Update on Pregnancy in Inflammatory Bowel Disease

Taylor Boyd, MD, MMSc,[1] and Sunanda Kane, MD, MSPH[2]

[1]Division of General Internal Medicine, Massachusetts General Hospital, Boston, Massachusetts

[2]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota

Corresponding author:
Sunanda Kane, MD, MSPH
Mayo Clinic
Division of Gastroenterology and Hepatology
200 First Street SW
Rochester, MN 55905
Tel: (507) 284-0959
Fax: (507) 284-0538
E-mail: kane.sunanda@mayo.edu

Abstract: Ongoing clinical and population health research continues to inform evidence-based management of patients with inflammatory bowel disease during pregnancy. Advances in noninvasive tools for disease monitoring highlight the expanding role of intestinal ultrasound for point-of-care assessments throughout pregnancy. Updates in medical management include recent data demonstrating the association between thiopurines and intrahepatic cholestasis of pregnancy, the role of low-dose aspirin in preventing hypertensive disorders of pregnancy, and guidance related to Janus kinase inhibitor safety. Evolving pharmacologic data inform the safety and increasing use of biosimilars during pregnancy, the emergence of newer targeted therapies such as selective interleukin-23p19 inhibitors, and emerging evidence to support the safety of rotavirus vaccination in infants exposed to biologics in utero. This article summarizes several key updates on diagnostics, treatment, and preventative care strategies aimed at improving maternal and fetal health.

Keywords
Pregnancy, Crohn's disease, ulcerative colitis, biosimilars, noninvasive disease monitoring, intestinal ultrasound

For patients with inflammatory bowel disease (IBD), active disease during pregnancy is associated with both maternal and fetal adverse outcomes.[1,2] This risk underscores the importance of achieving and maintaining remission prior to conception and monitoring for inflammation throughout pregnancy. Recent advances in diagnostics, therapeutics, and preventative care strategies in IBD continue to shape the management of patients with IBD during pregnancy. The increasing application of tools for noninvasive disease monitoring, such as intestinal ultrasound (IUS), enable point-of-care assessment and treatment early in pregnancy. The expanding body of safety data for biologics and biosimilars supports both continuation of effective therapies and, when necessary, transitions to optimized treatment strategies during pregnancy. In parallel, an increased emphasis on preconception counseling and preventative care helps to support shared decision-making with patients and multidisciplinary teams. This article highlights several recent developments related to pregnancy and IBD, including the use of IUS in disease monitoring; evolving data on medical therapies, including thiopurines, low-dose aspirin, Janus kinase (JAK) inhibitors, selective

