[98,99] Medication safety is often the most important concern for women with IBD in relation to preconception and pregnancy and should be discussed carefully.[100]

General preconception recommendations include folate supplementation for at least a month prior to conception, ensuring that vaccinations are up to date and that the IBD is in established remission on a safe medication regimen (Table 5). Preconception and pregnant patients with IBD should follow standard prenatal care guidelines for inactive vaccinations such as influenza and pertussis.[101] Of note, women on thiopurines, small molecule, or biologic therapy should not receive live vaccines.

Preconception Disease Optimization

IBD should ideally be in remission for 3 to 6 months prior to conception to optimize pregnancy outcomes. Active disease at conception is predictive of active disease in pregnancy as well as an increased risk of adverse pregnancy outcomes, whereas inactive IBD at conception is associated with increased likelihood of maintaining disease remission throughout pregnancy and pregnancy outcomes in keeping with the non-IBD population.[102,103] A Danish cohort study demonstrated that disease activity, assessed by the Physician's Global Assessment (PGA), within 6 months of conception was associated with an increased risk of disease activity during pregnancy (aOR, 5.3; 95% CI, 3.5–8.2; $P < .001$), highlighting the importance of striving to achieve disease remission prior to conception.[103]

An assessment of clinical symptoms should be undertaken preconception, in addition to confirmation of disease remission with objective markers. Establishing steroid-free clinical remission as well as biochemical remission with an FC <150 ug/g and normal C-reactive protein (CRP) preconception is important. Additional endoscopy or imaging (intestinal ultrasound [IUS], magnetic resonance imaging, computed tomography [CT]) for disease activity assessment should be performed based on individual disease severity. A recent large nationwide Swedish cohort study found an association between histologic inflammation found on colorectal biopsy specimens and reduced birth rates in women with UC and CD.[60] However, this study did not incorporate corresponding endoscopic, biochemical, or radiologic disease activity data. Confirmation of adequate preconception thiopurine metabolites and anti-TNF levels is recommended per usual local practice. Documented remission is hence defined as steroid-free clinical remission along with objective biomarkers as appropriate. Being medically optimized prior to conception indicates establishment of a clinically effective therapy suited to the individual patient including adequate drug levels where applicable.

If disease is active, we recommend escalating therapy as appropriate, delaying conception until disease control is optimal for the patient and providing education

Table 5. Recommendations for Preconception Care

Preconception counseling and recommendations
• Cessation of smoking and other substances (alcohol, recreational drugs, opioids, cannabis) • Stop potentially teratogenic medications and ensure established remission on new therapy ■ Methotrexate: cease at least 1 month prior to conception ■ JAKi, S1P receptor modulators (see medication section) • Disease remission 3 to 6 months prior to conception using optimal therapy for pregnancy o Clinical and biochemical remission (normal C-reactive protein, FC <150) o Optimize serum drug concentrations (thiopurines, anti-TNF agents) o Endoscopic and/or radiographic remission ■ Intestinal ultrasound ■ Magnetic resonance enterography or computed tomography • Nutritional assessment • Prenatal vitamin containing folic acid at least 1 month prior to conception ■ 2 mg folic acid daily for 3 months prior to conception if on sulfasalazine ■ 5 mg folic acid daily if extensive small bowel disease, malabsorption, or family history of neural tube defects • Achieve ideal weight range and record baseline weight to monitor adequate GWG • Ensure vaccinations and cervical cancer screening up to date. Vaccinations include: ■ Annual influenza vaccine ■ Hepatitis B, MMR, varicella o MMR and varicella are live attenuated vaccines and therefore avoided if on high-dose steroid, thiopurine, and/or biologic therapy o Live vaccines should be administered 28 days prior to pregnancy • Preconception maternal–fetal medicine and/or colorectal surgeon review where relevant • Communicate IBD treatment plan to other members of health care team • Fertility specialist review if not pregnant after 6 months of timed intercourse • Encourage regular physical activity

FC, fecal calprotectin; GWG, gestational weight gain; IBD, inflammatory bowel disease; JAKi, Janus kinase inhibitor; MMR, measles-mumps-rubella; S1P, sphingosine-1-phosphate; anti-TNF, anti-tumor necrosis factor.

regarding the maternofetal concerns associated with active IBD. It is important to acknowledge that in a small proportion of cases, patients cannot achieve sustained remission preconception despite optimized medical therapies—for example, patients with difficult-to-control disease who are of advanced maternal age. In these cases, it is appropriate to optimize disease control for the individual as much as possible if established remission cannot realistically be achieved in a timely manner.

Contraception in IBD

Contraceptive options may vary according to local availability as well as individual preferences, but some

Table 6. Selected Contraceptive Methods and Special Considerations in IBD[109]

Method	Disadvantages	Benefits
Barrier methods	Least effective: emphasize correct use	■ No side effects ■ Protection against STI's
Oral contraceptive pill: • COCP • POP	• Increased VTE risk with COCP and higher unintended pregnancies o Consider alternative if higher risk for VTE (eg, past history of VTE, current smoking, active disease, on steroids or JAKis, recent surgery) • POP must be taken at the same time each day (within 3 hours)	■ COCP may improve cyclical IBD symptoms ■ No increased VTE risk with POP
LARC: • IUD, contraceptive implant	Long-term options (IUD 5–10 years, implant 3 years) Consider if not planning pregnancy within 1 year Potential cost and pain associated with insertion	■ Most effective (failure rate <1%) ■ No estrogen, no concerns regarding absorption or VTE risk ■ Levonorgestrel IUD may improve cyclical IBD symptoms

COCP, combined oral contraceptive pill; IBD, inflammatory bowel disease; IUD, intrauterine device; JAKi, Janus kinase inhibitor; LARC, long-acting reversible contraception; POP, progesterone-only pill; STI, sexually transmitted infection; VTE, venous thromboembolism.

important considerations for women with IBD are outlined in Table 6.[104] Discussion of contraception options for women with IBD who are not trying to conceive is important. This is especially true for patients who have active disease and intend to delay conception until their IBD control is optimal or for those on a teratogenic medication such as MTX. These options can then be discussed further with the patient's primary care provider or gynecologist as applicable. Although a systematic review reported no association between oral contraceptive use and risk of IBD flare,[105] a subsequent study suggested an increased risk of Crohn's surgery with combined estrogen oral contraception, but not progesterone-only contraception.[106] This may add to the view that in terms of safety and efficacy, long-acting reversible non-estrogen-containing contraception (LARC) options are generally preferable for women with IBD desiring ongoing contraception. These include either an intrauterine device or a contraceptive implant. Utilization of LARC options avoids estrogen-containing contraception methods, which have been associated with an increased risk of thromboembolic events in the general population,[104] and includes more effective contraception therapies. There are limited data in women with IBD regarding contraception and venous thromboembolism (VTE) risk with estrogen-containing contraception. A retrospective study showed no increased risk of VTE with oral estrogen-containing contraception when IBD was in remission.[107] However, alternatives to the combined oral contraceptive pill should be considered in women with other risk factors for thrombosis such as active disease and/or use of JAKis. LARCs also negate the potential concern regarding the absorption of oral contraceptives and interactions with other medications including antibiotics.

Management of Active Disease During Pregnancy

GRADE statement	GRADE recommendation	Level of evidence
8 We suggest that urgent and emergent IBD surgery during pregnancy be completed when required and not based on trimester	Conditional	Very low

Consensus statements
6. Endoscopy during pregnancy among women with IBD is low risk but should only be performed if it may change management
7. If cross-sectional imaging is needed during pregnancy, intestinal ultrasound and MRI without gadolinium are preferred to CT
8. FC is useful for monitoring disease activity in pregnant women with IBD

There are no published data on the rate of acute severe UC in pregnancy or severe Crohn's flare without or without obstruction. The management principles and interventions in this setting remain the same as those for nonpregnant patient (Table 7), with the addition of greater focus on multidisciplinary teams to manage the mother and fetus and selecting more rapidly effective therapies to reduce inflammation quickly to protect the pregnancy.

Biomarkers for Disease Assessment

Traditional markers of IBD activity, such as hemoglobin, albumin, and sedimentation rate, are altered in pregnancy and are not reliable markers of inflammation. CRP has been found to be stable in pregnancy, but at higher than normal levels.[108] FC is a sensitive and reliable marker of intestinal inflammation. A prospective observational study included 98 normal healthy individuals without IBD and 172 maternal stool samples collected at specified end points during pregnancy. The median FC levels were 29.5 μg/g (range, 10–476 μg/g) at 16 weeks' gestation, 25.6 μg/g (range, 10–259 μg/g) at 34 weeks' gestation, 23.4 μg/g (range, 10–318 μg/g) at 4 weeks postpartum, and 29.4 μg/g (range, 10–216 μg/g) at 12 weeks postpartum. There was no significant change in median FC levels over the course of pregnancy and postpartum ($P = .29$), suggesting that FC is not affected by physiological changes during pregnancy and postpartum in healthy pregnant women without IBD.[109]

A prospective cohort study of 157 pregnancies in women with IBD was conducted from 2014 to 2018. A total of 265 FC measurements were obtained throughout the different gestational periods (preconception, n = 41; first trimester, n = 48; second trimester, n = 84; third trimester, n = 76; postpartum, n = 16). At least 1 FC measurement was available in all 157 pregnancies, with more obtained in 108 pregnancies (68.8%). FC levels were significantly correlated with PGA and disease activity indices such as the Harvey-Bradshaw index for CD and partial Mayo score for UC. The cutoff value >100 μg/g has the best sensitivity and negative predictive value to the presence or absence of disease activity as assessed by PGA and previous disease clinical scores.[110] A systematic review included 13 studies assessing the utility of fecal and laboratory tests in predicting IBD activity in pregnant patients, and 3 studies stratified FC levels by the presence of disease activity and specific gestational period. In all of them, the median FC was significantly higher in those patients with clinically active disease compared with inactive disease, suggesting that FC is a useful noninvasive test in the routine monitoring of disease activity in pregnant patients with IBD.[111] Other studies have found similar results.[112]

Table 7. Assessing Disease Activity During Pregnancy

	Assessment of disease activity	Comment
Laboratory tests	Serum inflammatory markers C-reactive protein, sedimentation rate	Can be elevated from pregnancy
	FC	Effective in pregnancy
	Serum drug concentrations • Thiopurines • Anti-TNF therapy	May vary in pregnancy
Cross-sectional imaging	Intestinal ultrasound	Low risk: Accurate in trimester 1 and 2 but technically challenging in trimester 3
	CT	Relatively safe. The cumulative radiation exposure of a single CT scan (~50 mGy) is below the level of concern
	Magnetic resonance imaging	Low risk. Avoid gadolinium (potential teratogen) during the first trimester
Procedures	Endoscopy	Low risk. Can be performed if indicated and will change management
	Surgery	perform if indicated regardless of trimester. Should be done at expert centers Indications: acute refractory colitis, perforation, abscess, refractory hemorrhage, bowel obstruction

anti-TNF, anti-tumor necrosis factor; CT, computed tomography; FC, fecal calprotectin.

Cross-sectional Imaging During Pregnancy

Objective noninvasive assessment of IBD activity is essential during active flares or obstructive symptoms. Magnetic resonance enterography without gadolinium is preferred over CT examination. However, a single CT scan is below the level of radiation (50 mGy) of concern for fetal development and should be done if needed when no other source of imaging is available. The use of magnetic resonance imaging during any trimester of pregnancy has not been shown to be harmful to the fetus. However, gadolinium should be avoided, particularly in the first trimester, given potential fetal toxicity.[113]

IUS is emerging as an effective tool for IBD assessment, although it is not universally available. A study by Flanagan showed a positive correlation between the thickness of the intestinal wall and the level of FC (r = 0.26; $P = .03$), allowing the diagnosis of IBD activity with a specificity of 83%, a sensitivity of 74%, and a negative predictive value of 90% compared with FC.[114] De Voogd et al confirmed this with 38 pregnant patients with IBD (22 CD and 16 UC), with IUS performed every 3 months,[115] with a sensitivity of 84% and a specificity of 98%. There was a strong correlation with clinical activity ($r = 0.60$; $P < .0001$) and FC (r = 0.73; $P < .0001$). However, one should take into account that the visualization of the sigmoid and terminal ileum decreases during the third trimester of pregnancy.[115]

Endoscopy During Pregnancy Among Women With IBD

The American Society of Gastrointestinal Endoscopy published a guideline in 2012 describing best practices for endoscopy during pregnancy that remains helpful.[116] Among patients with IBD, a systematic review that included 82 articles demonstrated that lower gastrointestinal endoscopy during pregnancy is of low risk for mother and child in all 3 trimesters of pregnancy.[117] A retrospective review of 48 pregnant patients with IBD demonstrated no harm, and 78% of procedures led to a change in therapy and 12% had no endoscopic evidence of disease despite symptoms.[118] However, as with any procedure in pregnancy, lower gastrointestinal endoscopy should only be done if needed and if it will change management. The majority of procedures done in IBD are flexible sigmoidoscopies and those are low risk as neither preparation nor sedation is required. When a full colonoscopy, endoscopy, or advanced procedure is needed, fetal monitoring is recommended. The use of capsule endoscopy should be avoided during pregnancy, given the risk of obstruction in patients with CD. If required, standard procedure should be followed with prior imaging and patency capsule if appropriate.

Timing of Surgery in the Pregnant Patient With IBD

The adage that surgery should only be done in the second trimester is not based on modern data and can be

harmful to patient care if treatment is delayed. Any elective surgery should be deferred until after pregnancy, but urgent and emergent surgery that significantly impacts maternal health (ie, fulminant colitis not responsive to therapy, bowel obstruction, etc) should be done when required and not based on trimester of pregnancy. Severe disease has its own risks to pregnancy. Retrospective series (44 patients[119] and 15 patients[120]) did not suggest a difference in harm by trimester of surgical exposure. However, patients undergoing surgery had more pregnancy complications. A Danish nationwide population-based cohort study including 1,202,870 pregnancies from 1997 to 2015 included 8556 IBD pregnancies (0.7%) where 137 cases (3.1%) underwent abdominal surgery. Appendectomy was the most common procedure conducted during pregnancy (30%), with most appendectomies (56.1%) and nonobstetric abdominal procedures (38.9%) conducted in the second trimester. Absolute risks in all surgically treated vs untreated patients were higher for SGA (3.4% vs 2.7%), very preterm birth (2.2% vs 0.8%), preterm birth (8.3% vs 4.3%), and miscarriage (8/2% vs 6.1%).[121] A systematic review of 32 publications (all case series and case reports) included 86 pregnant women undergoing surgery for IBD over a 60-year period. After 1980, there was no mortality, but there was a near 50% preterm delivery rate.[122] Surgery should ideally be performed at expert centers with adequate obstetric and neonatal support.

Management of Pregnancy

GRADE statement	GRADE recommendation	Level of evidence
9. We suggest that pregnant women with IBD take low-dose aspirin by 12–16 weeks' gestation to prevent preterm preeclampsia	Conditional	Low
10. We suggest that pregnant women with CD and active perianal disease undergo cesarean delivery	Conditional	Very low
11. We suggest that pregnant women with IBD and prior IPAA consider cesarean delivery	Conditional	Very low

Consensus statements
9. Pregnancies for women with IBD should be considered as high risk for complications
10. Women with current or past history of rectovaginal fistulas should have cesarean delivery
11. Women with IBD should be assessed early in pregnancy or preconception for nutritional status, weight gain, and micronutrient deficiency

IBD Pregnancies Are High Risk

A high-risk pregnancy is one that threatens the health or life of the mother or her fetus. As women with IBD are often young and otherwise healthy, they are not always recognized as high risk despite an association with adverse maternal and obstetric outcomes, particularly in those who have uncontrolled disease activity.[79,123,124] Even in patients with quiescent IBD, increased adverse pregnancy outcomes have been reported, notably inadequate gestational weight gain (GWG), gestational diabetes, severe eclampsia and preeclampsia, thromboembolic disease, and preterm delivery.[79,123–130] This suggests that every pregnancy in the setting of IBD should be considered as high risk, prompting more intense monitoring of the mother and fetus, if resources are available. It must be noted that most of these observations are from retrospective registry-based studies, which generally do not provide data on disease severity, location, or phenotype. In addition, not all studies were adjusted for maternal age. Table 8 notes recommendations for IBD pregnancy management by trimester.

Inadequate GWG in the setting of IBD was associated with adverse pregnancy outcomes, such as preterm delivery, SGA, and admission to the neonatal intensive care unit (NICU).[126] Inadequate GWG appears to be more common in patients with CD than UC. A large Norwegian database cohort study (166 CD, 217 UC, and

Table 8. Management of Pregnancy Across Trimesters

Trimester	Recommendation
First	■ Gastroenterology visit ■ Start low-dose aspirin by week 12–16 ■ Follow as high-risk obstetric patient o Refer to maternal–fetal medicine provider if available ■ Obtain IBD monitoring labs ■ Nutritional status assessment
Second	■ Gastroenterology visit or check in ■ Obtain IBD monitoring labs ■ Nutritional status assessment
Third	■ Gastroenterology visit or check in ■ Obtain IBD monitoring labs ■ Nutritional status assessment ■ Consider CS in the following nonobstetric settings: o Active perianal disease at the time of delivery (recommend) o Prior complex perianal disease or rectovaginal fistula o Ileal pouch–anal anastomosis ■ Consider VTE prophylaxis at delivery or postpartum if appropriate

CS, cesarean delivery; IBD, inflammatory bowel disease; VTE, venous thromboembolism.

79,125 non-IBD mothers) showed a higher risk of inadequate GWG in women with UC (33%; OR, 1.78; 95% CI, 1.27–2.5) and mothers with CD (39%; OR, 2.28; 95% CI, 1.57–3.31) when compared with non-IBD mothers (21%; 11,518/52,207).[126] Women with IBD and inadequate GWG had a 2-fold risk for SGA births compared with women with inadequate GWG without IBD.[127] Patients with CD and inadequate GWG had a several-fold increased risk for SGA compared with women with IBD with normal GWG. Active IBD was associated with reduced GWG, highlighting the need for optimal disease control.[127] The causes of inadequate GWG have not been fully elucidated but may reflect malnutrition or inflammation.

Gestational diabetes can complicate IBD pregnancies as noted in a large United States health care database of 8,079,828 pregnancies, of which 14,129 had IBD. The incidence of gestational diabetes in women with CD was significantly higher than in pregnant women without IBD (aOR, 1.89; 95% CI, 1.18–3.02; $P = .007$) but was not increased in UC (aOR, 1.05; 95% CI, 0.68–1.64; $P = .82$).[128] A recent systematic review included 53 studies (7917 IBD pregnancies and 3253 healthy control pregnancies). Of these, 9 studies (1075 pregnancies) reported the incidence of gestational diabetes in patients with IBD with an almost 3-fold increase in the incidence of gestational diabetes in patients with IBD compared with healthy controls, regardless of gestational corticosteroid use.[131]

The risk of VTE is increased in pregnant women with IBD, in both the antepartum and postpartum period, compared with women without IBD. A large Danish population-based study showed a relative risk of 1.72 (95% CI, 1.22–2.43) during pregnancy and 2.10 (95% CI, 1.33–3.30) in the postpartum period.[79,130] VTE prophylaxis should be utilized in the hospital and particularly after cesarean delivery.