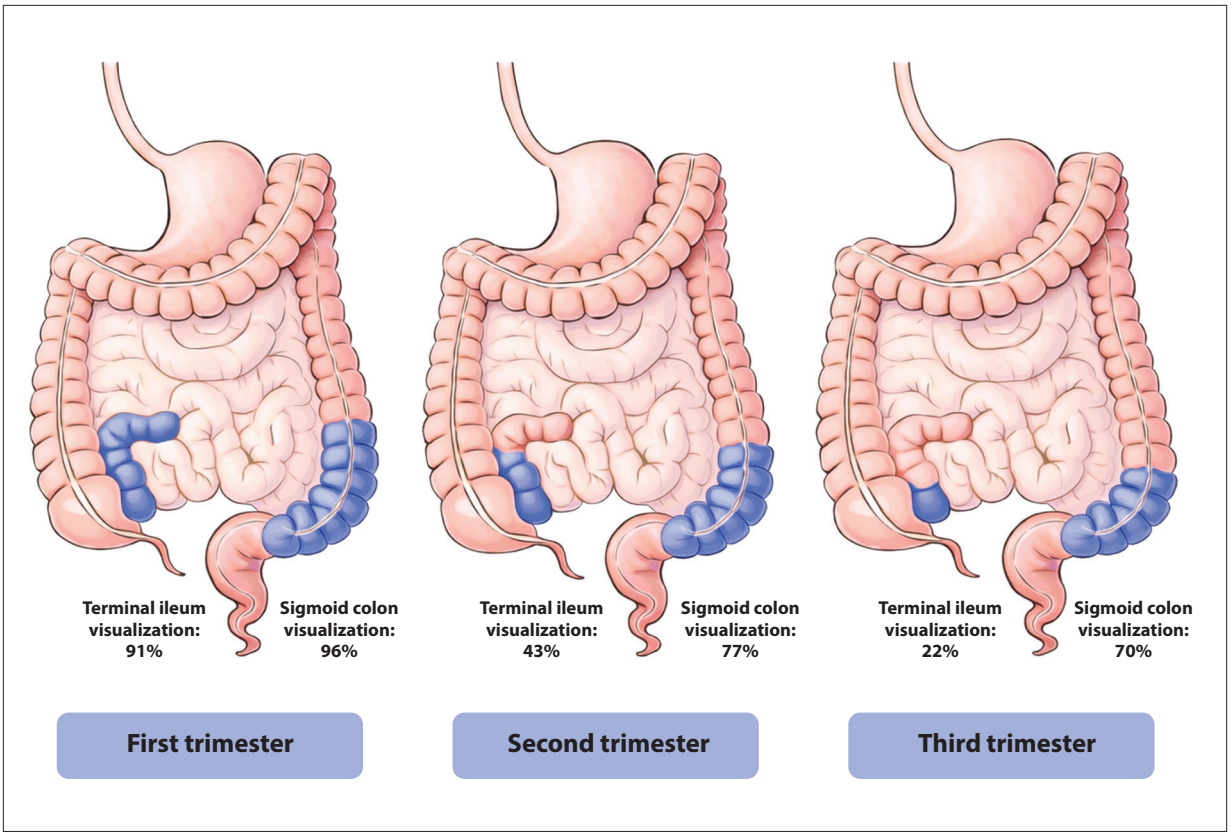

Figure 1. Bowel visualization with intestinal ultrasound by trimester of pregnancy. Visualization of the terminal ileum and sigmoid colon by transabdominal intestinal ultrasound decreases with advancing gestation.[3]

interleukin (IL)-23p19 inhibitors, and biosimilars; and emerging data informing vaccination considerations for infants exposed to biologic therapies in utero.

Intestinal Ultrasound

Active disease for patients with IBD is associated with adverse outcomes in pregnancy, including preterm delivery, small-for-gestational-age infants, and preeclampsia.[1] Accordingly, obtaining an accurate assessment of disease activity and monitoring for progression are essential components of antenatal care. IUS continues to emerge as a safe and noninvasive method for obtaining point-of-care imaging in pregnancy. Its clinical utility is greatest in the first trimester, after which the gravid uterus impairs bowel visualization.

IUS offers high-resolution visualization of the bowel wall and adjacent structures. Changes in bowel wall thickness, increased echogenicity of the surrounding mesentery, and evidence of hyperemia, as detected by Doppler ultrasound, serve as core markers of disease activity. These features correlate strongly with both biomarkers and clinical indices of inflammation.[2] A 2022 longitudinal study including 76 ultrasounds from a cohort of 38 pregnant patients with IBD highlighted the association between IUS and fecal calprotectin (Spearman $\rho = 0.73$; $P<.0001$), and near-perfect agreement with a reference composite of both fecal biomarkers and clinical assessment.[3] Beyond biomarker concordance, IUS may also offer the ability to detect subclinical inflammation, often missed by symptom-based assessments alone. In a retrospective review of 447 point-of-care IUS examinations, active inflammation was detected among 42% of patients who were otherwise asymptomatic.[4]

When compared with conventional modalities for assessing disease activity, including magnetic resonance enterography (MRE), biomarkers, and endoscopy, IUS may offer several distinct advantages during pregnancy. For example, biomarkers, such as erythrocyte sedimentation rate and serum albumin, are impacted by gestational physiology, often resulting in unreliable indicators of inflammation during pregnancy.[5] Fecal calprotectin remains a reliable marker of intestinal inflammation; however, it provides limited information regarding disease extent, severity, or location.[5] Cross-sectional imaging such as MRE may be limited in pregnancy owing to

risks associated with fetal exposure to gadolinium-based contrast agents.[6] Further, although endoscopy remains an important diagnostic and therapeutic tool, its use during pregnancy requires special consideration related to sedation and fetal monitoring.[5]

The diagnostic performance of IUS in pregnancy is supported by a growing body of evidence.[2-4] In a longitudinal prospective cohort study, De Voogd and colleagues found an overall accuracy of 78%, with sensitivity of 82% and specificity of 82%, for detecting changes in disease activity among the 23 patients with serial ultrasounds.[3] Beyond diagnostic accuracy, IUS has important implications for prognostication. In a multicenter prospective observational cohort study of 377 pregnant patients with IBD, a maximal bowel wall thickness correlated with a 4-fold increased risk of preterm delivery (risk ratio [RR], 4.01; 95% CI, 1.26-12.72), and a 2-fold increased risk of low birth weight (RR, 2.19; 95% CI, 1.01-4.72). Additionally, bowel wall hyperemia was associated with a 3-fold increased risk of preeclampsia (RR, 3.46; 95% CI, 1.03-11.12).[2] IUS may also hold significant potential for guiding real-time treatment decisions, with a retrospective review of 447 IUS examinations highlighting that imaging results led to a change in clinical management in 267 encounters (60%).[4]

Despite the growing potential for IUS in pregnancy, several limitations remain. For example, visualization of bowel segments such as the terminal ileum and sigmoid colon can be challenging owing to displacement of loops by the enlarging gravid uterus, particularly in the second and third trimesters (Figure 1).[3] Transabdominal ultrasound also has limited utility in assessing rectal inflammation, often necessitating perineal ultrasound for more accurate evaluation.[3] These limitations were highlighted in the study by De Voogd and colleagues in which the feasibility of terminal ileum visualization declined significantly across trimesters, from 91.3% in the first trimester to 43.3% in the second trimester, and just 21.7% in the third trimester.[3] Similarly, sigmoid colon visualization decreased from 95.6% to 69.5% between the first and third trimesters.[3] Finally, access to IUS may be limited by institutional resources and provider expertise, presenting a potential barrier to widespread and equitable adoption in prenatal IBD care.

A recent international Delphi consensus outlined core competency and knowledge requirements within the domains of technical performance, image interpretation, and clinical integration, establishing a framework for structured training and certification in IBD-focused IUS.[7] However, significant variation in IUS education for trainees in gastroenterology remains, ranging from informal apprenticeship models to formal certification pathways, to standardized, competency-based curricula.[7] Future directions include the development of validated IUS scoring indices tailored to pregnancy and the generation of prospective outcomes data evaluating IUS-guided treat-to-target strategies in this population, which may help further define its optimal role in antenatal IBD care.

Thiopurines and Intrahepatic Cholestasis of Pregnancy

Continuation of monotherapy treatment with thiopurines during pregnancy has generally been considered low risk and safe. However, emerging data suggest a clinically important association with intrahepatic cholestasis of pregnancy (ICP), a cholestatic liver disorder characterized by pruritus and elevated serum bile acids. Several early observational studies, including results from the Pregnancy Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry, did not demonstrate a significant increase in risk of congenital anomalies, preterm birth, or neonatal infections after fetal exposure to in utero thiopurines.[8] Fetal safety outcomes have been further supported by a nationwide analysis from a French health database, which showed no significant difference in occurrence of serious infections among children exposed to thiopurines in utero (adjusted hazard ratio, 0.94; 95% CI, 0.83-1.07).[9]

More recent population-based IBD data may suggest an association between thiopurine use during pregnancy and ICP, with downstream adverse obstetric outcomes such as preterm delivery and stillbirth, particularly when bile acids reach 40 μmol/L or higher. In a retrospective cohort study, Selinger and colleagues analyzed 386 pregnancies among women receiving care at a combined IBD–obstetric clinic.[10] ICP was found to occur more often in thiopurine-exposed vs nonexposed IBD pregnancies (9.0% vs 1.8%; odds ratio [OR], 5.34; 95% CI, 1.78-16.02). Notably, thiopurine-unexposed IBD pregnancies had a similar incidence of ICP in comparison to controls, and other IBD-related factors, such as disease activity, phenotype, and biologic or corticosteroid use, were not found to be associated with an increased risk. Similarly, among women in a large Swedish IBD cohort study, ICP occurred in 7.3% of patients taking thiopurines during pregnancy in comparison to 0.9% of unexposed pregnancies (adjusted RR, 7.78; 95% CI, 5.41-11.17).[11] Comparator analysis also showed that thiopurine exposure was associated with a higher risk of ICP compared with tumor necrosis factor (TNF) inhibitor exposure (adjusted RR, 11.33; 95% CI, 3.58-35.88). Importantly, pregnancies complicated by ICP had substantially increased rates of adverse obstetric outcomes, with spontaneous preterm delivery occurring in 19.6% of early-onset ICP cases and 8.1% of later-onset ICP cases, compared with 4.0% among pregnancies without ICP.