Aspirin Use During Pregnancy

Preeclampsia, defined as hypertension with proteinuria and other symptoms arising after 20 weeks' gestation, is classified as preterm (delivery <37 weeks) and term (delivery ≥37 weeks) and is increased with autoimmune disease.[132,133] Women with IBD may be at higher risk of developing preterm preeclampsia.[129,134] Most evidence comes from retrospective cohort studies often making no distinction between early- and late-onset preeclampsia, as well as gestational hypertension, analyzing these separate conditions as a single entity. In a large Danish cohort of 666 pregnant women with IBD (CD, 278; UC, 388), while the overall preeclampsia rate in women with IBD did not differ from that in women without IBD (HR, 1.21; 95% CI, 0.76–1.95), rates of severe preeclampsia were significantly higher. When adjusted for confounders, this increased risk was limited to women who used oral corticosteroids during pregnancy.[129]

In another large administrative data cohort study that included 48,986 patients with CD, 30,998 patients with UC, and 69,963,805 patients without IBD, patients with CD and UC had a higher risk of preeclampsia/eclampsia when compared with women without IBD (CD: aOR, 1.39; 95% CI, 1.28–1.51; UC: aOR, 1.27; 95% CI, 1.13–1.42). A limitation of this study is that preeclampsia and eclampsia were analyzed in combination.[134] Two smaller older studies did not find an association between IBD and preeclampsia.[135,136] A recent meta-analysis of 14 studies enrolling 7917 pregnancies with IBD and 3253 healthy pregnancies note a pooled incidence of preeclampsia was 2.0% (95% CI, 0.9%–3.1%), 3.8% (95% CI, 1.8%–5.9%) in patients with UC, and 1.0% (95% CI, 0%–2.2%) in patients with CD. The pooled OR of preeclampsia in patients with IBD compared with healthy controls was numerically higher but did not reach statistical significance (4.65; 95% CI, 0.76–28.35). This meta-analysis was limited by a high degree of heterogeneity of the included studies.[128]

The benefits of prophylactic low-dose aspirin in reducing the risk of preterm preeclampsia have been consistently shown in the at-risk general population, including a 2019 Cochrane review and a 2021 meta-analysis by the United States Preventive Services Task Force.[137–139] The largest randomized placebo-controlled study to date, the ASPRE trial, included 1776 women considered at high risk (0.1/100) of preterm preeclampsia.[140] Preterm preeclampsia occurred in 13 of 798 participants (1.6%) in the aspirin group, as compared with 35 of 822 (4.3%) in the placebo group (aOR, 0.38; 95% CI, 0.20–0.74; $P = .004$).[140] This protective effect of low-dose aspirin on the rate of preterm preeclampsia was confirmed by a recent meta-analysis, with a significant reduction in preterm preeclampsia (before 37 weeks' gestation: relative risk [RR], 0.62; 95% CI, 0.45–0.87) but not at term (RR, 0.92; 95% CI, 0.70–1.21)[141] and, importantly, only when it was initiated at ≤16 weeks' gestation and at a daily dose of ≥100 mg. For the patient with IBD, with guidance from obstetric colleagues, a dose of 150 to 162 mg should be given starting at week 12 to 16 of gestation. Although clinical practice guidelines differ, many suggest discontinuing aspirin after 36 to 37 weeks due to a possible increased risk of bleeding during delivery and postpartum.[142]

Concern regarding precipitating a disease flare has led to caution in prescribing aspirin as nonsteroidal anti-inflammatory use in patients with IBD has been historically associated with flare.[143] This does not seem to occur in pregnancy with low-dose aspirin.[144–146] A prospective registry of 764 nonpregnant patients with IBD[144] found that aspirin use was not associated with a risk of being hospitalized for an IBD-related complication (OR, 1.46; $P = .10$), corticosteroid use (OR, 0.99; $P = .70$),

or having an IBD-related surgery (OR, 0.99; $P = .96$).[144] Data evaluating aspirin safety in pregnant women with IBD are sparse but also suggest no increase in flares. A retrospective single-center cohort study of pregnant women with IBD compared IBD activity in 71 women receiving low-dose aspirin for preeclampsia prevention with 313 pregnant IBD patients not receiving aspirin and found no difference in clinical flares during pregnancy (16.9% vs 14.4%; $P = .6$).[145] Similar findings were reported from another single-center study of 358 patients in clinical remission at the time of conception, of whom 71 (18.5%) received low-dose aspirin during their pregnancy. There was no difference in the frequency of disease activity among patients taking low-dose aspirin for preeclampsia prevention compared with those not taking low-dose aspirin (OR, 1.27; 95% CI, 0.55–2.94).[146]

Assessment of Nutritional Status

Women with IBD are at risk of developing malnutrition and micronutrient deficiencies due to restrictive diets,[147] diarrhea, malabsorption, decreased oral intake, and uncontrolled disease activity.[148] Pregnancy may further worsen these deficits because of increased micronutrient, protein, and energy requirements essential for normal fetal development. Iron, vitamin B_{12}, vitamin D, and folic acid are the most common micronutrient deficiencies seen in patients with IBD, and inadequate stores during pregnancy may negatively impact maternal and fetal outcomes.[131,149–152] Iron deficiency with or without overt anemia is the most common micronutrient deficiency in IBD and has been associated with preterm delivery, low birth weight (LBW), stillbirth, and reduced iron stores in the newborn.[131,149] In a recent systematic review, low maternal vitamin B_{12} concentrations were associated with a high risk of adverse maternal and child health outcomes.[150] The prevalence of vitamin D deficiency is high among pregnant women and is associated with an increased risk of adverse pregnancy outcomes, notably preeclampsia, preterm delivery, LBW, and gestational diabetes.[151,152]

During the preconception period and in the first trimester, it is recommended that women with IBD be evaluated for folate, iron, vitamin B_{12}, and vitamin D deficiencies and treated with appropriate micronutrient supplementation. Clinical practice guidelines universally recommend folic acid supplementation (0.4 mg/d) for at least 4 weeks prior to conception to reduce the risk of neural tube defects.[153,154] A higher dose of folic acid may be required in women with IBD than that recommended for the general population, and those at increased risk of folate deficiency should continue supplementation throughout pregnancy. The World Health Organization recommends oral supplementation of 30 to 60 mg/d of elemental iron for all pregnant women; in the setting of IBD, higher doses up to 100 mg/d may be required.[153,154] If oral iron is not tolerated or is ineffective, intravenous iron may be administered in the second and third trimesters after assessing the risks and benefits to the mother and fetus and with close monitoring for adverse reactions.[155] Intravenous iron should be avoided in the first trimester due to possible teratogenicity. Consideration should be given for calcium supplementation if calcium intake from food is low.[154] Pregnant women treated with corticosteroids should receive routine calcium and vitamin D supplementation to prevent steroid-associated osteopenia.

Women with IBD should receive prenatal and antenatal counseling regarding a healthy diet during pregnancy. Restrictive diets are often used in women with IBD to control symptoms and reduce inflammation in luminal CD. Avoidance of specific food groups may worsen inadequate GWG, should be used with caution in pregnant women with IBD, and should be closely supervised by a dietitian.

Weight and body mass index should be recorded at each antenatal visit to ensure adequate GWG, which is essential for fetal development and growth, as well as maternal health. Assessment of GWG is based on preconception weight to identify target weight gain as reflected in recommendations of the Institute of Medicine.[156] Failure to achieve appropriate weight targets should prompt referral to a dietitian. Patients with risk factors for malnutrition, such as extensive small bowel surgery, should also be referred to a dietitian.

Mode of Delivery With Perianal CD

Whenever discussing the mode of delivery, individual maternal history and number of children desired (>3 CSs can result in complications such as uterine rupture) must be considered. With that caveat, CS is suggested in women with CD who have active perianal disease due to concerns that vaginal delivery (VD) may worsen the disease postpartum.[79,157] Risks associated with VD among those with active perianal disease may include damage to the sphincter, exacerbation of pelvic abscess, or progression of perianal disease. There are a number of factors that should be discussed in shared decision-making with the patient, including a small risk of severe perineal tear, a small risk of CS-related complication, and for some, a strong desire for a drug-free natural delivery. For those with inactive perianal disease at the time of delivery, the severity of prior perianal CD and surgeries should be considered and discussed as well.

Several studies have found that women with active perianal CD at the time of VD are at high risk of worsening their perianal symptoms. In a population-based study of pregnant women with IBD, there were 54 VDs and 10 CSs. Fifteen of the 54 patients who underwent VD had existing perianal disease; all of whom reported worsening of their perianal symptoms postpartum.[158]

This poor outcome is supported by a 2017 systematic review that evaluated 12 patients with active perianal CD who underwent VD, 8 of whom had worsening disease postpartum, whereas 4 remained stable.[159] In contrast, a separate study of 102 women with IBD from the Netherlands with perianal CD who gave birth found comparable rates of perianal disease progression among those with VD (18.8%) and CS (22.2%).[160] These data support the possibility of a more individualized approach surrounding delivery recommendations with patients, particularly for those who prioritize a VD and are counseled on the risks.

A retrospective study, from a large national database, found that active perianal disease is associated with an 11-fold higher risk of fourth-degree perianal tears independent of the presence of CD.[161] There is also a concern that the risk of worsening of active perianal CD may be exacerbated further by episiotomy, although there are no data specifically addressing this issue.

Whether quiescent perianal CD should also be considered an indication for CS is less clear. In a French retrospective study, VD with or without perineal tears or an episiotomy was not associated with the occurrence of perianal CD after delivery, even in patients with a prior history of perianal lesions.[162] Similarly, in the systematic review already mentioned, none of the women with inactive perianal disease who underwent VD (n = 37) had a relapse at 1 year of follow-up.[159] However, these numbers are small, and caution should always be taken in those with prior perianal disease, particularly if complex, to consider CS and to avoid prolonged labor.

A study by Cheng et al observed no significant difference in the recurrence of perianal disease in women with perianal CD who delivered vaginally when compared with those who delivered via CS, after adjusting for the propensity score according to the patient's risk.[163] It was unclear if patients had active or quiescent perianal CD at the time of delivery. A retrospective study of 190 patients with CD with 322 deliveries noted 169 (52%) were VDs and 153 (48%) were by CS.[164] Forty women had a history of perianal CD prior to delivery. Nineteen women (10%) experienced postpartum perianal disease flares. Independent predictors were prior perianal disease (OR, 22; 95% CI, 7–69; $P < .001$) or active perianal CD (OR, 96; 95% CI, 21–446; $P < .001$). Delivery by CS was not protective of ongoing perianal disease activity postdelivery.

Mode of Delivery With Rectovaginal Fistula

In the non-IBD population, prolonged labor and third- and fourth-degree lacerations along with episiotomies due to difficult labor can lead to the development of rectovaginal fistula (RVF). Limited evidence in the literature comes from studies evaluating non-IBD obstetric fistulas with reports of a 5% rate of recurrence after VD[165] and of delivery-related fistula recurrences occurring only among women who had VD or emergency CS.[166] Given the difficulty of healing an RVF in IBD, women with active or prior RVF should undergo planned CS.

Mode of Delivery With Ileoanal J Pouch

The data surrounding VD outcomes in women with IPAA are conflicting, with some but not all studies demonstrating an increased risk of impaired pouch function after VD when compared with CS.[167–174] CS in this population should ideally be performed in a center with surgical (ideally colorectal) support.

The largest systematic review to date included 470 patients who had undergone IPAA: 90% in the setting of UC with follow-up to 7.7 years.[159] Continence outcomes according to delivery mode were reported in 8 studies including 358 patients. This review showed no significant difference in terms of overall continence, daytime or night-time stool frequency, or incontinence. However, complicated VD appeared to negatively impact pouch function.[159] The results of this review need to be interpreted with caution, as postoperative follow-up in many of the included studies was too short to assess the long-term impact of VD. Furthermore, most studies evaluated outcomes of VD vs CS using fecal incontinence questionnaires, with only a single study by Remzi et al objectively evaluating anal sphincter function.[173] Using anorectal manometry, women who had undergone CS had significantly higher mean squeeze pressure than the VD group (150 vs 120 mm Hg), whereas anterior anal sphincter defects evaluated by endosonography were increased significantly following VD (OR, 4.8; 95% CI, 1.1–21.7). Moreover, quality of life was significantly worse after VD than after CS.[173]

Few studies have made a distinction between uncomplicated and complicated VD when evaluating pouch function postdelivery. One study by Polle et al attempted to address this question in women post-VD who were at high risk of obstetric injury when compared with those who were at low risk. High-risk factors included forceps or vacuum delivery, delivery with episiotomy, delivery with vaginal tears requiring perineoplasty, delivery of a baby weighing more than 4000 g, delivery that resulted in an emergency CS, or delivery with a prolonged second stage of labor (more than 2 hours). In this retrospective study, women who had a VD with an increased risk of obstetric injury had significantly higher incontinence scores with aging and increasing length of follow-up compared with those

without an increased risk of obstetric injury.[175] However, no discrimination between deliveries that occurred before or after IPAA was made.

Medications in Pregnancy

GRADE statement	GRADE recommendation	Level of evidence
12 For women with IBD who are pregnant or attempting conception, we recommend continuing maintenance 5-ASA therapy	Strong	Low
13 In women with IBD who are pregnant or attempting conception, we suggest continuing maintenance sulfasalazine therapy	Conditional	Very low
14 In women with IBD who are pregnant, we suggest the use of corticosteroid therapy when clinically necessary with appropriate monitoring	Conditional	Low
15 In women with IBD, we recommend discontinuing maintenance MTX therapy prior to conception	Strong	Very low
16 In women with IBD who are pregnant or attempting conception, we suggest continuing maintenance thiopurine therapy as data do not demonstrate an increased risk of congenital malformations or infant infections.	Conditional	Very low
17 In women with IBD who are pregnant or attempting conception, we recommend continuing maintenance anti-TNF therapy throughout pregnancy	Strong	Low
18 In women with IBD who are pregnant or attempting conception, we suggest continuing maintenance combination therapy with an anti-TNF and thiopurine therapy throughout pregnancy	Conditional	Very low
19 In women with IBD who are pregnant or attempting conception, we suggest continuing maintenance vedolizumab therapy throughout pregnancy	Conditional	Low
20 In women with IBD who are pregnant or attempting conception, we suggest continuing maintenance ustekinumab therapy throughout pregnancy	Conditional	Low

Consensus statements

12	Women with IBD who are pregnant and have active disease should start or optimize the same appropriate IBD therapies as in nonpregnant patients, except for thiopurines, MTX, JAKis, and S1P modulators
13	In women with IBD who continue thiopurines during pregnancy, precautions should be taken for intrahepatic cholestasis by measurement of liver enzymes and metabolite levels and consideration of split dosing
14	Women with IBD who are pregnant and have infections, fistula, or pouchitis that require antibiotics may take an appropriate course of a low-risk antibiotic
15	Women with IBD may initiate or continue calcineurin inhibitors (cyclosporine and tacrolimus) during pregnancy with careful monitoring if there are no viable alternate treatment options available
16	Women with IBD who are pregnant or attempting conception should continue biosimilars to existing biologics
17	Women with IBD who are pregnant or attempting conception should continue anti-interleukin 23 (IL23) therapy throughout pregnancy (mirikizumab, risankizumab, guselkumab)
18	Women with IBD should discontinue ozanimod at least 3 months prior to conception unless there is no effective alternative therapy to maintain maternal health.
19	Women with IBD should discontinue etrasimod at least 1 to 2 weeks prior to conception unless there is no effective alternative therapy to maintain maternal health
20	Women with IBD should discontinue tofacitinib at least 4 weeks prior to conception unless there is no effective alternative therapy to maintain maternal health.
21	Women with IBD should discontinue upadacitinib at least 4 weeks prior to conception unless there is no effective alternative therapy to maintain maternal health
22	Women with IBD should discontinue filgotinib at least 4 weeks prior to conception unless there is no effective alternative therapy to maintain maternal health.

The use of IBD medications in pregnancy remains one of the most controversial areas in the management of the patient with IBD. The placenta plays a key role in medication safety during pregnancy (Figure 1). Monoclonal antibodies are too large to passively cross the placenta during the key period of organogenesis (weeks 3–8) but will actively cross with increasing efficiency via Fc receptors after week 14 of gestation, with 80% of the

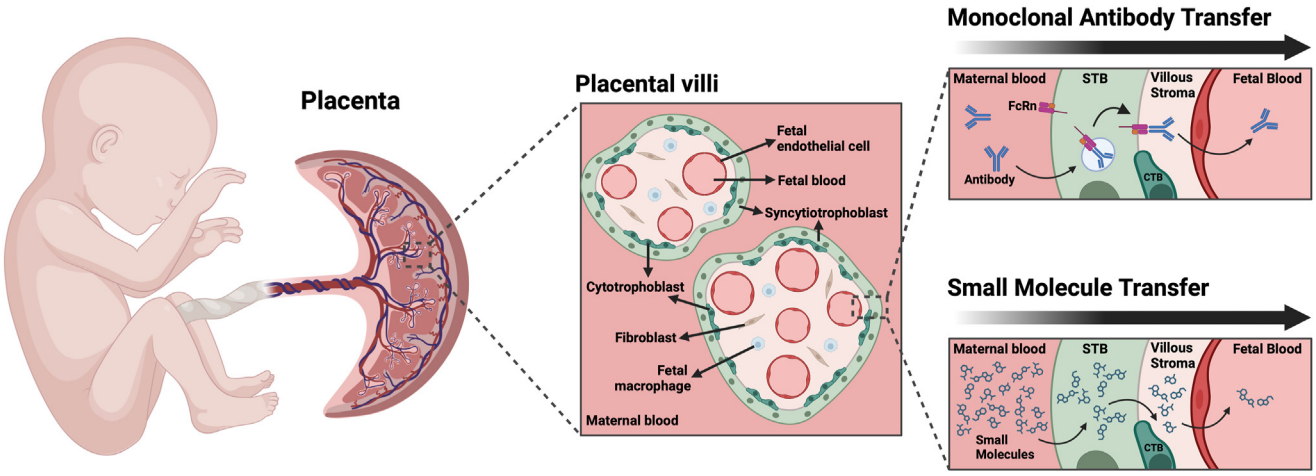

Figure 1. Placental transfer of monoclonal antibodies and small molecules. The human placenta (*left panel*) consists of placental villi (*middle panel*), finger-like projections containing mononuclear cytotrophoblasts that differentiate into the outer multinucleated syncytiotrophoblast (STB) layer, which faces maternal blood circulating in the intervillous space. The mononuclear cytotrophoblast layer is continuous early on but subsequently depleted as pregnancy progresses. The villous stroma houses fetal macrophages (Hofbauer cells), fibroblasts, and fetal capillaries lined with fetal endothelial cells that carry fetal blood. Antibody transfer from the maternal circulation to the fetal circulation across the intervening cells is facilitated by FcRn (*right panel*). Small molecule transfer, which is poorly understood, is thought to occur via diffusion.

transfer occurring in the third trimester.[176] Normally, the transfer of maternal antibodies occurs to provide protection to the infant. However, biologic agents that mimic natural antibodies with an Fc portion will also cross the placenta. Although the risk of congenital malformations may be reduced due to the lack of early exposure in utero, infants are born with significant serum concentrations of biologic agents. In contrast, early in pregnancy, small molecules and/or environmental chemicals could be trapped by various cell types in the placenta or enter the embryonic/fetal circulation, increasing the risk of teratogenicity. Some will be rapidly cleared after birth, but others could persist. These considerations, the constant emergence of new therapies, and increasing long-term data on established therapies have led to changes in guidelines. Table 9 summarizes recommendations for the use of IBD medications during pregnancy. The guidance reflects an understanding of the importance of controlling disease activity for both maternal and fetal health.