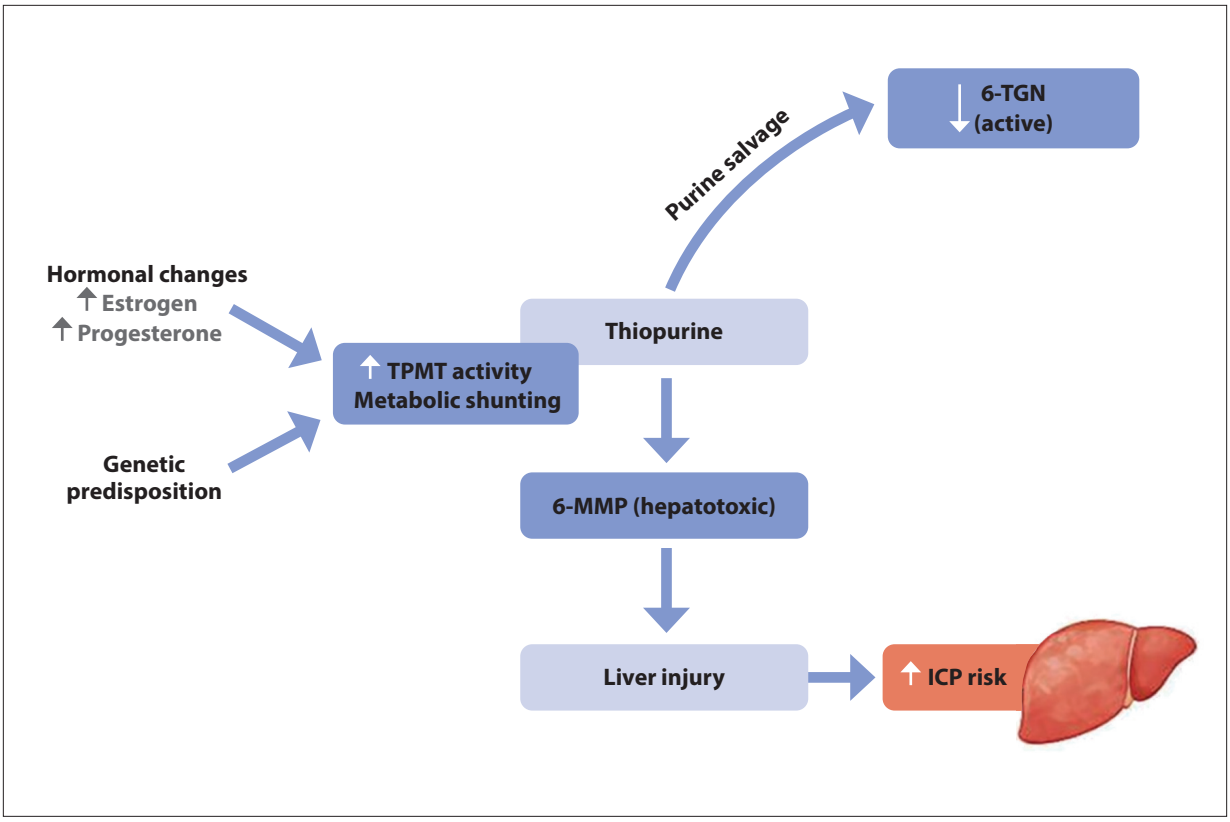

Figure 2. Pregnancy-associated thiopurine metabolic shunting toward hepatotoxic pathways. Flowchart shows pregnancy-associated hormonal and genetic influences on thiopurine metabolism, resulting in increased metabolic shunting toward hepatotoxic 6-MMP, reduced 6-TGN formation, and increased risk of ICP.

6-MMP, 6-methylmercaptopurine; 6-TGN, 6-thioguanine nucleotide; ICP, intrahepatic cholestasis of pregnancy; TPMT, thiopurine S-methyltransferase.

The pathogenesis of thiopurine-associated ICP is likely multifactorial and related to a combination of genetic, environmental, and hormonal changes in drug metabolism during pregnancy.[12] Hormonal fluctuations in estrogen and progesterone throughout pregnancy can result in a reduction in the active metabolite 6-thioguanine nucleotides (6-TGNs) and elevated levels of 6-methylmercaptopurine (6-MMP), a hepatotoxic compound, through increased metabolic shunting in predisposed individuals (Figure 2). In a prospective multicenter study comparing 131 thiopurine-exposed pregnancies with 147 control patients on biologic monotherapy, thiopurine shunting, defined as 6-MMP:6-TGN greater than 11, occurred in approximately 1 of every 4 pregnancies and was more likely to occur among those with antenatal thiopurine therapy dose escalations (multivariable RR, 8.10; 95% CI, 1.88-34.85).[12] In total, ICP occurred among 6.7% of thiopurine-exposed pregnancies and 0% of biologic monotherapy controls (P=.006). Notably, all ICP cases occurred among women with evidence of shunting, and patients with prior ICP were at high risk for having recurrence (RR, 17.83).

Monitoring thiopurine metabolite levels, particularly during the second and third trimesters, can help guide dose adjustments to maintain efficacy and reduce adverse effects.[12] From a clinical management perspective, discontinuation of thiopurines is recommended by the US Food and Drug Administration if evidence of ICP develops, to prevent progression of liver disease and potential adverse fetal and maternal outcomes.[13] For patients receiving combination therapy with anti-TNF agents, optimization of biologic dosing through therapeutic drug monitoring, including biologic levels and antidrug antibodies, may allow for deescalation and discontinuation of immunomodulators in cases where there are contraindications.

Split dosing of thiopurines into 12-hour dosing, before conception or in early pregnancy, may help reduce 6-MMP production without fetal harm.[5] Strategies to address shunting such as the addition of allopurinol have been described, although data related to safety in

pregnancy remain limited.[12] For patients with persistent shunting, a transition in the prenatal period to thioguanine may be considered; however, thioguanine is not commonly used in combination therapy and at higher doses has been associated with nodular regenerative hyperplasia.[13] In a multicenter case series of 117 thioguanine-exposed pregnancies, thioguanine was not associated with an increased risk of adverse pregnancy outcomes, including ICP, although larger studies are needed.[14]

Janus Kinase Inhibitors in Pregnancy

Janus kinase (JAK) inhibitors, including tofacitinib (Xeljanz, Pfizer), upadacitinib (Rinvoq, AbbVie), and filgotinib (Jyseleca, Eisai), are relatively contraindicated during pregnancy.[5] Current guidelines and expert consensus from the Global Consensus Statement on the Management of Pregnancy Inflammatory Bowel Disease recommend discontinuation of tofacitinib and upadacitinib at least 4 weeks prior to conception, and filgotinib at least 1 week prior.[5]

Although data in humans are limited, preclinical embryofetal development studies have shown that small molecules such as JAK inhibitors cause disruption of processes related to embryogenesis, hematopoiesis, and neural development.[5,15] With a low molecular weight, these agents readily cross the placenta via passive diffusion, resulting in fetal exposure throughout pregnancy and dose-dependent teratogenicity, including cardiac, skeletal, and musculoskeletal malformations.[15]

In a case series of 6 women with ulcerative colitis exposed to tofacitinib during conception or early pregnancy, cord blood analysis at delivery revealed substantial placental transfer, with a cord-to-maternal plasma concentration ratio of 0.74 at delivery.[16] One pregnancy was electively terminated owing to safety concerns, while the remaining 5 resulted in healthy term live births without congenital anomalies. A separate analysis of 106 pregnancies, with 55 live births following tofacitinib exposure, 30 with upadacitinib, and 21 with filgotinib, similarly found no consistent pattern of congenital anomalies.[17] However, most cases involved first-trimester exposure with subsequent drug discontinuation, limiting long-term interpretability.

Data from manufacturer safety databases have provided additional insight. In an analysis of 128 pregnancies with known outcomes following upadacitinib exposure, 80 were reported in clinical trials, of which 54% resulted in live births (53% without and 1% with a congenital anomaly), approximately 24% of pregnancies resulted in spontaneous abortions, 21% in elective terminations, and 1% in ectopic pregnancy.[18] Notably, the rate of spontaneous abortions differed by exposure pattern, occurring in 17% of pregnancies with upadacitinib monotherapy compared with 43% among those also exposed to methotrexate. The remaining 48 upadacitinib-exposed pregnancies were reported in postmarketing data and showed similar findings with 46% live births, 38% spontaneous abortions, 15% elective terminations, and 2% ectopic pregnancy, without a clear teratogenic signal. Across 74 reported pregnancies from manufacturer postmarketing data, among pregnant women with exposure to tofacitinib and a history of autoimmune diseases, including ulcerative colitis, rheumatoid arthritis, psoriasis, and psoriatic arthritis, most pregnancies resulted in healthy live births, with a single congenital malformation reported and no fetal or neonatal deaths.[19] There are also limited human data on the safety in breastfeeding; although tofacitinib has been detected in small amounts in human breast milk, manufacturer guidance advises against breastfeeding.[20] It is important that both sets of manufacturer-derived data be interpreted with caution, given reliance on potential confounding factors related to disease activity and concomitant teratogenic medications.[18,19]

In the setting of potential risks based on animal models and case studies, along with a paucity of long-term safety data, continuation of JAK inhibitors during pregnancy should be reserved for exceptional cases involving severe, refractory disease where other therapies have failed or are contraindicated.[5] In such circumstances, thorough discussion of potential risks and benefits and close collaboration with maternal–fetal medicine specialists are essential.