5-Aminosalicylates

5-ASA therapy including mesalamine, olsalazine, and balsalazide is low risk in pregnancy despite placental transfer. Concentrations of 5-ASA in the fetal plasma are lower than in maternal plasma.[177] Two systematic reviews with meta-analyses published in 2021 and 2008, plus a number of large observational studies, demonstrate no increased risk of congenital malformations with exposure to 5-ASA after accounting for confounders such as other therapies during pregnancy. Leung et al[178] performed a meta-analysis of 2 registry studies by Ban 2014[179] and Nørgård 2007[180] providing a pooled OR of 0.82 (95% CI, 0.50–1.33; $I^2 = 0\%$) for congenital malformations. Rahimi et al[181] performed a broader systematic review and meta-analysis of 7 studies on 5-ASA and sulfasalazine use during pregnancy. Two of the 7 studies[182,183] included only 5-ASA products, whereas others[180,184] included 5-ASA along with sulfasalazine, and the remaining studies were exclusive to sulfasalazine exposure. There was no increased risk of congenital abnormalities (CAs) (OR, 1.16; 95% CI, 0.76–1.77; $P = .57$), but the estimates are imprecise for 5-ASA use, given the mixed cohorts. CAs in the pooled 5-ASA group were 6.7% (38 of 565) and 5.2% (80 of 1524) in the group on no medications.

Nørgård et al utilized observational cohort data from a nationwide database, of which there were 3618 infants exposed to 5-ASA in utero and 7128 unexposed infants.[185] There was no increased risk of congenital anomalies. The adjusted OR for congenital anomalies in women with UC utilizing 5-ASA was 0.76 (95% CI, 0.56–1.04) and adjusted OR for CD was 1.44 (95% CI, 0.84–2.47). Contrary to other studies, Kallen et al reported an increased risk of major congenital malformations (1.37; 95% CI, 1.17–1.62) and specifically for cardiovascular defects (1.74; 95% CI, 1.37–2.22) in 3721 infants with exposure to 5-ASA in early pregnancy identified through a Scandinavian registry.[186] The authors did report a strong association with concurrent systemic glucocorticosteroids or immunosuppressants, which could have confounded the analysis.

Other considerations to address regarding the use of 5-ASA in pregnancy include documented poor adherence to 5-ASA therapy during pregnancy, prior formulations containing dibutyl phthalate (DBP), and the safety of rectal 5-ASA formulations.[187–189]

Mesalamine is better tolerated than sulfasalazine, with intolerance likely related to the sulfapyridine moiety.[190] Maintenance of remission is key in pregnant patients as it has been demonstrated that almost a quarter of women with IBD who were previously adherent to

Table 9. IBD Medications From Preconception Through Pregnancy and Lactation

Medication	Preconception	First trimester	Second trimester	Third trimester	Lactation
Aminosalicylates o Folic acid supplementation with sulfasalazine	✓	✓	✓	✓	✓
Thiopurine o Monitor metabolites, liver enzymes	✓	✓	✓	✓	✓
Methotrexate o Teratogen o Cessation 1–3 months prior to conception	✗	✗	✗	✗	✗
Corticosteroids o Minimize use o Employ steroid-sparing therapy	✓	✓	✓	✓	✓
Anti-TNF	✓	✓	✓	✓	✓
Anti-integrin	✓	✓	✓	✓	✓
Anti interleukin-12/23 or anti interleukin-23	✓	✓	✓	✓	✓
JAKi o Avoid o Use only if no other viable option for maternal health	!	!	!	!	!
S1P receptor modulator o Avoid o Use only if no other viable option for maternal health	!	!	!	!	!

NOTE. Check mark = appropriate to use during pregnancy; X = avoid during pregnancy; ! = avoid unless no viable option for maternal health.
anti-TNF, anti-tumor necrosis factor; JAKi, Janus kinase inhibitor; S1P, sphingosine-1-phosphate.

medical therapy are not adherent during pregnancy.[189] Furthermore, there was lesser adherence to aminosalicylates than to more advanced therapies, and nonadherence was an independent risk factor for relapse.[188,189,191] Current commercially available formulations of aminosalicylates do not contain DBP, which has been associated with higher odds of preterm birth in humans and anogenital anomalies in mice studies.[192,193] Based on superiority of a combined approach with oral and rectal aminosalicylates[194,195] and the safety of these respective formulations in pregnancy, enemas can be utilized in pregnant individuals with UC, especially those with predominant rectal symptoms including urgency and tenesmus. There is one small observational study (n = 19) on the use of topical/rectal aminosalicylates during pregnancy, which demonstrated effectiveness and safety.[196] There is no evidence to support prior beliefs that rectal therapy increases miscarriage rates.

Sulfasalazine

Sulfasalazine therapy is low risk in pregnancy even though there is transfer into fetal plasma, resulting in low fetal concentrations.[197,198] Data for its safety include a systematic review and meta-analysis published in 2008 by Rahimi, which included 3 studies that were sulfasalazine-specific plus 2 studies that were a mixed cohort of 5-ASA and sulfasalazine, birth registry data, and a smaller case–control study, all of which demonstrated no increased risk of congenital malformations.[181] There was no increased risk of CAs in the Rahimi's meta-analysis (OR, 1.16; 95% CI, 0.76–1.77; $P = .57$). However, the estimates are imprecise for sulfasalazine use, given the mixed cohorts. Nørgård et al also reported on exposure to sulfasalazine, but the number of cases of congenital malformations in each group was very small, with 17 in the sulfasalazine group and 26 in the control

group.[199] Overall, there was no increased risk of CAs with sulfasalazine exposure (aOR, 1.2; 95% CI, 0.6–2.1). Viktil et al reported 119 exposures to sulfasalazine from a Norwegian birth registry, and although no increased risk of congenital exposures was demonstrated, the evidence was indirect as data were derived from a rheumatology population.[200] If a patient is maintained on sulfasalazine, supplementation with folate 2 mg/d is recommended as sulfasalazine impairs folic acid absorption and metabolism. Alternatively, a 5-ASA agent (oral ± rectal) can be substituted.

Corticosteroids

Park-Wyllie et al followed 184 women exposed to prednisone in pregnancy and performed a meta-analysis of the literature.[201] In the prospective study, 34 women were on steroids for CD and 28 for UC. There was no statistical difference in the rate of major anomalies or live-born infants between the steroid-exposed and control groups. Infants born to exposed mothers were smaller, born earlier, and more likely to be premature. In the meta-analysis portion of their study, 10 papers were analyzed, 6 were cohort studies, and 4 were case–control studies, ranging from years 1962 through 1999. Studies included women with varying underlying diseases, not just IBD. Sample sizes range from 22 to more than 50,000. There were 4 case–control studies examining the risk of oral clefts; the summary OR for case–control studies examining oral clefts was significant at 3.35 (95% CI, 1.97–5.69). In the meta-analysis, the summary OR for major malformations within all cohort studies was 1.45 (95% CI, 0.8–2.6), although it was noted that the OR for major malformations rose to 3.03 (95% CI, 1.08–8.54) when the large study by Heinonen et al[202] with incomplete data was removed. It should be noted that this removal may have reduced precision as the total cohort size of meta-analyzed data dropped from >50,000 in the unexposed cohort to 708 and from 535 to 390 in the exposed cohort. In a study by Leung et al, a population-based administrative discharge database was used to identify women with IBD and compare pregnancy outcomes with controls.[203] A total of 116 patients with IBD were age-matched to 381 pregnant women without IBD. The authors found that 7% of patients with IBD who received steroids during pregnancy developed gestational diabetes. Women on steroids with IBD were more likely to develop gestational diabetes with an of OR 4.5 (95% CI, 1.2–16.8) compared with non-IBD controls. For women with IBD on steroids compared with women with IBD not on steroids, the OR was 2.0 (95% CI, 0.01–15.3). In the PIANO registry, a total of 1490 mothers with IBD were enrolled, and corticosteroid use was found to be associated with an increased risk for preterm birth, SGA, LBW, intrauterine growth restriction, and NICU admission.[204] On adjusted multivariable models, steroid use was associated with preterm birth (OR, 1.79; 95% CI, 1.18–2.73), LBW (OR, 1.76; 95% CI, 1.07–2.88), and NICU admission (OR, 1.54; 95% CI, 1.03–2.3). Late corticosteroid use (ie, second or third trimester) was associated with serious infections at 9 and 12 months. The recommendation based on these results was emphasis on the importance of controlling disease activity before and during pregnancy with steroid-sparing therapy. Lastly, in a study by Jolving et al, the Danish national registry was used to examine outcomes and children exposed in utero to corticosteroids compared with those not exposed.[205] The aHR for major congenital malformation was 1.28 (95% CI, 0.82–2.00) compared with children born to women with IBD not exposed to steroids. After in utero exposure to steroids at any time during pregnancy, the aOR was 2.45 (95% CI, 1.19–3.13) for preterm birth, 1.21 (95% CI, 0.76–1.9) for SGA, and 0.91 (95% CI, 0.33–2.52) for low five-minute APGAR score. The HR for overall infections in the first year of life was 1.14 (95% CI, 0.94–1.39). The authors concluded that children of women exposed to corticosteroids in utero had almost a two-and-a-half-fold increased risk of preterm birth. The use of steroids is closely related to disease activity and is difficult to separate in any analysis.

For mild to moderate UC not responsive to oral and topical 5-ASA, one may consider colonic release corticosteroids (ie, once daily 9 mg budesonide multimatrix formulation). However, there are only 4 reported cases of its use in pregnancy.[206,207] There is a case series of 8 patients using ileal release budesonide for CD demonstrating safety in the absence of corticosteroid adverse effects.[208] The decision to use second-generation steroids vs conventional corticosteroids requires an assessment of disease severity, given that timely and effective induction of remission is paramount in a pregnant individual with active disease to reduce adverse maternofetal outcomes. Rectal corticosteroids have not demonstrated benefit over topical aminosalicylates for clinical, endoscopic, or histologic outcomes, but there is no increased safety concern.[209]

Methotrexate

MTX use during pregnancy can result in a variety of anomalies affecting the craniofacial, musculoskeletal, central nervous, and cardiac systems. The indication for maternal use varies between studies and is not limited to IBD. Verberne et al performed a systematic review that identified 29 cases of congenital anomalies after in utero exposure to MTX for a variety of maternal indications.[210] Anomalies included microcephaly, craniosynostosis, tetralogy of Fallot, pulmonary valve atresia, limb reduction defects, and syndactyly. Another systematic review limited to rheumatological indications by Martinez-Lopez reported 5 of 101 MTX-exposed pregnancies resulted in minor neonatal malformations.[211]

Weber-Schoendorfer performed a prospective multicenter observational study of 324 mothers with mixed immune-mediated disorders (15 of whom had IBD) who were exposed to MTX within 12 weeks preconception or after conception.[212] Eleven infants had major congenital anomalies; none of these were born to mothers with IBD. Although none of the malformations were clearly consistent with MTX embryopathy, importantly, there was an increased risk of major congenital malformations in women with autoimmune diseases on MTX compared with those without autoimmune diseases (aOR, 3.1; 95% CI, 1.03–9.5). There was no association for the disease-matched cohort not exposed to MTX (aOR, 1.8; 95% CI, 0.6–5.7). The data were further confounded as more than one-half of the women were exposed to corticosteroids or other immunomodulatory drugs. Dawson et al performed a case–control study of 16 MTX-exposed pregnancies but not for the maternal indication of IBD.[213] The congenital anomaly rate was low at 0.06% (n = 16/27,623) of exposed pregnancies; however, the majority (11/16) had a congenital heart defect. Lewden et al reported data on first trimester exposure obtained from a large number of pharmacovigilance centers and teratology information services in France.[214] The vast majority (26/28) ended MTX exposure by 8 weeks' gestation, although a single child who was exposed until 8.5 weeks' gestation had minor anomalies including metatarsus varus and eyelid angioma.

Exposure should not necessitate termination; however, a detailed discussion with the mother regarding options should be undertaken. Hernanadez-Diaz demonstrated that folic acid consumption in the presence of dihydrofolate reductase inhibitors (including MTX) reduced the relative risk of developing cardiac defects, and as such, folic acid supplementation should be continued or initiated to reduce the risk of adverse effects.[215] Ideally, cessation of MTX 1 to 3 months prior to conception should be undertaken, to allow for clearance of MTX conjugates, in addition to allowing the mother to transition to other appropriate therapies.

Thiopurines

Thiopurine monotherapy for the maintenance of disease remission in pregnancy is considered low risk with no increased risk of congenital malformations observed in meta-analysis and cohort studies.[2,80,216,217] Leung et al[80] included 3 registry studies in the meta-analysis[179,180,218] assessing congenital malformations with thiopurine exposure with a pooled OR of 1.92 (95% CI, 0.95–3.85; $I^2 = 0\%$).

With respect to the risk of infection, a large retrospective study from the French national health database showed no increase in serious infection risk in the first 5 years of life with thiopurine exposure (n = 3392) when compared with nonexposed children of mothers with IBD (aHR, 0.94; 95% CI, 0.83–1.07), with only a higher risk observed in children exposed to combination thiopurine and anti-TNF therapy (n = 816) (aHR, 1.36; 95% CI, 1.04–1.79).[219] This was a propensity score–weighted marginal Cox model accounting for maternal, IBD, and pregnancy characteristics. A smaller retrospective multicenter study showed no significant association between thiopurine monotherapy (n = 240) or combination thiopurine and anti-TNF therapy (n = 60) and either antibiotic-treated infection or severe infection in the first 5 years of life.[216] This was an adjusted analysis taking into account treatment groups, pregnancy smoking status, obstetric complications, and breastfeeding for antibiotic-treated infections.

Additionally, 2 prospective studies including the large PIANO registry and a Dutch cohort of more than 100 infants showed no increase in congenital malformations or infant infections to 1 year associated with maternal thiopurine use.[2,216] These prospective studies also show no increase in preterm birth associated with thiopurines. For patients in established remission with adequate biologic serum trough concentrations and without a high-risk disease phenotype, cessation of a thiopurine and maintenance on anti-TNF monotherapy can be considered as an individual risk–benefit discussion.

The metabolism of thiopurines is altered in pregnancy, with an increased risk of shunting of thiopurine metabolites (the MMP:TGN ratio increases) in late pregnancy.[220–222] If available, thiopurine metabolites can be measured in the second and third trimesters to avoid high levels of 6-methylmercaptopurine and potential hepatotoxicity. Thiopurines have been associated with an increased risk of intrahepatic cholestasis of pregnancy (baseline incidence of 1.1% in the general population), triggering a warning from the United States Food and Drug Administration. The cholestasis is likely due to shunting of metabolites.[216,220,223] If shunting does occur, split dosing of the thiopurine can be trialed with close follow-up of metabolites and liver function tests. The addition of allopurinol to low-dose thiopurine can be beneficial to avoid shunting. A recent case series and systematic review reported on 144 patients, not all IBD, exposed to allopurinol in pregnancy, with mixed results.[224] Overall, there are insufficient data regarding the safety of allopurinol in pregnancy to recommend continuing this drug routinely, unless there is no other alternative to maintain adequate disease control during pregnancy.[225] Alternative options in these settings include consideration of biologic monotherapy or split dosing of thiopurine. Thioguanine is a less commonly used alternative to azathioprine or mercaptopurine, with the potential advantage being fewer enzymatic steps involved in the conversion of thioguanine to pharmacologically active 6-thioguanine nucleosides metabolites. Only a single cohort study exists suggesting no excess adverse maternal or neonatal outcomes.[226]

There have also been small case series and historic reports of hematological and biochemical abnormalities

in infants following thiopurine exposure in utero.[221] However, there is no current concern regarding significant neonatal or infant anemia following in utero thiopurine exposure.[222,227] Rather, there can be thrombocytosis and increased liver transaminases observed without clinical consequence, and these findings appear largely related to maternal inflammation, not medication.[228] There are no known long-term adverse effects on childhood growth, development, or risk of chronic disease related to thiopurine exposure in utero.[2,14,216,217]

Anti-TNF Agents and Disease Control

When addressing the safety of monoclonal antibody, we follow the general principle that stringent disease control of IBD results in the most favorable maternal and fetal outcomes. Almost all commercially available biologics/monoclonal antibodies for the treatment of IBD are immunoglobulin G1 (IgG1) monoclonal antibodies. The exceptions are natalizumab and mirikizumab, which have an IgG4 backbone. Certolizumab is a Fab' fragment without the Fc portion so it does not actively cross the placenta. All IgG monoclonal antibody therapies used for the treatment of IBD should not exhibit transplacental transfer in the first trimester but demonstrate steady transfer in the second and third trimesters, generally resulting in detectable levels in the infant. IgG1 is more efficiently transferred than IgG4, but it is unclear if there are clinical advantages of an IgG4 monoclonal antibody during pregnancy (ie, mirikizumab) over other anti-IL23 products.[229]

There is an increased risk of maternal disease flare in women who discontinue anti-TNF therapy before, during, or after pregnancy, consistent with data in the nonpregnant state. Maternal disease flare has been variably defined by the different studies but included prescription of a new medication (most commonly corticosteroids), a change in prescription medication, surgery, or hospitalization. Of marked importance, bias is innate to uncontrolled studies, and the following data should be interpreted with caution. The decision to discontinue therapy was not random and those who stopped anti-TNFs during pregnancy were more likely to have disease in remission at the time of discontinuation so they were potentially a more favorable prognostic group with lower predicted risk of flare. Data should be interpreted cautiously due to this confounding, specifically, withdrawal of therapy and timing are not considered random events. Variability in the use of concomitant immunomodulation, the long half-life of anti-TNFs, and the altered pharmacokinetics of infliximab in pregnancy, resulting in higher drug concentrations in the later trimesters, may have also been protective against flare, therefore decreasing the effect estimate of flare, shifting it toward null. This increase in serum drug concentrations later in pregnancy occurred despite maintaining prepregnancy dosing, supporting the practice of using stable dosing during pregnancy regardless of pregnancy weight gain.[230]

Malhi et al performed a systematic review and meta-analysis examining risk factors for postpartum disease activity in women with IBD.[231] Four studies, 3 retrospective and 1 prospective, were included for the analysis of the impact of biologic discontinuation in the third trimester, demonstrating an increased odds of postpartum disease activity compared with those who continued therapy through pregnancy (OR, 1.77; 95% CI, 1.01–3.10).[232–235] Of note, active disease at conception (OR, 10.59; 95% CI, 1.48–76.02) and during pregnancy (OR, 4.91; 95% CI, 1.82–13.23) increased the odds of postpartum disease activity. This may have influenced the decision to continue vs discontinue therapy during pregnancy and contributes to the unmeasured confounding. Torres et al[232] performed a systematic review, including 1 abstract and 2 full publications. Notably cohort sizes were small (<100 in each of the discontinuation groups), and there was heterogeneity in the use of concomitant immunomodulators (ranging from 17.5%–36%).

Meyer et al performed a target trial emulation with a large cohort size of 2403 in the continuation group and 2890 individuals in the anti-TNF discontinuation group and demonstrated that continuation of therapy was associated with a decreased frequency of maternal IBD relapse (35.8% vs 39.0%; aRR, 0.93; 95% CI, 0.86–0.99).[219] Even with propensity score matching, the decision to stop therapy was still not considered a random event. Mahadevan et al utilized the prospective PIANO cohort and identified that a significantly greater proportion of women with IBD who had flares in the first trimester, third trimester, and postpartum were not on biologic agents or immunomodulators.[2] However, unlike other studies, discontinuation of a biologic (anti-TNFs comprised >90% of the cohort) in the third trimester was not associated with an increased risk of postpartum flare (robust follow-up of 100 patients in the discontinuation group at months 4, 9, and 12 postdelivery and over 500 patients in the continuation cohort). Luu et al utilized a large retrospective cohort of 1456 patients with IBD exposed to anti-TNFs in pregnancy, with one-half in the continuation and one-half in the discontinuation groups.[233] They concluded that discontinuation of anti-TNF after 24 weeks' gestation increased disease relapse (45.8% vs 30.6%; $P = .005$). The analysis was adjusted for disease severity, age, IBD type, IBD duration, and concomitant immunomodulation, but those who discontinued therapy were at almost twice the odds for disease relapse (aOR, 1.98; 95% CI, 1.25–3.15).

In the setting of combination immunomodulator and anti-TNF therapy, conclusions from a recent meta-analysis of all patients with IBD, not necessarily restricted to those who are pregnant, demonstrated a 2.4 times higher risk of relapse with anti-TNF withdrawal

compared with continuing combination therapy.[234] The multicenter open-label SPARE study demonstrated an HR of 3.45 for infliximab withdrawal vs ongoing combination therapy and an HR of 4.76 for infliximab withdrawal vs immunosuppressant withdrawal.[235] The decision to withdraw therapy in pregnant patients is of higher consequence when there are potentially both maternal and infant adverse outcomes including maternal disease flare and preterm birth. Active disease in pregnancy has been well demonstrated to increase the risk of preterm birth and neonatal infections and may impact neurodevelopmental outcomes. Based on the evidence of efficacy and the safety of anti-TNF agents, anti-TNF therapy should be continued throughout pregnancy.

Anti-TNF Agents and Preterm Birth

Nielsen et al[236] performed a systematic review and meta-analysis on the safety of biologics during pregnancy and assessed the impact of continuing or stopping biologic therapy on the outcome of preterm birth. There were 3 relevant studies by Julsgaard et al,[237] de Lima et al,[238] and Kammerlander et al,[239] comprising 455 pregnant women with IBD. The overall pooled prevalence of preterm birth was 9% (95% CI, 7%–11%; I^2 = 89.9%), with biologic use in pregnancy. This was compared with 10% preterm birth in a cohort of women with IBD and 11% in the background population. The RR estimate was not significant for continuation (n = 244) vs discontinuation (n = 211) of biologic therapy (RR, 1.41; 95% CI, 0.77–2.69; I^2 = 0%). However, as per discussion of the risks of maternal disease flare, the decision to stop therapy was likely not random, with potential preference to discontinue therapy in those who had inactive disease. Data were not always adjusted for maternal disease activity. Individual studies would not have the power to detect a difference due to the low event rate and small cohort sizes. The large emulation trial by Meyer et al included 5293 pregnancies, of which 2403 women continued anti-TNF therapy and 2890 discontinued therapy.[240] Continuation of therapy was associated with a lower frequency of prematurity (7.6% vs 8.9%; aRR, 0.82; 95% CI, 0.68–0.99). The study was propensity-matched, and additional analysis based on cloning, censoring, and inverse probability weighting showed a similar association for preterm births (aRR, 6.8% vs 10.1%; aRR, 0.67; 95% CI, 0.57–0.78) and was also significant for the outcome of very preterm births (aRR, 1.0% vs 1.3%; aRR, 0.81; 95% CI, 0.71–0.98). Truta et al performed a retrospective study based on administrative data, with 318 in the drug continuation cohort and 68 in the drug discontinuation group.[241] There were significantly more preterm births in the early vs late cessation of infliximab group (13.24 vs 6.29%; $P = .049$). In contrast, the PIANO study, in which 786 women continued biologics and 212 discontinued biologics (the vast majority of biologic exposure was with anti-TNF therapy), did not demonstrate an increase in preterm birth in those who were exposed throughout gestation vs those who stopped in the third trimester.[2] The proportion of preterm births was 10%, similar to the background rate ($P = .69$).

Despite the contrasting results, considering cohort sizes, study designs, and potential for unmeasured confounding, specifically data not always being adjusted for maternal disease activity (a known risk factor for adverse perinatal outcomes), discontinuation of anti-TNF therapy may be associated with an increased risk of preterm birth. As such, anti-TNF discontinuation during pregnancy should be avoided.

Anti-TNF Therapy and Congenital Anomalies

Three systematic reviews and meta-analyses have investigated the effect of anti-TNF on the risk of congenital malformations. Leung et al[178] included 784 women exposed to anti-TNF and 1065 not exposed to anti-TNF during pregnancy based on 6 studies. Nielsen et al[242] included 36 abstracts and manuscripts but noted to be imprecise, with marked heterogeneity and an I^2 of 80%. Despite the large number of included individuals after combination, there were small cohort sizes in many of the studies, which could contribute to imprecision. Barenbrug et al included anti-TNF use for IBD and other immune-mediated disorders in their analysis.[243] Leung et al concluded that there was no increase in congenital anomalies in infants born to mothers exposed to anti-TNF therapies during pregnancy (OR, 1.37; 95% CI, 0.73–2.58; I^2 = 3.0%). Nielsen et al reported a pooled prevalence of 1% (95% CI, 1%–2%; I^2 = 78.3%) for congenital malformations, which was comparable to the general population, and on further analysis, there was no increased risk of congenital malformations with anti-TNF exposure during pregnancy (RR, 1.28; 95% CI, 0.47–3.49; I^2 = 0%). Barenbrug et al reported on anti-TNF use in IBD and with other immune-mediated disorders. In total, 21 of the 39 studies included women with IBD, totaling 20,030 pregnancies. There was no increased risk for congenital anomalies, with cohort studies demonstrating a pooled incidence of 3.6% (95% CI, 2.1%–5.5%), and controlled studies showing a pooled incidence of 3.0% (95% CI, 0.4%–8.0%) (with unexposed IBD women as the comparator, 3.6%; 95% CI, 0.6%–9.1%; OR, 0.81; 95% CI, 0.33–1.98; $P = .64$).

Two other large observational studies are not included in the above systematic reviews, Mahadevan et al[2] and Kanis et al,[216] which were published after the 3 systematic reviews. The prospective PIANO registry by Mahadevan et al included 1431 live births, with 642 exposed to biologics.[2] The OR was 1.5 (95% CI, 0.9–25) for congenital malformations and (n = 227) the OR was 1.6 (95% CI, 0.8–3.1) for combination biologics with thiopurines. These data were 'indirect,' as the biologic use population was not specific for anti-TNF therapies, although the vast majority of biologic exposed were on

anti-TNF agents (795/869; 91.4%). The Kanis study followed 1000 children born to mothers with IBD and identified 27 major congenital malformations (2.7%). There were insufficient cases to allow for construction of a multivariable model, but on univariable analysis, there was no association between major CAs and anti-TNF therapy (OR, 1.85; 95% CI, 0.73–4.67; $P = .19$).

The congenital anomaly rate for those exposed to anti-TNF therapies is no different than that of the general population. Notably, the biologics are IgG1 monoclonal antibodies, large proteins that do not cross the placenta during the critical first trimester period of organogenesis. Therefore, from a biologic plausibility standpoint, causation would be unlikely as per the Bradford Hill criteria.

Anti-TNF Therapy and Infant Infections

Regarding infant infections, preterm birth appears to be the major risk factor for adverse outcomes, not drug exposure. When disease activity and/or preterm birth are accounted for, anti-TNFs are not associated with increased infection. The rationale for ongoing therapy is to maintain disease control, which will result directly and indirectly in favorable maternal and infant outcomes.

Barenbrug et al pooled the frequency of neonatal infections in controlled studies based on anti-TNF use in pregnant women with IBD.[243] There was no significant difference in infections with a pooled incidence of 14.2% (95% CI, 6.7%–23.9%) in those exposed to anti-TNF vs 10.1% (95% CI, 3.3%–20.0%) in those who were not exposed to anti-TNF, with an OR of 1.11 (95% CI, 0.98–1.25l $P = .094$). Meyer et al reported 3399 infants exposed to anti-TNF monotherapy with risks of serious infections within the first year of life similar to those of unexposed infants (aHR, 1.10; 95% CI, 0.95–1.27).[219] Importantly, there was a higher risk observed in children exposed to combination thiopurine and anti-TNF therapy (aHR, 1.36; 95% CI, 1.04–1.79). The PIANO registry did not demonstrate an increase in serious infections (infections requiring hospitalization), nonserious infections (infections not requiring hospitalization), or any infection in the first year of life in infants exposed to biologics in utero (the majority exposed to anti-TNF agents).[2] The most common infections were otitis media and upper respiratory infections. Data were provided for infections at birth, by 4 months of life, and within the first year of life, and all comparisons were not significant. Analyses controlling for preterm birth, maternal age, and disease activity were undertaken, and subgroup analyses were performed specifically for anti-TNF agents. Preterm birth was the only independent risk factor for infection (OR, 1.73; 95% CI, 1.19–2.51), and no significant association between exposure and neonatal infections was detected. No association was identified between the risk of infection and drug concentrations. A retrospective multicenter European cohort study included 388 infants exposed to anti-TNF therapies with or without thiopurines compared with 453 who were not exposed.[244] There were low infection rates overall (1.6% vs 2.8% per PY; HR, 1.2; 95% CI, 0.8–1.8), which may contribute to imprecision of estimates; however, similar to the PIANO study, preterm delivery was the only variable associated with a higher risk of severe infection (HR, 2.5; 95% CI, 1.5–4.3). Luu et al did not demonstrate an increased risk of infection in 1457 IBD anti-TNF-exposed pregnancies (aOR, 0.89; 95% CI, 0.76–1.05).[233] Moens et al also conducted an IBD-specific study, with 186 anti-TNF exposed pregnancies, and did not demonstrate a significant difference between infants exposed to vedolizumab, conventional therapies, or anti-TNF agents.[245] Kanis et al identified 140 children who had infections requiring antibiotics in the first year of life (based on general practitioner-reported information) out of a cohort of 1000 children.[216]

Kanis and Meyer performed specific analyses to determine the association between third trimester exposure to anti-TNF therapy and antibiotic-treated infections and severe infections.[216,219] Kanis did not find an association for either antibiotic-treated infections (IRR, 1.06; 95% CI, 0.68–1.66; $P = .78$) or severe infections (IRR, 0.46; 95% CI, 0.16–1.32; $P = .15$). Similarly, Meyer restricted their analysis to 2403 exposed infants with third trimester anti-TNF exposure and did not identify a significant increase in serious infections compared with infants born to 2890 mothers who stopped anti-TNF prior to the third trimester (aHR, 1.08; 95% CI, 0.94–1.25). The anti-TNF serum concentration at birth showed no correlation with the risk of infections during the first year of life.[2,246]

Combination Therapy With Anti-TNF and Thiopurines

Meyer et al identified a higher risk of serious infection during the first year of life in children exposed to combination therapy (aHR, 1.36; 95% CI, 1.04–1.79).[219] The PIANO registry concluded that combination therapy did not lead to an increase in congenital malformations in 227 exposed infants (OR, 1.6; 95% CI, 0.8–3.1) nor an increased risk of any infection in the first year of life (OR, 0.93; 95% CI, 0.66–1.32).[2] Similarly, Kanis et al did not demonstrate an increase in major congenital anomalies (OR, 2.25; 95% CI, 0.59–6.86; $P = .27$) nor antibiotic-treated infections on multivariable modeling accounting for smoking during pregnancy, obstetric complications, and breastfeeding (aIRR, 0.74; 95% CI, 0.45–1.22; $P = .24$) for the use of combination therapy.[216]

Biosimilars

There are limited data on biosimilar use for the management of IBD in pregnancy. There are 2 published observational studies with small cohorts and 1 abstract.[247–249] Of note, existing published data

especially from regions with more widespread biosimilar use (eg, Asia and Europe) may not necessarily differentiate originator from biosimilars but rather may refer to the generic name. The effectiveness, safety, and pharmacokinetic profile of biosimilars likely mirror that of the originator (see anti-TNF and IL23 section). As with all new therapies, close postapproval monitoring should ensue to ensure there are no new safety signals.

Vedolizumab

The risks of exposure to vedolizumab during pregnancy in IBD patients had been evaluated in 2 meta-analyses. The first one was published by Bell et al in 2021.[250] A total of 4 studies were included, with 213 patients exposed to vedolizumab and 628 patients nonexposed. The exposure to vedolizumab was associated with a higher risk of preterm birth and early pregnancy loss. There was no difference in the odds of live births or congenital malformations in pregnancies exposed to vedolizumab in comparison with nonexposed patients. The authors acknowledged some limitations, such as the limited number of studies and events, raising concern about the possibility of overestimating differences between groups that are simply due to chance.[250] Nielsen et al published a second meta-analysis including studies estimating the prevalence of adverse pregnancy outcomes in IBD when using biologics.[236] A total of 48 studies were included; among them, 4 in patients treated with vedolizumab. Subgroup analysis revealed higher prevalence of early pregnancy termination and preterm birth in pregnancies exposed to vedolizumab in comparison with pregnancies exposed to anti-TNF. However, the risk of stillbirth, LBW, or congenital malformation was similar between these 2 groups. Of note, it was not possible to control for relevant confounders such as disease activity or medically refractory disease. More recent prospective studies have shown no increased risk of adverse pregnancy outcomes (including congenital malformations) in vedolizumab-exposed pregnancies.[251–254] The largest study on vedolizumab safety during pregnancy in IBD was published by Meyer et al and included patients from the EPI-MERES registry in France.[255] A total of 398 pregnancies exposed to vedolizumab were compared with 1592 pregnancies exposed to anti-TNF. Overall, compared with anti-TNF, vedolizumab was not associated with increased risks of abortion, CS, stillbirth, preterm birth, serious infections, malignancies, or CA in children.

A recently published systematic review analyzed the pharmacokinetics of monoclonal antibodies during pregnancy.[256] Maternal vedolizumab concentrations seem to decrease over the course of pregnancy in association with increasing weight.[254] However, the transplacental transport of vedolizumab is less efficient than the transport of other biologic agents, and the clearance is faster, with a mean time to clearance of about 3 months and 100% clearance by 6 months.[252,254] Finally, the risk of infections seems not to be increased in children exposed to vedolizumab in utero during their first year of life nor are vedolizumab concentrations at birth associated with the risk of infections.[251,252,254,255]

Ustekinumab

Nielsen et al published a meta-analysis including studies estimating the prevalence of adverse pregnancy outcomes in IBD when using biologics.[236] A total of 48 studies were included; among them, 3 in patients treated with ustekinumab. Subgroup analysis revealed a higher prevalence of early pregnancy termination in pregnancies exposed to ustekinumab in comparison with pregnancies exposed to anti-TNF. Nevertheless, the risk of preterm birth or stillbirth was similar between these 2 groups. Subgroup analyses showed a difference in congenital malformations among children exposed to ustekinumab in comparison with anti-TNF.[236] More recent prospective studies showed no increased risk of adverse pregnancy outcome (including congenital malformations or infections in the infants) in ustekinumab-exposed pregnancies.[251,253,254,257–261] The largest study on ustekinumab safety during pregnancy in IBD was published by Meyer et al and included patients from the EPI-MERES registry in France.[255] A total of 464 pregnancies exposed to ustekinumab were compared, with 1856 pregnancies exposed to anti-TNF. Overall, compared with anti-TNF, ustekinumab was not associated with increased risks of abortion, CS, stillbirth, preterm birth, serious infections, malignancies, or CA in children. However, women exposed to ustekinumab had an increased risk of SGA births. The study is based on administrative data; information on IBD activity was not available, and confounding by IBD activity could not be excluded.[255]

A recently published systematic review analyzed the pharmacokinetics of monoclonal antibodies during pregnancy.[256] Maternal ustekinumab serum concentrations remain stable during pregnancy.[254,256] The mean time to clearance in infants exposed to ustekinumab in pregnancy was about 4 to 6 months and correlates positively with infant delivery concentrations.[254,260] Regarding infections, no increased risk has been observed in children exposed to ustekinumab in utero.[251,253–255,257–261] The ustekinumab serum concentration at birth was not associated with an increased risk of infections during the first year of life.[2,260] The main limitations of these studies include limited sample sizes and the lack of a control group.