Interleukin-23p19 Inhibitors in Pregnancy

IL-23p19 inhibitors, such as guselkumab (Tremfya, Johnson & Johnson) and risankizumab-rzaa (Skyrizi, AbbVie), represent a newer class of biologic therapies that provides targeted suppression of IL-23–mediated inflammation while preserving IL-12 signaling and type 1 helper T cell–dependent host defenses. In patients with moderate-to-severe IBD, IL-23p19 inhibitors have shown efficacy comparable to IL-12/23 blockade agents, although pregnancy-specific data remain limited.[21,22] In contrast, a larger body of safety data supports the use of ustekinumab, an IL-12/23 inhibitor, during pregnancy, with findings that have been largely reassuring with respect to maternal and fetal outcomes. Results from the PIANO registry showed no increased risk of adverse maternal or neonatal outcomes, including congenital anomalies or infections, findings that may reasonably be extrapolated to the more selective IL-23p19 therapies.[23]

Available data related to IL-23p19 inhibitor safety have not shown a consistent teratogenic signal, with rates of reported pregnancy loss and congenital anomalies remaining within expected background ranges.[24,25] For

guselkumab, postmarketing safety databases, including an analysis of 178 pregnancies, reported that 63.5% of pregnancies resulted in live births, 22.5% in spontaneous abortion, and 1.1% in fetal death.[24] Notably, the majority of exposures occurred during the first trimester, and only a small proportion of the cohort (approximately 1.5%) had a diagnosis of IBD. A more recent pooled analysis of 400 guselkumab-exposed pregnancies, which included a slightly larger proportion of patients with Crohn's disease (3.8%) and ulcerative colitis (2.5%), reported 65.0% live births without congenital anomaly, 21.0% spontaneous abortions, and 1.5% live births with congenital anomaly.[25] In a multicenter cohort of 444 risankizumab-exposed pregnancies, adverse maternal and fetal outcomes were rare, with fewer than 10 events reported and no cases of preterm birth observed.[26] Current evidence, while still evolving, is increasingly reassuring and supports individualized, shared decision-making for IL-23p19 inhibitor continuation during pregnancy to maintain maternal remission.

Biosimilar Use in Pregnancy

Based on results from randomized noninferiority trials and switch cohort studies, no difference has been identified between originator biologics and anti-TNF biosimilars with respect to immunogenicity, loss of response, or adverse events in the treatment of IBD.[27,28] Although therapeutic equivalence of biosimilars among the general IBD population has been well-demonstrated, data regarding safety during pregnancy remain an area of emerging research. As a result of identical fragment crystallizable structure and shared properties such as molecular size and pharmacokinetics, active placental transport of biosimilars is expected to occur in a manner similar to that of originator biologics. In the prospective PIANO biosimilar analysis, which included 100 pregnancies with exposure to infliximab and 20 with exposure to the biosimilar agents (65% infliximab-dyyb; 35% infliximab-axxq), no significant difference in pregnancy complications was appreciated (48% vs 35%; P=.29).[29] Preterm birth occurred in 5% of both groups; low birth weight (9% vs 5%), intrauterine growth restriction (2% vs 5%), congenital malformations (7% vs 10%), and spontaneous abortion (2% vs 0%) did not differ significantly. Additionally, at 12 months, infant developmental outcomes were assessed by the Ages and Stages Questionnaire and found to be comparable across domains of communication, gross and fine motor, and personal-social skills. Data from smaller cohorts across immune-mediated diseases further reinforce these findings. In a retrospective cohort study of 18 pregnancies exposed to TNF inhibitor biosimilars at conception (including 9 women with IBD or IBD overlap), all 18 resulted in live births, with 1 preterm delivery and no congenital anomalies or neonatal intensive care unit admissions reported.[30] A rheumatology series of 5 biosimilar-exposed pregnancies similarly observed no major congenital anomalies or serious neonatal infections.[31]

Current expert guidance emphasizes maintenance of remission and avoidance of treatment interruption as paramount during pregnancy. Accordingly, insurance or cost-driven transition to biosimilars should generally proceed when clinically indicated, as available data do not demonstrate increased obstetric or neonatal risk.[5,32] Although biosimilars have been shown to have efficacy and safety comparable to originator biologics, adoption in clinical practice may be influenced by a combination of factors, including patient perceptions and counseling practices among providers. Findings from a global survey of IBD specialists reported patient concerns centered primarily on fears of reduced effectiveness (36%) and the potential for a disease flare (24%).[33] Prospective studies suggest that structured physician-led counseling prior to switching may improve patient acceptance, highlighting the importance of proactive communication and shared decision-making in successful biosimilar implementation.[34]

Low-Dose Aspirin Use and Pregnancy

Low-dose aspirin is considered a key strategy in preventative care for patients at increased risk of hypertensive disorders of pregnancy. The 2025 Global Consensus Statement on the Management of Pregnancy in Inflammatory Bowel Disease recommends aspirin initiation before 16 weeks at a daily dose of at least 100 mg with continuation until the time of delivery.[5] This recommendation is informed by evidence of an elevated risk of preeclampsia among patients with IBD (adjusted OR, 1.65; 95% CI, 1.02-2.68) and aligns with the American College of Obstetricians and Gynecologists, which advises low-dose aspirin for women categorized as high risk for preeclampsia, including those with a history of autoimmune diseases.[35]