IL23 Agents

A recently published series of risankizumab use during pregnancy in women with IBD noted a lower level of drug in the infant vs the mother at birth.[262] From a

mechanistic standpoint, there are emerging data demonstrating a positive association between maternal IL23 levels and preeclampsia, and further data are required to determine if inhibition of this cytokine lowers the risk of preeclampsia or unexplained recurrent spontaneous abortions in pregnant women.[263,264] Although there are currently no published human data on mirikizumab and guselkumab in pregnancy, based on previously discussed placental transfer mechanics and safety of class, these agents can be continued during pregnancy.

Antibiotics (Amoxycillin–Clavulanic Acid, Metronidazole, Ciprofloxacin, Rifaximin)

Control of sepsis is key in any pregnant women, including those with IBD who may also require a combined medical–surgical approach for the management of fistulizing disease. Furthermore, antibiotics are used for the treatment of pouchitis. The safety of metronidazole,[265] amoxicillin[266] (± clavulanic acid), and ciprofloxacin[267] (recent data have not demonstrated an increased risk of major malformations despite early canine and rodent data suggesting a potential risk of arthropathies) has been well-demonstrated in systematic reviews, meta-analyses, and large observational studies, although these have not necessarily been specific for women with IBD. There are no published human data on rifaximin in pregnancy. Finally, a test for GBS is done around week 36 of gestation, and intravenous penicillin-based antibiotics are given during labor if this testing is positive. This is an important treatment to prevent infant infection and should be given to the patient with IBD if appropriate based on testing.

Calcineurin Inhibitors

There are several meta-analyses on the use of cyclosporine in pregnancy, but data are mainly derived from transplant populations rather than IBD. No increase in congenital malformations was reported; however, other adverse outcomes, including spontaneous abortion, prematurity, preeclampsia, and LBW, have been reported.[268,269] These studies could not differentiate the effect of disease activity from calcineurin inhibitor effect vs other medication effect (for example, in the transplant setting, multiple immunosuppressants may be utilized) nor could they account for existing (non-IBD) comorbidities. It should be noted that the use of calcineurin inhibitors in a transplant setting is for a chronic not acute indication, dosages are different, and the patient profile is quite distinct from a patient with IBD. All reported data are indirect and not necessarily extrapolatable to the IBD population, as the studies also had different outcome measures. Furthermore, the need for careful monitoring and the adverse effect profile may limit acceptability and use of cyclosporine. There are even more limited data for tacrolimus use in pregnancy, again derived from transplant populations.

Calcineurin inhibitor data specific to IBD relate to its use as salvage therapy to avoid colectomy. The largest IBD pregnancy series of calcineurin inhibitor use (N = 8) was reported by the GETAID group. There was 1 in utero death; however, the investigators attributed this to protein S deficiency.[270] Other case reports of IBD in pregnancy exist, but there is only a single case report of tacrolimus use in a pregnant woman with IBD.[271–275] Although cyclosporine may be an option for salvage therapy for severe IBD in pregnancy not responding to steroids, the overall safety data may favor the use of anti-TNFs, given both its effectiveness and safety.

S1P Receptor Modulators

Ozanimod and etrasimod are S1P receptor modulators. Teratogenicity has been observed in animal studies. S1P receptors are involved in early developmental processes including angiogenesis, cardiogenesis, limb development, and neurogenesis. Ozanimod was linked to fetal death and severe malformations in rabbits at a dosage equivalent to human exposure (0.92 mg/d). Animal data in rats and rabbits for etrasimod have raised concerns, including embryo lethality and fetal malformations at doses 5 to 6 times higher than those used in human exposure. There is also concern for fetal malformations, skeletal anomalies, and neurobehavioral changes. Recent pharmacovigilance data on ozanimod included 78 pregnancies with 42 live births (10% preterm births), with the remaining comprised of spontaneous abortions and elective terminations (although none were attributed to known congenital anomalies). There were 14 pregnancies in women with UC and 6 pregnancies in women with CD, with no preterm deliveries or congenital anomalies among the reported total 9 live births. Ozanimod was discontinued in all pregnancies with no exposures beyond the first trimester.[276] Etrasimod reports 9 maternal exposures in their clinical program, resulting in 2 healthy newborns, 4 medical terminations, 1 congenital malformation (patent foramen ovale), and 1 spontaneous abortion.[277]

Given the lack of data, the oral small molecule class of S1P receptor modulators is currently relatively contraindicated during pregnancy. Shared decision-making is imperative. If there is no effective alternative therapy to maintain maternal health, general principles are that stringent disease control of IBD results in the most favorable maternal and fetal outcomes.

Janus Kinase Inhibitors

JAKis are small molecules that passively traverse the placenta throughout pregnancy. Concerns about teratogenicity arise from animal studies. Preclinical investigations in rabbits demonstrated that tofacitinib

exhibited feticidal and teratogenic effects at a dosage 6.3 times higher than the maximum human dose of 10 mg twice daily.[278] Similarly, exposure to a dose equivalent to a human dose of 200 mg of filgotinib resulted in fetal death and severe malformations in rats and rabbits.[279] In pregnant rats and rabbits, upadacitinib administration led to musculoskeletal and cardiovascular malformations at doses comparable to those used in humans.[280] Human data are limited by small numbers and the fact that most information comes from first-trimester exposure before women stopped the drug at the detection of pregnancy. Monfared et al report 2 serious congenital malformations in 55 live births exposed to tofacitinib, 1 serious malformation in 21 live births exposed to filgotinib, and no malformations in 30 live births exposed to upadacitinib.[281] For tofacitinib, 74 maternal exposures have been reported, with no pattern of spontaneous abortion or congenital anomalies.[282] In a total of 128 pregnancies among women exposed to upadacitinib (mean, 5 weeks 3 days), similar results were found.[283] Consequently, JAKis are relatively contraindicated during pregnancy. Manufacturers recommend discontinuation of these medications at least 4 weeks prior to planned conception for tofacitinib and upadacitinib and at least 1 week prior for filgotinib.

A detailed discussion should take place with females of childbearing age regarding the use of oral small molecules. In general, one would discourage the use of oral small molecules in the preconception, pregnancy, and lactation phases, unless there is no effective alternative therapy to maintain maternal health. However, this is distinct from simply having childbearing potential. Women with no plans for conception in the immediate future should not be denied small molecules if most appropriate for their disease. For women for whom there is no other option to maintain remission, JAKis can be continued after a detailed discussion of benefits (keeping disease under control for better maternal and fetal outcomes, avoiding profound illness in mother including colectomy) versus the risks (potential risk of birth defects).

Use of IBD Medications During Lactation

	GRADE statement	GRADE recommendation	Level of evidence
21	We recommend breastfeeding as it is NOT associated with an increased risk of disease exacerbation in women with IBD	Strong	Very low
22	We suggest counseling that infants born to mothers on anti-TNF who breastfeed have no increased risk of infection in the first 12 months of life	Conditional	Very low

Consensus statements

23	Mothers with IBD currently on 5-ASA/sulfasalazine may breastfeed
24	Mothers with IBD currently on thiopurines may breastfeed
25	Mothers with IBD currently on corticosteroids may breastfeed
26	Mothers with IBD currently on anti-TNF agents (infliximab, adalimumab, golimumab, certolizumab) may breastfeed
27	Mothers with IBD currently on anti-integrins (vedolizumab, natalizumab) may breastfeed
28	Mothers with IBD currently on anti-IL12/23 and anti-IL23 agents may breastfeed (ustekinumab, risankizumab, mirikizumab, guselkumab)
29	Mothers with IBD currently on biosimilars may breastfeed
30	Mothers with IBD currently on S1P receptor modulators (etrasimod or ozanimod) should not breastfeed
31	Mothers with IBD currently on JAKi (tofacitinib, upadacitinib, filgotinib) should not breastfeed

Is Breastfeeding Beneficial or Harmful in IBD

In animal studies, normal breast milk was shown to limit the development of colitis in IL10-deficient mice, and milk exosomes prevented intestinal inflammation in a genetic mouse model of UC.[284] In human studies, 4 systematic reviews studying different durations of breastfeeding demonstrated a consistent protective effect of breastfeeding against the risk of IBD.[25,285–287] Specifically, in an earlier systematic review of 35 studies, being breastfed was associated with a lower risk of CD (OR, 0.71; 95% CI, 0.59–0.85) and UC (OR, 0.78; 95% CI, 0.67–0.91), with the strongest inverse association for those who had at least 12 months of breastfeeding.[287] The study also found that the magnitude of protection from breastfeeding against CD was significantly higher among Asians (OR, 0.31; 95% CI, 0.20–0.48) than Caucasians (OR, 0.78; 95% CI, 0.66–0.93). One recent meta-analysis, including 2 cohort studies and 40 case–control studies, further supported the notion that breastfeeding was protective against IBD, both CD and UC.[25] However, only 3 studies within this meta-analysis have adjusted for family history of IBD or paternal history of IBD.[288–290] To date, most of the evidence for breastfeeding's protective role has been derived from observational studies of healthy mothers

without IBD.[291,292] Therefore, this putative protective effect of breastfeeding might be biased by maternal IBD status, and it is unclear whether this protective effect can be directly inferred for the offspring of mothers with IBD.[291] Additionally, other studies report that early-life breastfeeding was not associated with IBD diagnosis in childhood or later in life.[293,294] A population-based case–control study from northern France reported that partial or exclusive breastfeeding was a risk factor for pediatric CD with an OR of 1.6 (95% CI, 1.1–2.4; $P = .01$) and an OR of 1.6 (95% CI, 1.1–2.5; $P = .01$), respectively, but not for pediatric UC.[286,295] One hypothesis is that pollution in breast milk, such as drugs, industrial chemicals, and environmental contaminants, in highly industrialized regions, may be contributing factors.[295]

It is also important to consider the impact of inflammatory chemicals or profile of breast milk among mothers with IBD. Human studies have shown that breast milk of mothers with IBD had lower soluble immunoglobulin, higher inflammatory mediators, and higher fat content than those of mothers without IBD.[296,297] A recent case–control study indicated that mothers with IBD displayed a lower abundance of immune regulation-related proteins in their breast milk than control mothers, which negatively correlated with the baby's FC and microbiome composition at different time points.[298] Currently, the long-term impact of these findings is not clear, and it is uncertain whether these observed differences in breast milk affect the risk of IBD in their offspring.

The literature supports breastfeeding as a generally safe and beneficial practice for mothers with IBD. However, misconceptions around the safety of this practice persist.[291,292] Furthermore, well-designed and large-scale prospective human studies, especially focusing on the role of breastfeeding and subsequent development of IBD in offspring of mothers with IBD, are necessary as are preclinical studies in germ-free animals to assess the impact of breast milk of the mothers with IBD on susceptibility to IBD in the next generation.

Breastfeeding and Disease Activity

Four retrospective cohort studies have been published, including 543 women with IBD who delivered a baby, of whom 414 (76%) breastfed their baby.[299–302] A meta-analysis did not show a significant effect of breastfeeding on postpartum disease activity (OR, 0.89; 95% CI, 0.35–2.29, $I^2 = 74.0\%$; Tau2 = 0.67, $\chi^2 = 11.63$; $P = .01$).[231] A single-center study by Kane et al demonstrated a lower frequency of breastfeeding overall (54/122; 44%).[301] This was driven, in part, by cessation of IBD medications after delivery and throughout the duration of breastfeeding by many women. The women who ceased IBD medications prior to commencing breastfeeding (40/54; 74%) were at an increased risk of disease activity in the postpartum period, underscoring that IBD medications should not be stopped in the postpartum period.

Medications

For most drugs, the weight-adjusted percentage of the maternal dosage, also known as the relative infant dose (RID), of ≤10% is considered low risk during breastfeeding. Table 9 summarizes the medications compatible with use during lactation.

5-Aminosalicylates and Sulfasalazine

Low levels of mesalamine and its N-acetyl-5-ASA metabolite have been detected in breast milk, resulting in an RID of less than 1%.[303] A case–control study compared the infants of mothers taking mesalamine (n = 117), olsalazine (n = 2), or sulfasalazine (n = 2) with infants of matched controls (n = 121). Infants were exposed to mesalamine through milk for a mean of 5.3 months (range, 3 days–24 months), were breastfed for an average of 7.4 months, and were followed up at an average age of 22 months. No difference in the frequency or characteristics of maternally reported adverse events was found between exposed and control infants.[304] In addition, 10 case reports of mesalamine use during breastfeeding found diarrhea in only 1 infant.[305,306] A few cases of infant diarrhea have been reported with maternal mesalamine use. In one case, diarrhea recurred 4 times after rechallenge with breastfeeding.[307]

Sulfasalazine itself appears in milk at undetectable to low levels (RID <1%); however, its metabolite, sulfapyridine is found in higher levels in milk and the serum of breastfed infants.[198] One case of bloody diarrhea was reported in a breastfed infant, which ceased after the mother, who was a slow acetylator, stopped taking sulfasalazine.[308] The reaction was thought to be caused by sulfapyridine. Although the amounts of sulfapyridine are not high enough to cause kernicterus,[198,309] mesalamine derivatives that do not contain a sulfonamide are preferred over sulfasalazine.

Thiopurines

Measurements of various thiopurine metabolites in breast milk have generally found either undetectable levels of the drugs and their active metabolites or very low levels leading to an RID of less than 1%.[310–312]

Three cohort studies and 1 prospective study of women with IBD taking azathioprine or mercaptopurine (total N = 252) during nursing were followed for periods from 1 to 6 years.[313–316] No differences in growth, development, and infant risk of infections were found between the breastfed and nonbreastfed infants. Multiple studies, case series, and case reports in women taking azathioprine for non-IBD conditions while breastfeeding have reported no serious adverse effects in infants.[307] A multicenter case series of 37 breastfed infants whose mothers were taking thioguanine for IBD also reported no adverse events.[226]

Allopurinol–Thiopurine Combination Therapy

Low-dose (50–100 mg/d) allopurinol is used in combination with reduced-dose azathioprine or mercaptopurine to enhance the production of an active metabolite and shunt metabolism away from a toxic metabolite. Information on allopurinol during breastfeeding is limited to data from 1 patient and a survey of gastroenterologists. The patient was taking allopurinol 300 mg daily, and her breastfed infant had oxypurinol blood levels of 33% to 48% of the measured maternal plasma oxypurinol levels. The infant had no observable side effects and no changes in clinical chemistry or hematology values.[317] The survey of gastroenterologists in Australia identified 21 infants exposed to allopurinol and thiopurine during breastfeeding. At a median follow-up of 6 months (range, 0–48 months), 2 infant deaths were reported at 3 months of age but thought to be due to other causes (sudden infant death syndrome and preterm birth).[318] Therefore, although the authors support breastfeeding while on thiopurines, breastfeeding while on allopurinol plus thiopurines should be avoided, given little supportive data and reports of possible harm.

Methotrexate

MTX is used in IBD at a low dose once weekly. Only a few cases of breastfeeding by MTX-treated mothers have been reported, with no adverse effects noted in the infants.[319,320] MTX passes into breast milk, and the RID is low (0.11%).[320] However, the active metabolite 7-hydroxymethotrexate is detectable in breast milk. The MTX exposure of breastfed infants decreases by 40% 24 hours after maternal MTX intake.[307] It has been speculated that breastfeeding can be maintained during low-dose weekly MTX treatment ($\leq$25 mg/wk), provided that breastfeeding is not initiated within the first 24 hours of MTX intake.[307] If breastfeeding on low-dose weekly MTX is undertaken, clinical and biochemical monitoring of the infant should be considered.[307] However, given the potential harmful effects in suckling infants due to measurable concentrations of the active metabolite 7-hydroxymethotrexate and the limited data available regarding the use of MTX during breastfeeding, breastfeeding should be avoided among mothers on MTX. If low-dose MTX ($\leq$25 mg/wk) is used and no alternative drug compatible with breastfeeding is available, and the mother strongly desires breastfeeding, it may be considered with close monitoring of the infant.

Corticosteroids

Prednisone and prednisolone. Prednisone is converted to prednisolone, which is the active drug. However, both prednisone and prednisolone are excreted into milk, and the infant can convert prednisone into prednisolone. Thus, the total concentration of the 2 drugs in milk is the relevant value. Prednisone and prednisolone have been measured in the milk of 24 women; 21 taking prednisone and 3 taking prednisone.[307] "Worst-case" amounts in milk have been less than 100 μg/d with maternal maintenance doses up to 120 mg/d.[321,322] In 1 case of a single 1-g intravenous dose of prednisolone, the daily infant dose would be 0.32 mg/kg, which is about one-sixth of a therapeutic child's dosage of 2 mg/kg daily.[323] Prior recommendations to wait 4 hours after a dose before breastfeeding with high maternal doses have been shown to be unnecessary in recent studies.[321] The National Transplantation Pregnancy Registry reports that as of December 2013, 124 women with transplants have taken prednisone while breastfeeding 169 infants for periods as long as 48 months, with no reported infant harm.[324] In addition, another 34 case reports and series of infants breastfed during maternal therapy with up to 60 mg/d have reported no adverse effects in their breastfed infants.[307]

Budesonide. There is very little published information on the effects of budesonide on infant outcomes during breastfeeding. The estimate of passage into breast milk relies on manufacturer's data from the product information. After oral administration, budesonide undergoes ~90% first-pass metabolism to 2 inactive metabolites, so little reaches the bloodstream. The manufacturer reports that the maximum budesonide plasma concentration following a 9 mg/d oral dose is low, with a range from 2.2 to 4.3 μg/L.[307] Because the drug is only about 9% absorbed orally, the infant's systemic RID would be about 0.27%.[307]

Biologic Agents

Monoclonal antibodies penetrate milk poorly (Figure 2). Among 30 studies that were reviewed in 2020, most found undetectable levels in milk; the maximum concentration in milk was less than 1% of the maternal serum concentration for biologics used to treat IBD.[325] Studies of oral administration of IgG antibodies to infants found that an average of 50% (range, ~30%–70%) of the IgG antibody in the infant's gut is digested.[326–329] Absorption of the remaining IgG may depend on infant age, because in the early postpartum (ie, colostral and transitional) phases of breastfeeding, the infant's gut is somewhat permeable to macromolecules. One study found only about 0.01% absorption of IgG in adults using a radiolabeled technique.[330] If these values are multiplied, an older breastfed infant would receive (RID) less than 0.005% of the maternal serum concentration attributable to breastfeeding (Figure 3). Of note, in infants exposed in utero to infliximab, adalimumab, vedolizumab, or ustekinumab, maternal breastfeeding did not affect neonatal clearance of the monoclonal antibody.[246,252,260]

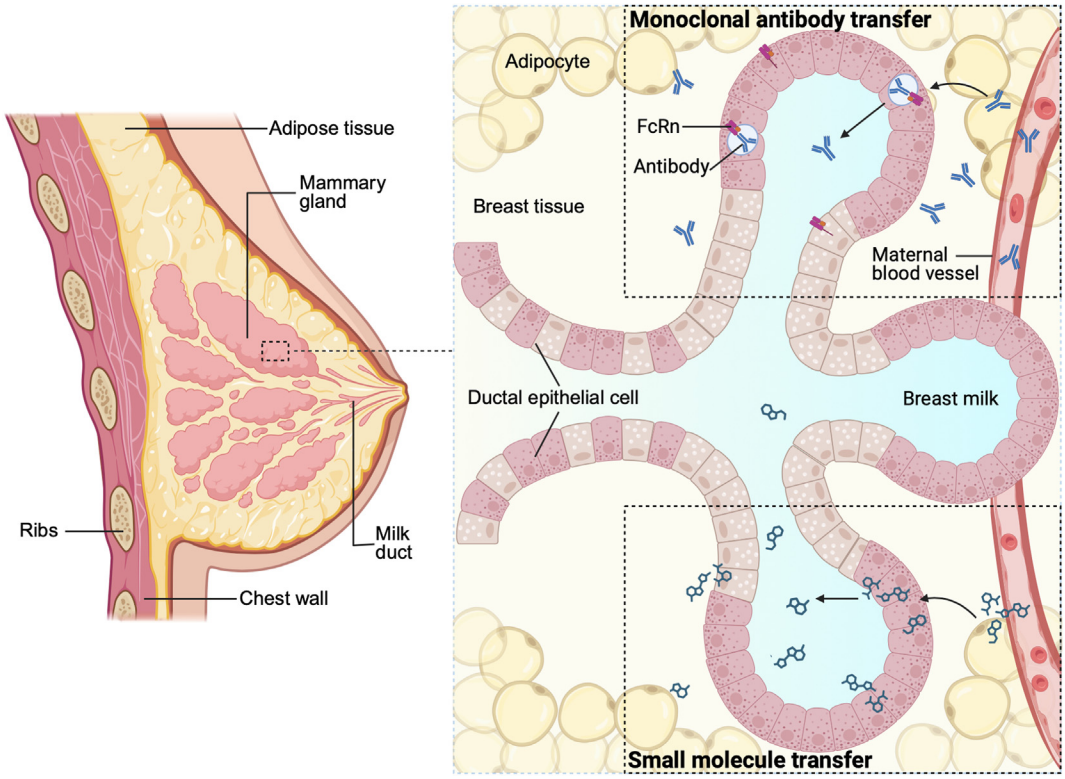

Figure 2. Passage of monoclonal antibodies and small molecules into breast milk. Low antibody transfer from maternal blood to breast milk is mediated by FcRn. The transfer of small molecules is believed to occur through diffusion across mammary epithelial cells.