Findings from the multicenter ASPRE trial demonstrated that low-dose aspirin as prophylaxis significantly reduced the incidence of preterm preeclampsia with rates decreasing from 4.3% to 1.6% (adjusted OR, 0.38).[36] These results have been further supported by a systematic review from the US Preventive Services Task Force, consisting of 23 randomized trials and 26,952 participants. Low-dose aspirin (50-150 mg daily) significantly reduced the risk of preeclampsia (RR, 0.85; 95% CI, 0.75-0.95), perinatal mortality (RR, 0.79; 95% CI, 0.66-0.96), and preterm birth (RR, 0.80; 95% CI, 0.67-0.95), with no significant increase in maternal bleeding or other harms.[37]

Although high-dose and long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) is traditionally

avoided in IBD owing to concerns related to peptic ulcers and NSAID-induced enteropathy, most clinical data evaluating low-dose aspirin in IBD have been reassuring.[38-40] At low doses, aspirin is thought to reduce the endothelial dysfunction and prothrombotic state by attenuating platelet activation and vasoconstriction via preferential thromboxane A2 inhibition.[35]

In a retrospective cohort study of 764 patients with IBD, daily aspirin use was not found to be associated with an increase in IBD-related hospitalizations, surgery, or corticosteroid use over a median of 45 months of follow-up.[40] Similarly, in a cohort of 232 pregnant women with IBD, Memel and colleagues found that 28% of patients were initiated aspirin at a median of 12 weeks' gestation and while disease flares occurred in approximately 1 of every 4 patients either during pregnancy or within 6 months postpartum, there was no difference seen between groups with and without low-dose aspirin (20% vs 26%, respectively; *P*=.36).[38] There was also no observed difference in hospitalization, surgery, medication escalation, endoscopic activity, or fecal calprotectin. A third study by DeBolt and colleagues examined outcomes for a cohort of 384 pregnant patients with IBD.[39] Of the 18.5% of patients who used low-dose aspirin (81-162 mg), there was no association appreciated with disease activity (OR, 1.27; 95% CI, 0.55-2.94), elevations in C-reactive protein or fecal calprotectin, or preeclampsia.

Preeclampsia and other hypertensive diseases of pregnancy are increasingly recognized as part of a broader spectrum of conditions that serve as important predictors of long-term maternal cardiovascular health. A prior systematic review and meta-analysis highlighted this risk, noting an increased odds of cardiovascular death (OR, 2.18; 95% CI, 1.8-2.7) and major cardiovascular events (OR, 1.80; 95% CI, 1.6-2.0) among patients with preeclampsia compared with those with normotensive pregnancies.[41] Patient education related to low-dose aspirin initiation among patients with IBD may serve as an important form of preventative care when centered around a framework of shared decision-making, lifestyle and nutritional counseling, and close postpartum follow-up.[42]

Rotavirus Vaccination in Infants Exposed to Biologic Therapy in Utero

Prior to widespread availability of vaccination, rotavirus was the leading cause of severe diarrhea in infants and young children, resulting in an estimated 500,000 deaths annually worldwide.[43] In the general population, the first dose is recommended within the first 15 weeks of life, with 2 oral, live-attenuated rotavirus vaccines currently available as either a 3- or 2-dose series completed by 7 and 5 months of age, respectively. Both vaccines demonstrate high efficacy, reducing incidence of severe disease by 80% to 98%.[43] Current guidelines endorsed by organizations such as the Canadian Association of Gastroenterology and the European Crohn's and Colitis Organisation recommend deferring live vaccines for infants exposed to biologic therapy in utero for the first 6 to 12 months of life or until biologic drug levels are no longer detectable.[1,44] These guidelines are largely informed by both pharmacokinetic data, which have shown significant placental transfer of immunoglobulin G subclass 1 monoclonal antibodies, particularly in the third trimester, as well as a fatal case of disseminated Bacillus Calmette-Guérin infection following vaccination in an infant with in utero exposure to infliximab.[45]

In the general population, the rotavirus vaccine is well-tolerated in infancy, and an accumulating body of both immunologic and clinical evidence supports a favorable fetal safety profile among biologic-exposed infants. In a study involving a comprehensive immunologic evaluation of 57 infants born to 52 mothers with IBD exposed to biologics in the third trimester, Ernest-Suarez and colleagues found normal immune profiles, including quantitative immunoglobulins and extended B- and T-cell subsets, among the entire cohort.[46] Although most infants had detectable circulating drug levels, administration of the rotavirus vaccine at a median of 13 weeks was uneventful in all infants, with no serious or infectious adverse events reported.