Infant Clinical Outcomes

In the PIANO registry, 243 women received biological monotherapy, primarily with an anti-TNF (96%), while breastfeeding their infants. Among those who received a biologic agent while breastfeeding, infant growth, development, or infection rate during the first year of life was no different from infants whose mothers did not breastfeed (n = 79). This was also the case among an additional 67 breastfed infants of mothers receiving combination therapy with a biologic (primarily anti-TNF) and thiopurine compared with 33 nonbreastfed infants of mothers receiving combination therapy.[316]

In addition to data from the PIANO registry, there are numerous reports of nursing infants of mothers receiving treatment with a monoclonal antibody. The following case reports, case series, and studies that report infant infection status have been abstracted from the Drugs and Lactation Database (LactMed).[307] For infliximab, adalimumab, and certolizumab, an additional 22, 7, and 10 exposed infants, respectively, were followed for approximately 12 months with no reports of serious infections. For natalizumab, 17 additional infants in the German MS and Pregnancy Registry were followed for 1 year, revealing no increased risk of serious infections. For vedolizumab, 106 additional infants, with most being followed for at least 10 months, and no increased risk of infections was reported. For ustekinumab, 122 additional infants had no increase in infections in 3 to 12 months of follow-up. No data are available on breastfeeding while being treated with risankizumab, mirikizumab, guselkumab, or biosimilars to monoclonal antibody originators for the treatment of IBD. However, given that they are all monoclonal antibodies, they may

Figure 3. Relative infant dose: estimating infant exposure to monoclonal antibodies via breast milk.

also be considered low risk during breastfeeding based on pharmacokinetics of transfer into breast milk and minimal to no absorption through the infant gut.

S1P Receptor Modulators

Etrasimod and ozanimod currently have no available human lactation data. European labeling recommends that women receiving etrasimod or ozanimod should not breastfeed.[331,332] United States labeling highlights the need for risk–benefit evaluation with respect to breastfeeding while receiving etrasimod or ozanimod but does not contraindicate the drugs during breastfeeding.[333,334] The plasma protein binding of both etrasimod and ozanimod and its metabolites is ≥98% per United States Food and Drug Administration–approved labeling.[333,334] Given the limited amount of free drug accessible to enter breast milk, the passage into human milk ought to be extremely small.[307] Human data are needed to elucidate this.

Janus Kinase Inhibitors

Tofacitinib was detected in all breast milk samples (N = 55) of 2 lactating women with UC on tofacitinib 10 mg twice daily and 5 mg twice daily, respectively,[335,336] with the lowest concentration 14 hours after oral intake. The tofacitinib concentration was higher in human milk than in plasma at 2 single time points at 5.5 and 8 hours after oral tofacitinib intake.[336] Based on the highest milk concentration, both cases revealed that the infant would receive (RID), at worst, 3.4% of the mother's weight-adjusted dosage.[335,336] This percentage is higher than that found in other drugs used to treat IBD, but lower than the internationally accepted arbitrary safety cutoff value of 10%.[310,320,335–339] Considering these findings, along with a mean tofacitinib half-life of 3.2 hours, the labeling recommendation to refrain from breastfeeding for at least 18 hours after oral intake of the immediate-release product and 36 hours after the sustained-release product makes breastfeeding not feasible in a mother regularly taking this medication.[278] Of note, in 3 infants exposed to tofacitinib during pregnancy and breastfeeding, normal infant development was noted at the age of 3.5, 12, and 14 months of age, respectively.[335,340] Moreover, at 12 weeks of age, a comprehensive immunologic assessment was conducted on a fully breastfed infant exposed to tofacitinib, with normal results.[341]

With respect to upadacitinib and filgotinib, it is currently unknown whether these drugs or their metabolites are excreted in human milk. Both European and United States labeling recommend avoidance of breastfeeding.[279,280,307]

In summary, due to limited or no human safety data including unknown effects on the immune system of the suckling infant, breastfeeding should be avoided on S1P receptor modulator or a JAKi therapy at this time. Careful monitoring of the infant is recommended if the patient chooses to breastfeed despite the current recommendation against it.

Antibiotics

Short-term use of most antibiotics during lactation is generally considered low risk. Metronidazole and ciprofloxacin are the most frequently prescribed antibiotics for patients with IBD. Metronidazole and its metabolite are excreted into breast milk with a median absolute infant dose of 1.59 mg/kg/d equivalent to 10.61% of the "therapeutic infant dose."[342] Passmore et al calculated that a breastfed newborn consuming 500 mL of milk daily from a mother taking 400 mg of oral metronidazole 3 times daily would receive less than 10% of the recommended metronidazole dose for newborns.[343] Infants exposed to metronidazole through breast milk have shown instances of diarrhea and increased growth of *Candida* species in oral and perianal swabs.[307] After a single 2-g dose of metronidazole in breastfeeding women, peak drug concentration in breast milk occurs 2 to 4 hours postadministration, gradually decreasing over 12 to 24 hours.[344] Given relatively high exposure to metronidazole and its metabolite through breast milk, and its unknown effects on the microbiome and immune system of the infants, we generally advise against breastfeeding for mothers taking metronidazole. However, if a short course of oral metronidazole (eg, 1 week) is necessary, we recommend closely monitoring the infant for possible effects on gastrointestinal flora, such as diarrhea or candidiasis.

Ciprofloxacin, a fluoroquinolone, has minimal concentrations in breast milk. Although milk calcium could potentially reduce absorption of small fluoroquinolone amounts in milk, there are insufficient data to confirm or refute this hypothesis.[307] In a study of 3 nursing women receiving 750 mg ciprofloxacin twice daily, the peak concentration in breast milk of 3.79 mg/L occurred 2 hours after maternal intake, equivalent to an estimated low maximum infant exposure of 0.57 mg/kg/d. Of note, the ciprofloxacin concentration in milk at 12 and 24 hours after intake reached a very low concentration of 0.20 and 0.02 mg/L, respectively.[345] Very few side effects have been reported in newborns of mothers treated with ciprofloxacin during lactation.[307] In summary, ciprofloxacin is of low risk in nursing mothers. Monitoring of the infant for potential effects on the gastrointestinal flora such as diarrhea or candidiasis is advisable. Other commonly used antibiotics in IBD, including amoxicillin and vancomycin, are also considered low risk in nursing mothers.[307]

Medication for Endoscopy While Breastfeeding

As highlighted in the 2012 guideline for endoscopy in pregnant and lactating women by the American Society for Gastrointestinal Endoscopy (ASGE), the sensitivity to

and risks of sedation in a lactating woman are comparable to those for any adult.[116]

Midazolam is excreted in low doses in breast milk.[307] A mother undergoing surgery received a single intravenous dose of 6 mg of midazolam for anesthesia induction. The concentration of midazolam in her breast milk was 25 μg/L at 30 minutes postdose, 12 μg/L at 1 hour postdose, and 7 μg/L at 2 hours postdose. After 4 hours, the drug was undetectable (<5 μg/L).[307,346] In another study, 5 women who were 6 to 15 weeks postpartum, were given a single 2-mg intravenous dose of midazolam before undergoing general anesthesia with propofol and fentanyl. Multiple milk samples were collected from each woman between 5 and 24 hours after the injection. It was estimated that the infants would receive an average of 0.016 μg/kg of midazolam in the 24 hours following a single dose, which corresponds to 0.06% of the RID. Hydroxymidazolam levels were not measured.[307,347] This amount of midazolam in breast milk is unlikely to affect a healthy full-term infant. The 2012 ASGE guideline recommends withholding nursing of the infant for 4 hours following the administration of midazolam, given the paucity of data. With a newborn or preterm infant, a cautious approach would be to wait a period of 6 to 8 hours before resuming nursing.[307] After conscious sedation, breastfeeding can be resumed as soon as the mother has recovered sufficiently to nurse.[307]

Fentanyl is excreted in low doses in breast milk.[307] Five women, who were 6 to 15 weeks postpartum, received a single intravenous dose of 100 μg of fentanyl before undergoing general anesthesia. Multiple milk samples were collected from each woman between 5 and 24 hours after the injection. It was estimated that infants would receive an average of 0.005 μg/kg of fentanyl in the 24 hours following a single dose, which is approximately 0.38% of the RID.[347] This small amount of fentanyl in breast milk is unlikely to affect a healthy full-term infant. Therefore, no waiting period or discarding of milk is required before resuming breastfeeding after fentanyl is used for endoscopy. After conscious sedation, breastfeeding can be resumed as soon as the mother has recovered sufficiently to nurse.[307]

Propofol is excreted in very low doses in breast milk.[307] Five women, who were 6 to 15 weeks postpartum, received a single intravenous dose of 2.5 mg/kg of propofol before undergoing general anesthesia. Multiple milk samples were collected from each woman between 5 and 24 hours after the injection. It was estimated that infants would receive an average of 0.0052 mg/kg of propofol in the 24 hours following a single dose, which corresponds to 0.2% of the RID.[347] Therefore, breastfeeding can be resumed after maternal propofol administration as soon as the mother has recovered sufficiently from conscious sedation to nurse.[116,307]

Imaging Studies While Breastfeeding

Intravenous iodinated contrast media and gadolinium-based contrast are poorly excreted into breast milk and poorly absorbed orally, making it unlikely for them to enter an infant's bloodstream or cause adverse effects in breastfed infants.[307] The plasma half-life of intravenous iodinated contrast agents is 2 hours, with nearly 100% excreted in 24 hours. The iodinated contrast agents have poor lipid solubility, and less than 1% of the dose enters breast milk. Furthermore, less than 1% of this ingested dose is absorbed by the infant's gastrointestinal system. Therefore, the RID will be less than 0.01%. A report indicating trace amounts of iodine from iodixanol in breast milk supports this conclusion.

The plasma half-life of intravenous gadolinium-based contrast agents is 2 hours, with nearly 100% excreted in 24 hours. It is estimated that less than 0.0004% of the maternal dose is absorbed by the infant, and it is also thought that any gadolinium in breast milk is in a stable chelated form. In accordance with guidelines from international radiology societies, breastfeeding does not need to be interrupted after a nursing mother receives an iodine-containing or gadolinium-based contrast medium. However, if the mother is concerned about infant exposure to contrast agents, a breastfeeding abstinence period of 24 hours is more than adequate to avoid any infant exposure.

Pregnancy Adverse Events

GRADE statement	GRADE recommendation	Level of evidence
23 We suggest counseling that women with IBD as compared with women without IBD have an increased risk of adverse pregnancy outcomes including LBW and preterm delivery	Conditional	Very low
24 We suggest counseling that women with IBD with moderate to severe disease activity have an increased risk of spontaneous abortion as compared with women without IBD or women with mild IBD	Conditional	Very low
25 We suggest counseling that pregnant women with IBD have an increased risk of VTE during pregnancy as compared with pregnant women without IBD	Conditional	Low

Continued

GRADE statement	GRADE recommendation	Level of evidence
26 We suggest counseling that pregnant women with IBD have an increased risk of VTE during postpartum as compared with pregnant women without IBD	Conditional	Low
Consensus statement		
32 Controlling disease activity during pregnancy among women with IBD is critical to reduce adverse outcomes		

Preterm Birth, LBW, and Congenital Malformations

Data have been consistent on the risk of LBW and preterm birth. The earliest data come from a meta-analysis by Cornish et al published in 2007.[348] Eight of the 12 studies reported on the incidence of premature birth in 1716 patients with IBD vs 298,105 controls. Patients with IBD were more likely to have premature infants than controls (OR, 1.87; 95% CI, 1.52–2.31; $P = .001$). Analysis of patients with CD vs controls (OR, 1.97; 95% CI, 1.36–2.87; $P = .001$) and patients with UC vs controls (OR, 1.34; 95% CI, 1.09–1.64; $P = .005$) also showed significant differences in the incidence of premature gestation. Three studies reported on the incidence of LBW in infants born to patients with IBD vs controls. A difference was observed in the incidence of LBW in infants born to mothers with IBD (OR, 2.1; 95% CI, 1.38–3.19; $P = .001$). Although the incidence of LBW was not significant in UC, there was increased incidence of LBW in infants born to mothers with CD (OR, 2.82; 95% CI, 1.42–5.60; $P = .003$). Four studies reported on the incidence of CAs between patients with IBD and controls, and overall, did not show a difference. However, a difference was found in the incidence of CAs in patients with UC vs controls (OR, 3.88; 95% CI, 1.41–10.67; $P = .009$) but not in patients with CD vs controls ($P = .06$). One of the major weaknesses of this early work was the lack of information on disease activity and outcomes.

In 2011, Bortoli et al published their experience of patients from the ECCO (European Crohn's Colitis Organization) cohort.[349] There was no difference in preterm deliveries, LBW, and CAs compared with non-IBD pregnant controls. A population-based Swedish cohort from 2014[350] reported pregnancies from 2006 to 2010, prior to biologic exposure. Preterm births were more common (8.4%) in women with UC or CD as compared with women without IBD (5.0%). The aORs for preterm births were 1.78 (95% CI, 1.49–2.13) for UC and 1.65 (95% CI, 1.33–2.06) for CD. The highest risk for preterm birth and spontaneous preterm birth was found among those with active disease. Analyses of LBW exhibited a similar pattern with risks for UC in general at an aOR of 1.64 (95% CI, 1.31–2.04) and for CD at an aOR 1.86 (95% CI, 1.46–2.38). For active UC, the risk estimate in the adjusted analysis was doubled, and for CD, tripled.

A Dutch population-based cohort of 86,591 women included 666 diagnosed with IBD (278 CD, 388 UC).[129] Overall, women with IBD had rates of preterm birth that were 2-fold greater than those observed in women without IBD (HR, 2.20; 95% CI, 1.71–2.84). This association appeared stronger for UC than for CD, but the estimates were not significantly different from one another ($P = .29$). Women with IBD who used oral corticosteroids during pregnancy (likely a marker of active disease) were at particularly high risk of delivering prematurely (HR, 6.32; 95% CI, 3.13–12.7).

A meta-analysis published by O'Toole et al in 2015 found that women with CD (OR, 1.77; 95% CI, 1.52–2.06) and UC (OR, 1.77; 95% CI, 1.53–2.04) were more likely to deliver preterm. A higher OR of 2.28 (95% CI, 2.00–2.60) was obtained for those with unspecified IBD. In the 11 studies looking at SGA infants, the pooled OR was 1.36 (95% CI, 1.16–1.60), but there was statistical heterogeneity found for this outcome as well as for CAs (OR, 1.29; 95% CI, 1.05–1.58). Similar data were reported from New South Wales, Australia in 2016 by Shand et al,[351] by Abdul Sultan et al[352] from the Clinical Practice Research Datalink, a large longitudinal UK database, from Korea by Lee et al in 2020,[59] from Canada by Tandon et al[353] in 2021, and from Yu et al[354] with the United States National Inpatient Sample. In a second study using the National Inpatient Sample, Tarar et al studied 14,129 IBD pregnancies between 2016 and 2018.[123] Pregnant women with IBD had a higher rate of preterm delivery compared with those without IBD (2.97% vs 2.06%; $P < .01$). Pregnancies with a codiagnosis of IBD led to poor fetal growth (aOR, 1.27; 95% CI, 1.00–1.63; $P = .04$) and a higher odds of preterm delivery (aOR, 1.41; 95% CI, 1.13–1.76; $P = .003$).

In the French national health care database, 31,904 patients with IBD and 8,595,562 controls completed a pregnancy between April 1, 2010, and December 31, 2018. Pregnancies in women with IBD vs those without IBD more frequently resulted in preterm birth (8.0% vs 5.5%; aOR, 1.51; 95% CI, 1.45–1.58), SGA (11.1% vs 9.8%; aOR, 1.15; 95% CI, 1.10–1.20), and LBW (8.2% vs 6.1%; aOR, 1.38; 95% CI, 1.31–1.45). As compared with non-IBD pregnancies, ORs were higher for pregnancies with active IBD than for those without active IBD during pregnancy for preterm birth (aOR, 2.14; 95% CI, 1.99–2.30 and aOR, 1.28; 95% CI, 1.22–1.36, respectively), LBW (aOR, 1.82; 95% CI, 1.67–1.98 and aOR, 1.22; 95% CI, 1.15–1.29, respectively), and SGA birth (aOR, 1.27; 95% CI, 1.17–1.38 and aOR, 1.10; 95% CI, 1.05–1.16, respectively).

Marild et al[355] reported outcomes of infants of women with vs without histologic inflammation documented during or up to 12 months prior to pregnancy. Preterm birth was noted in 9.6% (n = 117) and 6.5% (n = 41), respectively (aRR, 1.46; 95% CI, 1.03–2.06).

Histologic inflammation was associated with preterm birth in UC (aRR, 1.64; 95% CI, 1.07–2.52), especially extensive colitis (aRR, 2.37; 95% CI, 1.12–5.02), but not in CD (aRR, 0.99; 95% CI, 0.55–1.78). In sensitivity analyses, the aRRs for preterm birth were similar for histologic inflammation within 6 months before pregnancy (aRR, 1.41; 95% CI, 0.90–2.21) and histologic inflammation during pregnancy (aRR, 1.38; 95% CI, 0.72–2.64). Neither inflammation 0 to 6 months before pregnancy (aRR, 0.83; 95% CI, 0.54–1.25) nor inflammation during pregnancy (aRR, 1.21; 95% CI, 0.58–2.52) was significantly associated with SGA. However, a sensitivity analysis of 726 children of women with clinically quiescent IBD found that the presence of histologic inflammation (vs no inflammation) was not significantly associated with preterm birth (aRR, 1.20; 95% CI, 0.68–2.13) nor associated with SGA.

Spontaneous Abortion

Spontaneous abortion is associated with active disease, but not necessarily IBD alone. Bortoli et al did not find a difference in the ECCO cohort for spontaneous abortion between CD (OR, 1.30; 95% CI, 0.41–4.06) and UC (OR, 0.62; 95% CI, 0.26–1.52).[349] In a meta-analysis by Tandon et al including 22 studies (4094 pregnancies),[128] the pooled incidence of early pregnancy loss in patients with IBD was 10.8% (95% CI, 9.1%–12.5%), 11.5% (95% CI, 7.4%–15.5%) in UC, and 10.9% (95% CI, 7.2%–14.6%; $I^2 = 67.2\%$) in CD. The pooled OR of early pregnancy loss in patients with IBD compared with healthy controls was 1.63 (95% CI, 0.49–5.43). In the Korean population-based study, spontaneous abortion rates of the control, UC, and CD groups were 11.9%, 13.3%, and 12.9%, respectively.[59] However, Magnus et al[356] found a 21% miscarriage rate in their Norwegian registry study. The OR was 1.31 in CD (95% CI, 1.18–1.45) and 1.07 (95% CI, 0.98–1.16) in UC. Although it seemed that women with IBD had higher spontaneous abortion rates compared with the control group, the difference was not significant on multivariable analyses (controls vs UC: OR, 1.12; 95% CI, 0.96–1.31; controls vs CD: OR, 1.15; 95% CI, 0.90–1.46). However, with moderate to severe disease, higher rates of spontaneous abortion are seen (14.9% vs 11.9%; OR, 1.33; 95% CI, 1.04–1.68). The PIANO registry also reported higher rates of spontaneous abortion (HR, 3.41; 95% CI, 1.51–7.69) with increased disease activity.[2]

VTE in Pregnancy and the Postpartum

In 2016, Abdul Sultan et al[352] reported an increased odds of VTE in IBD (OR, 2.48; 95% CI, 1.23–5.00), driven by an increased odds for UC (OR, 3.49; 95% CI, 1.43–8.47) and unchanged odds for CD. The VTE risk may be further increased with the use of long-term corticosteroids for IBD.[357] From the meta-analysis published by Kim et al,[358] a significant increase in VTE risk during pregnancy was found in women with IBD compared with non-IBD controls with a pooled RR of 2.13 (95% CI, 1.78–2.66; $P < .001$). The pooled RR of VTE during pregnancy increased significantly in patients with UC (RR, 2.24; 95% CI, 1.61–3.11; $P < .001$) and CD (RR, 1.87; 95% CI, 1.09–3.19; $P = .001$). The pooled RRs of pregnancy-associated VTE during disease flares increased to 7.81 (95% CI, 0.90–67.78). In the previously cited study by Yu et al,[354] an aRR of 2.76 (95% CI 2.39–3.18) for VTE was reported. The RRs were all higher when at least one episode of disease was coded as active (RR, 11.69; 95% CI, 11.08–12.33). The obstetric providers should be aware of this risk and provide prophylaxis as appropriate.

In the previously described study by Shand et al,[351] women with IBD had twice the rates of postpartum VTE compared with women without IBD (aRR, 2.05; 95% CI, 1.02–4.10). However, when stratified by the mode of delivery (VD vs CS), the risk of VTE was no longer significant (aRR, 1.88; 95% CI, 0.94–3.77). Also in a meta-analysis by Kim et al, postpartum VTE was increased in patients with IBD (2.61; 95% CI, 1.83–3.67; $P < .001$).[358] This increased risk was only significant in UC (RR, 2.85; 95% CI, 1.79–4.52; $P < .001$) and not CD (RR, 1.69; 95% CI, 0.84–3.38; $P = .14$). Women who undergo CS should be considered for VTE prophylaxis postpartum.

Role of Disease Activity in Adverse Outcomes

As discussed in prior sections, including preconception counseling and medication use, disease activity has been associated with a higher risk of adverse outcomes. From the De Lima study, active IBD was associated with reduced GWG, which in turn leads to increased adverse events.[94] Women with IBD and inadequate GWG had a 2-fold risk for SGA births, more so with CD, compared with women with inadequate GWG without IBD.[94] Oron et al demonstrated that in patients with IBD, weight gain of less than 12 kg during pregnancy was significantly associated with adverse pregnancy outcomes, such as preterm delivery, SGA, and admission to NICU.[126] A large Norwegian cohort study (166 CD, 217 UC, and 79,125 non-IBD mothers) showed a significantly higher risk of inadequate GWG in women with UC (33%; OR, 1.78; 95% CI, 1.27–2.5) and mothers with CD (39%; OR, 2.28; 95% CI, 1.57–3.31) when compared with non-IBD mothers (21%; 11,518/52,207).[126]

When using corticosteroid use as a surrogate for disease activity, live-born infants in the exposure groups had significantly increased odds of preterm delivery (OR, 2.54; 95% CI, 2.04–3.15 for CD; OR, 1.86; 95% CI, 1.52–2.27 for UC), SGA (OR, 1.99; 95% CI, 1.26–3.15 for CD; OR, 1.80; 95% CI, 1.18–2.75 for UC), and LBW (OR, 2.25; 95% CI, 1.74–2.91 for CD; OR, 1.81; 95% CI,

1.42–2.30 for UC).[359] Cessation of anti-TNF therapy during pregnancy has been associated with an increased risk of preterm birth.[240] The same was shown for thiopurines in a Swedish health registry study that showed a significantly increased risk of preterm birth in women with IBD who ceased thiopurine therapy 90 days before pregnancy or in the first trimester though disease activity was not considered at the time of thiopurine discontinuation (aOR, 6.56; 95% CI, 1.44–29.82).[240]

Management of Postpartum Pain

Women undergoing a CS will invariably suffer pain in the days following the procedure, often severe. Clinical practice guidelines recommend a multimodal approach to analgesia in this setting, with first-line therapy being scheduled acetaminophen and nonsteroidal anti-inflammatory agents (NSAIDs), either alone or in combination.[360] Opiates carry a risk of addiction and transfer to the neonate through breastfeeding and are reserved for breakthrough pain. Intravenous ketorolac is one of the most used NSAIDs for postpartum pain management. It is a highly effective analgesic and reduces the need for opiates.[361] In women with IBD, there has been a concern that NSAIDs may precipitate a flare of disease, and as such, they are often avoided as postoperative analgesia.[362] However, a recent retrospective cohort study of 366 patients with IBD, 246 of whom received intravenous ketorolac as postpartum analgesia, did not show a significant increase in clinical disease activity up to 6 weeks postpartum in women treated with ketorolac.[363] In addition, ketorolac significantly decreased postpartum pain scores, especially among those who underwent CS, and reduced the need for opiates when compared with other forms of analgesia.

Fetal and Neonatal Adverse Events

Grade statement	GRADE recommendation	Level of evidence
27 We suggest counseling that children born to women with IBD have an increased rate of neonatal ICU admissions and hospitalizations in the first year of life compared with children born to women without IBD	Conditional	Very low
28 We suggest counseling that children born to women with active IBD have an increased rate of SGA and LBW compared with children born to women with inactive IBD	Conditional	Very low
29 We suggest counseling that children born to women treated with anti-TNF therapy, ustekinumab, or vedolizumab during pregnancy have no increased risk for early childhood malignancy	Conditional	Very low
30 We suggest counseling that children born to women treated with anti-TNF therapy, ustekinumab, or vedolizumab during pregnancy have no increased risk for early childhood developmental delay	Conditional	Very low
31 We suggest counseling that children born to women treated with thiopurine therapy during pregnancy have no increased risk for early childhood developmental delay	Conditional	Very low

Neonatal ICU and Hospital Admissions

Women with IBD are more likely to deliver infants with LBW, SGA, and preterm birth, all risk factors for NICU admission.[80,348,364,365] These complications are 2- to 3-fold higher in the setting of active disease, and therefore, it seems plausible to assume that active disease may increase the risk of NICU admission.[350] A systematic review and meta-analysis synthesized the data from 14 observational (2 prospective) and 2 registry studies reporting the risk of NICU admission.[178] The pooled incidence of NICU admission in observational studies was 4.9% (95% CI, 2.9–6.9; $I^2 = 81.8\%$), conferring a pooled OR of 3.33 (95% CI, 1.83–6.05; $I^2 = 0\%$) of NICU admission for infants born to women with IBD as compared with controls. The increased risk for NICU admission was also confirmed in registry studies, where a pooled OR of 1.25 (95% CI, 1.13–1.37; $I^2 = 0\%$) was reported.[178] Of note, 2 studies reported higher incidence of NICU admission in infants exposed to anti-TNF during pregnancy (OR, 2.42; 95% CI, 1.31–4.45; $I^2 = 0\%$). Anti-TNF exposure was deemed a likely surrogate for active disease or more severe disease course in the mother, rather than the risk being conferred by the drug itself.[244,366]

A Danish nationwide cohort (1995 to 2015) demonstrated that in utero corticosteroid exposure (30 days prior to conception through the first trimester; n =

1336) was associated with an aOR of 1.14 (95% CI, 0.94–1.39) for infections in the first year of life.[205] In another Danish population-based cohort study, offspring born to mothers with CD had an 18% increased risk of infection-related hospitalization (HR, 1.18; 95% CI, 1.10–1.26) and a 16% increased frequency of prescribed antibiotics (IRR, 1.16; 95% CI, 1.11–1.21).[367] The association between prenatal anti-TNFα and frequency of antibiotics attenuated after additional adjustment for maternal CD (IRR from 1.23 [95% CI, 0.98–1.55] to 1.10 [95% CI, 0.87–1.40]). Regarding surgery, a retrospective study enrolled 44 cases after 1998, and the results showed that of the 40 live newborns, 61% were premature and 47% had LBW; 42% of newborns needed hospitalization (25% NICU).[119]

Disease Activity and Risk of SGA and LBW

Disease activity in the mother has an adverse impact on outcomes in the newborn. A cohort study based on linkage between the Danish National Registry of Patients and the Medical Birth Registry showed that, in women with active disease, the adjusted risks of LBW, LBW at term, and preterm birth were 0.2 (95% CI, 0.0–2.6), 0.4 (95% CI, 0.0–3.7), and 2.4 (95% CI, 0.6–9.5), respectively. The crude risk of preterm birth was 3.4 (95% CI, 1.1–10.6) in those with moderate–high disease activity.[368] In a prospective case–control study, older age and disease activity at any time during pregnancy were associated with a lower birth weight (mean, 3146 g vs 3343 g; $P = .02$ and 3110 g vs 3268 g; $P = .04$, respectively).[369]

A cohort from the Swedish health registers included 470,110 singleton births (1833 UC and 1220 CD) in Sweden (2006 to 2010). The highest risks for preterm birth and spontaneous abortion were found among those with flaring disease.[350] Analyses of LBW exhibited a similar pattern with UC, aOR of 1.64 (95% CI, 1.31–2.04), and CD, aOR 1.86 (95% CI, 1.46–2.38). For flaring UC, the risk estimate in the adjusted analysis was doubled, and for CD, it was tripled. Women with CD had increased risks of SGA births, with the highest risks among those with disease flare during pregnancy.[350]

A systematic review and meta-analysis of 28 studies demonstrated that in women with active IBD, the pooled ORs for LBW, preterm birth, and SGA were 3.81 (95% CI, 1.81–8.02), 2.42 (95% CI, 1.74–3.35), and 1.48 (95% CI, 1.19–1.85), respectively, compared with women with inactive IBD.[370] The same meta-analysis demonstrated that in women with active IBD, the pooled OR for stillbirths was 2.27 (95% CI, 1.03–5.04) compared with women with inactive IBD.[370] As compared with non-IBD pregnancies, ORs for stillbirths were higher for pregnancies with active IBD than for those without active IBD during pregnancy (aOR, 1.43; 95% CI, 1.09–1.86 and aOR, 1.06; 95% CI, 0.88–1.29, respectively).[370] Medical treatment did not increase the risk of preterm birth, SGA, and stillbirth.[216]

Risk of Childhood Malignancy

There is no evidence to suggest in utero exposure to biologics leads to childhood malignancy. In a multicenter, non-population-based, retrospective study from the Netherlands, 1000 children born to 626 mothers with IBD were studied; overall, there was no evidence for an association between intrauterine exposure to anti-TNF during pregnancy and malignancies in the first 5 years after birth with 196 anti-TNF exposure and 564 no exposure.[216] Another cohort study from Meyer et al included 5725 children with intrauterine exposure to anti-TNF and 26,092 unexposed children with a median follow-up of 6.1 years (interquartile range [IQR], 3.5–8.7 years).[371] No increased risk of early life malignancy between children unexposed to anti-TNF during pregnancy and those exposed to anti-TNF (crude HR, 0.50; 95% CI, 0.18–1.39; aHR, 0.49; 95% CI, 0.18–1.38) was observed. The overall rate of malignancies was 269/million PYs (95% CI, 205–347). This rate was 135/million PYs (95% CI, 37–346) in children exposed to anti-TNF and 270/million PYs (95% CI, 196–362) in children unexposed to anti-TNF.[371] Recently, a large French nationwide study compared the outcomes of infants exposed to vedolizumab or ustekinumab with anti-TNF. A total of 262 children were exposed in utero to vedolizumab with a median follow-up of 1.7 years (IQR, 0.8–2.9 years), and a total of 291 children were exposed in utero to ustekinumab and followed up for a median of 1.3 years (IQR, 0.6–2.3 years). No malignancies were observed in children exposed to vedolizumab or ustekinumab.[255]

Risk of Developmental Delay

Children exposed to biologics in utero achieve developmental milestones at the same rate as unexposed children. In the prospective observational PIANO study, developmental milestones were assessed through the nationally validated Ages and Stages Questionnaire (ASQ3) at 12, 24, 36, and 48 months of age. There were no significant differences in developmental milestones in the first 48 months of life between children exposed to biologics during pregnancy (total, $N = 222$; anti-TNF, $n = 211$; vedolizumab, $n = 8$; ustekinumab, $n = 3$) and those not exposed ($n = 108$),[2,372] as well as compared with national averages. In a prospective, multicenter, observational study by Mitrova et al, 20 ustekinumab-exposed and 16 vedolizumab-exposed children were compared with 49 anti-TNF exposed children, with no significant differences in psychomotor development being demonstrated.[253] The prospective multicenter "In Utero Exposure to Vedolizumab" (NOVA) study documented normal or above average developmental milestones at 12 months in 34 children exposed to vedolizumab during

pregnancy.[252] Finally, a recent prospective study of 78 infants exposed in utero to ustekinumab showed that in >90% of infants, developmental milestones were normal.[260]

Children exposed to thiopurines also have no evidence of developmental delay. The PIANO study prospectively followed children who were exposed in utero to thiopurines and assessed their developmental outcomes at 12, 24, 36, and 48 months. There were no differences in the total ASQ3 score nor any of the specific categories of milestones evaluated including communication, fine motor skills, gross motor skills, personal social, and problem solving, in those children exposed to thiopurines in utero.[2] These data are further supported by a nationwide cohort study based on Danish health registries of 1,311,009 live-born children, including 1048 children exposed in utero to thiopurines, where no increased risk of autism spectrum disorder (ASD)/attention-deficit hyperactivity disorder was found.[373]

Long-Term Childhood Outcomes

Several cohorts have tried to explore the link between neurodevelopmental outcomes and neuropsychiatric outcomes in children exposed to parental IBD. In a large nationwide cohort study of more than 1 million births in Denmark, there was no evidence of an increased risk of autism in the offspring of parents with IBD.[374] Likewise, in another large national cohort of women with IBD and their children followed at multiple points for 7 years, children did not have statistically different scores for emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, or social problems compared with children of non-IBD mothers.[375] In a large nationwide registry from Korea with data for more than 3 million women who gave birth during study periods, 5191 women with IBD who had 7230 children were identified and matched to non-IBD controls. There was no significant increased risk of neurodevelopmental disorders or metabolic diseases in IBD offspring compared with non-IBD offspring.[376] These findings have been further confirmed in other studies.[377] However, in a large nationwide population-based cohort study using Swedish registers, an association between parental diagnoses of IBD and autism in children was found. This association may be linked to perinatal immune dysregulation, micronutrient malabsorption, and anemia.[374]

The long-term health outcomes of children born to mothers with IBD were assessed in a multicenter retrospective study from the Netherlands; the primary aim was to assess infection rate, and the secondary aims were to assess adverse reactions to vaccinations, growth, autoimmune diseases, and malignancies. In total, 196 (20%) had intrauterine exposure to anti-TNF (60 with concomitant thiopurine) and 240 children (24%) were exposed to thiopurine monotherapy, whereas 564 children (56%) were not exposed to anti-TNF and/or thiopurine and served as a control group. There was no association between adverse long-term health outcomes and in utero exposure to IBD treatment. All outcomes were similar to the general age-adjusted population. There was no association between in utero exposure to anti-TNF-α and/or thiopurine and adverse reactions to vaccinations, growth failure, malignancies, or autoimmune diseases.[216] These long-term data are reassuring for mothers on IBD therapy during pregnancy.

Vaccines

GRADE statement	GRADE recommendation	Level of evidence
32 We recommend that inactive vaccines be provided to children born to mothers with IBD on anti-TNF agents	Strong	Very low
33 We suggest that live rotavirus vaccine may be provided in children with in utero exposure to biologics	Conditional	Very low
34 We recommend that live Bacillus Calmette-Guérin vaccine be avoided in the first 6 months[a] of life in children with in utero exposure to anti-TNF due to risk of disseminated tuberculosis and associated mortality	Strong	Very low

Consensus statements
33 Inactive vaccines should be given on schedule to infants of women with IBD regardless of in utero IBD medication exposure
34 Children exposed to JAKis or S1P modulators in utero may receive live vaccines after 1 month
35 Live vaccines can be given to infants of mothers breastfeeding while on biologics

[a]Regional risk should be considered.

Response to Inactive Vaccines

Multiparameter immunophenotyping of major B-cell and T-cell subsets demonstrated that the adaptive newborn immune system develops largely unaltered after exposure to anti-TNF monotherapy and combination therapy.[378] This was confirmed in a second study where T-cell and B-cell immunity was fully mature, and immune function was normal in infants exposed in utero to anti-TNF therapy.[379] This suggests that response to vaccines

should not be compromised among infants exposed to in utero IBD therapy.

Several studies have investigated the impact of biological therapy on response to vaccines among infants born to mothers with IBD. Beaulieu et al conducted a prospective study to evaluate serologic responses to tetanus or hemophilus influenza B vaccines in infants born to mothers exposed to different classes of biological therapy, including anti-TNF monotherapy or combination therapy, at any time between conception and delivery. In a sample of 179 women, 153 were using biological therapy, and vaccine titers were available for infants born to 50 of these women, 42 of whom were exposed to biologics, with 39 on anti-TNF therapy.[380] The study concluded that the use of biological therapy by pregnant women with IBD does not affect infant response to vaccines, with no difference in the proportion of adequate serologic response between those on biologic monotherapy and combination therapy groups. The response rates were comparable to infants born to mothers not on immunosuppression.[380] In another study by de Lima et al, hepatitis B virus (HBV) vaccination was effective in children exposed to anti-TNF therapy in utero, as evidenced by anti-Hbs levels at 12 months, which were comparable to a control group.[381] Additionally, a Korean retrospective cross-sectional study by Lee et al[382] evaluated the influence of anti-TNF therapy on pregnant women with IBD and their children's immunity. Eighteen Korean women with IBD who had received anti-TNF during pregnancy and 12 children with 3 regular vaccinations to HBV were included. Four children initially showed negative results for anti-HBs, but seroconversion occurred after 1 booster vaccination. Finally, a systematic review and meta-analysis by Barenbrug et al[243] examined pregnancy and neonatal outcomes in women with immune-mediated inflammatory diseases exposed to anti-TNF during pregnancy. The review found that the majority of inactive vaccines, including tetanus, *Streptococcus pneumoniae*, diphtheria, and HBV, elicited an adequate immune response when administered according to regular regimens.

Adverse Events to Inactive Vaccines

There is a small series of infants exposed to anti-TNF in utero who received inactive vaccines that report no increase in adverse events compared with unexposed infants. In a series of 15 children exposed to anti-TNF in utero and 12 unexposed who received hepatitis B vaccines, there were no adverse reactions to vaccinations.[381] Among 72 children exposed to anti-TNF in utero and 69 unexposed children who received a hexavalent inactive vaccine (HBV, hemophilus influenza B, diphtheria, tetanus, pertussis, and inactivated polio), adverse events were reported in 17 exposed and 8 controls ($P = .06$) including fever and local skin reaction, but no serious adverse events were reported.[383] In a series of 17 infants exposed in utero to anti-TNF monotherapy, 4 to thiopurines, 3 to anti-TNF and thiopurine, who received tetanus, diphtheria, HIB, and hepatitis vaccines, no adverse events were reported.

A large systematic review and meta-analyses of 14 studies focused on vaccinations in children with chronic conditions treated with biologics, including 6 IBD studies on children on anti-TNF therapy.[384] Among these patients with IBD, there was no increased risk of adverse events after vaccination including erythema (RR, 4.134; 95% CI, 0.254–67.219; $P = .319$), pain (RR, 0.725; 95% CI, 0.524–1.004; $P = .053$), fever (RR, 0.055; 95% CI, 0.002–1.308; $P = .073$), invasive infection (RR, 2.656; 95% CI, 0.110–63.836), or myalgia/arthralgia/malaise/diarrhea (RR, 0.957; 95% CI, 0.623–1.472; $P = .842$). Although this systematic review looked at children with IBD who were receiving treatment with an anti-TNF, not specifically infants exposed to biologics in utero, the findings do support the safety of inactive vaccines in anti-TNF-exposed children.

No negative effects of IBD medications, including biologics, on the efficacy and safety of vaccines in children exposed during pregnancy have been described.[380–382,384] There is currently no information on the novel IL23 inhibitors, but they would not be expected to be different from studied biologics (eg, ustekinumab). Regarding new small molecules, such as JAKis and S1P receptor modulators, there are almost no data on the efficacy and safety of vaccines, but due to the short half-life of these drugs, no interference is anticipated,[341] and vaccines should proceed on schedule.

Rotavirus Vaccine (Live)

The rotavirus vaccine is a live attenuated vaccine typically given between 2 and 6 months of age. Administration past this time may be associated with a rare risk of intussusception. As infants exposed to biologics in utero may have detectable levels at 6 months of age, it has generally been recommended that this vaccine not be given in this setting. However, data on inadvertent rotavirus administration have not demonstrated harm, and now a recent prospective study demonstrated safety in the setting of infants exposed to biologics in utero.

In a prospective Spanish registry, there were 65 infants exposed to biologics during the third trimester of gestation who received at least the initial dose of rotavirus vaccine, with no serious adverse events observed.[385] A systematic review of the outcomes of live-attenuated vaccines in infants under 12 months of age exposed to biological agents in utero included 46 cases of rotavirus vaccination, with only 7 mild reactions to the vaccine reported.[386] The largest, and only prospective, study on rotavirus vaccination in children exposed to biologic agents in utero was published by Fitzpatrick et al.[387] The authors prospectively assessed the safety of administering rotavirus vaccine to 168 infants exposed

to biologic agents (including anti-TNF, vedolizumab, and ustekinumab), with no reports of serious adverse events following immunization.[387] A substudy of patients with IBD in that trial[340] reported the immune function in 57 children born to mothers with IBD and exposed to biologics in the third trimester (21 infliximab, 19 adalimumab, 10 vedolizumab, and 7 ustekinumab). Six mothers on anti-TNF were also on thiopurines. Immunologic assessments validated for age were normal in all infants despite median infliximab concentrations of 6.1 μg/mL (range, 0.4–28.8 μg/mL), adalimumab 1.7 μg/mL (range, 0.7–7.9 μg/mL), ustekinumab 0.6 μg/mL (range, 0–1.1 μg/mL), and undetectable for vedolizumab at 10.7 weeks (IQR, 9.4–12.4 weeks) of age. The live oral rotavirus vaccine series was provided to 50 infants, with the first dose given at a median of 13 weeks of age. No adverse effects following immunization were reported.[340] A separate multicenter prospective cohort of pregnant women with IBD on vedolizumab or ustekinumab measured cord and infant serum concentrations until undetectable. The median time to undetectable level was 11 weeks (range, 5–19 weeks) for vedolizumab and 14 weeks (range, 9–36 weeks) for ustekinumab. A total of 20 infants with undetectable drug levels by 15 weeks of age were provided rotavirus vaccine (15/28 vedolizumab-exposed infants and 5/10 ustekinumab-exposed infants) with no adverse events reported.[254]

Based on the retrospective and prospective studies, rotavirus can be given to infants exposed to biologics in utero; small molecules should have been cleared by the time of rotavirus vaccination and should not impact vaccination schedules as noted above.

Bacille Calmette-Guérin vaccine

Unlike the rotavirus vaccine, the Bacille Calmette-Guérin (BCG) vaccine is more vital in some parts of the world where it is given within the first month of life, as well as more dangerous to the biologic exposed infant. A systematic review on live vaccine outcomes in infants exposed to biologic agents in utero due to maternal immune-mediated diseases, including IBD, reported safety outcomes in a total of 215 infants vaccinated with BCG vaccine within the first year of life (over 80% vaccinated $\leq$6 months of age).[386] One child with in utero exposure to infliximab in the third trimester due to maternal CD who was vaccinated at 3 months of age died of disseminated BCG infection aged 4.5 months.[388] Additionally, 7 infants (all exposed to infliximab) experienced adverse reactions to vaccination, with 6 of them vaccinated within 1 month and 1 at 6 months after birth. In 3 mothers, the last administration of infliximab was given during the third trimester, whereas this information was not clear in the remainder. The side effects included injection site swelling and/or axillary lymphadenopathy. All side effects resolved without the need for antituberculous therapy.[389,390] Finally, 4 deaths related to BCG vaccination in infants exposed to anti-TNFa in utero (2 to infliximab, 1 to adalimumab, and 1 to unspecified anti-TNF) were reported in the United Kingdom's Medicines and Health Products Regulatory Agency (MHRA). However, no further details, such as the age at vaccination, were available.[391]

The evidence on the safety of BCG vaccination after 6 months to infants with prenatal exposure to anti-TNF is limited. A study by Park et al[390] reported 90 infants exposed to anti-TNF in utero, 9 of whom had exposure after 6 months of age, and no adverse events were reported. Some of those with earlier vaccination had minor reactions but no serious adverse events. All published reports of adverse events including the abovementioned case of fatal outcome after the vaccination occurred in infants vaccinated less than 6 months of age (caveat: United Kingdom's Medicines and Health Products Regulatory Agency data did not report age). However, in each individual patient, the risk of tuberculosis and the drug of exposure should be considered. In high-risk countries where BCG must be given early, serum concentrations of drug can be measured prior to vaccination, and consideration can be given to holding the biologic in the mother in midpregnancy to reduce transfer to the infant.

There is almost no data on the effect of in utero exposure to small molecule inhibitors, such as JAK and S1P1 inhibitors, on infants' response to inactive or active vaccination.[341] However, due to the short half-life of these drugs, it is expected that they will be undetectable in the first few days after birth (even if the mother continued treatment throughout pregnancy). Therefore, inactive vaccines should be given on schedule and live vaccines after 1 month of age with in utero exposure to JAKi and SIP agents, and the child's physician should be informed to carefully monitor for adverse events.

Live Vaccines While Breastfeeding

Physiologically, there should be minimal to no transfer of monoclonal antibody across the infant gut. Therefore, the negligible amounts transferred through breast milk are unlikely to induce systemic immunosuppression in infants. Breastfeeding by mothers exposed in utero to infliximab, adalimumab, vedolizumab, or ustekinumab did not affect neonatal clearance of the drug.[246,252,260]

In March 2022, the European Medical Agency issued a Direct Healthcare Professional Communication concerning live vaccines in infants exposed to infliximab during breastfeeding.[392] The marketing authorization holders of infliximab, in conjunction with the European Medical Agency, conveyed controversial information stating that low levels of infliximab have been detected in breast milk, and it has also been found in infant serum after exposure to infliximab via breastfeeding. Furthermore, the communication advised against administering a live vaccine to a breastfed infant if the mother is receiving infliximab, unless infant infliximab serum levels are

undetectable. This recommendation was based on a case report involving 2 mothers receiving infliximab while breastfeeding. In the first infant, infliximab serum levels were undetectable, whereas in the second infant, a serum level of 1.7 μg/L was found during maternal infliximab induction treatment, equivalent to approximately 2% of the simultaneous maternal serum infliximab level.[393]

PIANO reported the largest exposure study on biological treatment during breastfeeding, encompassing 29 women receiving infliximab treatment, and confirmed very low levels of infliximab in breast milk. Moreover, it demonstrated that breastfed infants of mothers on biologics, including infliximab, had similar risks of infection and rates of milestone achievement compared with nonbreastfed infants or infants unexposed to biologics.[316] A Spanish registry, assessing the risk of serious adverse events related to the administration of live-attenuated vaccines in children breastfed by mothers receiving biological agents during lactation, found no serious adverse events related to the administration of these vaccines.[385] In the Canadian multicenter prospective cohort study by the Canadian Immunization Research Network assessing safety of live rotavirus vaccination after antenatal exposure to immunomodulatory biologic agents, 162 of the infants (85%) were breastfed at the time of assessment.[387] Of all the infants, they reported 90% had initiated rotavirus vaccination, 80% completed the series, and no serious adverse events were reported from the vaccines.

In summary, based on the implausibility of significant IgG transfer across breast milk, available literature on the safety of live vaccines in infants breastfed by women receiving biological therapies, and the benefits of breastfeeding and adhering to national infant immunization programs, live vaccines should not be withheld in infants breastfeeding from mothers on biologic therapy.

Summary

In this global consensus statement on the management of pregnancy in IBD, practical recommendations are provided to transform the care of women with IBD worldwide. We summarize data from preconception to postdelivery for mothers with IBD and their infants and include geographic and resource considerations that may influence implementation of these recommendations.

There are a number of strengths to this consensus document. Multidisciplinary physicians, scientists, and patient partners were included in the consensus process to inform the statements and resulting evidence summaries and emphasize the patient voice. All statements were generated with the input of the diverse group. The consensus statement is comprehensive in scope and relevance. From a methodological standpoint, the GRADE methodologists were formally trained at McMaster University in GRADE. There are also a number of limitations to this consensus document, which often pertain to balancing clinical practicality with methodological rigor. Data on pregnancy in IBD are limited; there are no randomized controlled trials to assess comparative safety outcomes in pregnant women with IBD. Therefore, the GRADE statements relied on observational data, where ultimately the level of evidence ranged from low to very low. As it was beyond the scope of this document, a new meta-analysis was not performed for each statement; instead, a formal literature search was performed, and GRADE was implemented utilizing the highest level of evidence. Several societies, such as the American College of Gastroenterology, standardly use this approach. Given the limited evidence base in several important arenas, including newer therapeutics without adequate human data in pregnancy, a RAND/UCLA process was utilized to measure appropriateness of statements, with review of evidence appropriateness based on expert opinion. Therefore, we acknowledge the limitation of expert opinion in these arenas.

A standardized approach utilizing these recommendations in clinical practice will enhance the care of patients through improved counseling, fertility considerations, therapeutic management of IBD during preconception and pregnancy, breastfeeding considerations, and vaccination of infants postdelivery. This process demonstrated understudied areas, particularly in understanding why pregnant women with IBD have more complications (impact of inflammation, diet, placental changes, etc) as well as the need for more formal safety monitoring, ideally before a drug is approved. Finally, the recommendations need to be nimble and adapt with new medications and new data. The consortium plans to meet in 5-year intervals to update the statements, and in between, statements will be updated on the website (pianostudy.org) with important new recommendations and supporting data. The ultimate goal of the PIANO global consensus on pregnancy in IBD is patient-centric, to improve the lives and pregnancy outcomes of patients with IBD worldwide.

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Conflicts of interest

These authors disclose the following: Uma Mahadevan reports consultant for Abbvie, Bristol Myers Squibb, Boeringher Ingelheim, Celltrion, Enveda, Gilead, Janssen, Lilly, Merck, Pfizer, Protagonist, Roivant, and Takeda. Cynthia H. Seow reports advisory boards for Janssen, Abbvie, Takeda, Lilly, Ferring, Shire, Pfizer, Sandoz, Pharmascience, Fresenius Kabi, Amgen, Bristol Myers Squibb, and Celltrion; and speaker for Janssen, Abbvie, Takeda, Lilly Ferring, Shire, Pfizer, Pharmascience, and Fresenius Kabi. Edward L. Barnes reports consultant for AbbVie, Boomerang, Eli Lilly, Pfizer, Takeda, and Target RWE. María Chaparro has served as speaker, consultant, or received research or education funding from MSD, Abbvie, Hospira, Pfizer, Takeda, Janssen, Ferring, Shire Pharmaceuticals, Dr Falk Pharma, Tillotts Pharma, Biogen, Gilead, and Lilly. Emma Flanagan reports speaker fees from Abbvie, Ferring, Janssen, Sandoz, and Takeda; and a research grant from Ferring. Mette Julsgaard has received research grants for other investigator-driven studies from Takeda and the NOVO Nordisk Foundation (grant no.NNF23OC0081717); has received consultation fees from Ferring and Takeda; and has received speaker's fees from Tillotts Pharma, MSD, Ferring, and Takeda. Sunanda Kane reports consultant for Boerhinger Ingelheim, Bristol Meyers Squibb, Fresenius Kabi, Gilead, Janssen, Lilly, Pfizer, and Takeda; and editor for UptoDate. Siew Ng has served as an advisory board member for Pfizer, Ferring, Janssen, and Abbvie; has received honoraria as a speaker for Ferring, Tillotts, Menarini, Janssen, Abbvie, and Takeda; has received research grants through her affiliated institutions from Olympus, Ferring, and Abbvie; is a founder member, non-executive director, non-executive scientific advisor, and shareholder of GenieBiome Ltd; receives patent royalties through her affiliated institutions; and is named inventor of patent applications held by the CUHK and MagIC that cover the therapeutic and diagnostic use of microbiome. Joana Torres reports advisory board/consultancy for Abbvie, Pfizer, Sandoz, Janssen, and Lilly; speaker bureau for Abbvie, Janssen, Pfizer, and Lilly; and grants from Janssen and Abbvie. Jesus Yamamoto-Furusho reports speaker bureau for AbbVie, Alfasigma, Asofarma, Bristol Myers Squibb, Carnot, Celltrion, Chinoin, Farmasa, Ferring, Janssen, Siegfried Rhein, and Takeda; clinical research investigator for Bristol Myers Squibb and Takeda; advisory boards for AbbVie, Celltrion, Ferring, Janssen, and Takeda; and research grants from Takeda. Christopher Robinson reports research grants from Abbvie; pregnancy registry for Ubrelvy; pregnancy registry Risankizumabrzaa (Skyrizi); media editor for American Journal of Obstetrics and Gynecology; and deputy editor for American Journal of Perinatology. Richard Gearry reports speaker for AbbVie, Takeda, J&J, and Celltrion; advisory boards for AbbVie, Takeda, J&J, Celltrion, and Zespri; and research grants from J&J and Zespri. Dana Duricova reports lecture fees/consultancy for AbbVie, Takeda, Pfizer, Eli Lilly, Janssen, Ferring, Celltrion, and Bristol Myers Squibb. Marla Dubinsky reports consultant for Abbvie, Abivax, Astra Zeneca, Bristol Myers Squibb, Boeringher Ingelheim, Celltrion, Genentech, Janssen, Johnson and Johnson, Lilly, Merck, Pfizer, Prometheus Labs, Spyre, and Takeda. Millie Long reports consultant for AbbVie, BMS, Celltrion, Janssen, Intercept, Lilly, Pfizer, Prometheus, Takeda, and Target RWE; and research support from Lilly, Takeda, and Pfizer. The remaining authors disclose no conflicts.

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