In a systematic review by Schell and colleagues, which included 10 studies, a total of 226 biologic-exposed infants who received rotavirus vaccination were found to have no serious adverse events reported.[47] Population-based data, including a nationwide French cohort study of 153 pregnancies exposed to anti-TNF therapy, reported similar findings.[48] Of the biologic-exposed infants, 10 received rotavirus vaccination at a median age of 86 days, and fever was observed in 1 infant exposed to adalimumab.[48]

Although the majority of real-world data remains relatively reassuring, vaccination rates are overall low in this patient population. In the PIANO registry, only 35% of biologic-exposed infants received the rotavirus vaccination, compared with significantly higher rates among unexposed infants (*P*=.001).[49] Uptake was especially low among infants exposed to combination therapy. Infants in the study exposed to biologic plus immunomodulator therapy in utero had a vaccination rate of 16% compared with biologic monotherapy (41%). In total, among 43 biologic-exposed infants who did receive rotavirus vaccination, 17.5% experienced mild reactions, primarily fever, rates that are comparable to those reported in large clinical trials of healthy infants. There was no reported association between infant drug concentrations at birth and risk of reaction. The most commonly cited reason for

Table. Summary of Key Updates in the Management of IBD During Pregnancy

Update	Key evidence	Clinical implications
Disease assessment and monitoring		
IUS as an important diagnostic and monitoring tool in pregnancy	Strong correlation between IUS and fecal calprotectin (ρ = 0.73)[3] Bowel wall thickness is associated with preterm birth (RR, 4.01; 95% CI, 1.26-12.72)[2] Doppler hyperemia showed association with preeclampsia (RR, 3.46; 95% CI, 1.03-11.12)[2] Terminal ileum visualization declines from 91.3% in the first trimester to 21.7% in the third trimester; similarly, sigmoid colon visualization decreases from 95.6% to 69.5%[3]	IUS provides a noninvasive point-of-care method to assess disease activity. It can help identify active or subclinical inflammation and inform obstetric risk stratification. Notably, IUS visualization is poor for the rectum and declines in later trimesters for the terminal ileum and sigmoid colon.
Medication safety in pregnancy		
Thiopurines association with ICP	Several studies show ICP incidence of up to 7.3% among thiopurine-exposed patients vs 0.9% of unexposed pregnancies (adjusted RR, 7.78; 95% CI, 5.41-11.17); higher risk vs TNF inhibitors (adjusted RR, 11.33)[11] Thiopurine metabolic shunting (elevated 6-MMP:6-TGN) is strongly associated with ICP[11] Antenatal dose escalation of thiopurines may increase ICP (RR, 8.10)[12]	Thiopurine exposure during pregnancy is associated with a substantially increased risk of ICP, and patients should be counseled regarding symptoms and undergo bile acid monitoring if clinically indicated. Risk-mitigation approaches include split dosing or transition to alternative agents (eg, thioguanine) in select patients.
JAK inhibitors (tofacitinib, upadacitinib) remain relatively contraindicated in pregnancy	Teratogenicity has been observed in animal models; limited human data largely involving early medication discontinuation Significant placental transfer has been demonstrated, with cord-to-maternal concentration ratio of approximately 0.74 at delivery[16]	JAK inhibitors should be discontinued prior to conception and avoided during pregnancy and while breastfeeding. Continued use should be reserved for exceptional cases of severe, refractory disease when alternative therapies are ineffective or contraindicated.
Interleukin-23p19 inhibitors (guselkumab, risankizumab) in pregnancy	Postmarketing safety database with 178 known outcomes (1.5% of patients with IBD) notable for 63.5% live births, 22.5% spontaneous abortion, 1.1% fetal death; majority first-trimester exposure[24] Pooled analysis of 400 known outcomes (CD 3.8%, UC 2.5%) has shown 65.0% live births without congenital anomaly, 21.0% spontaneous abortion, 1.5% live births with congenital anomaly[25]	Pregnancy-specific data remain limited and largely derived from pharmacovigilance datasets with small IBD-specific samples. No consistent teratogenic signal has been identified. Available data are increasingly reassuring and support individualized, shared decision-making when continuation is necessary to maintain remission.
Biosimilar use during pregnancy	Randomized noninferiority and multiple-switch studies show no increased immunogenicity, loss of response, or adverse events after transition from originator anti-TNF agents[27,28] PIANO analysis (100 originator vs 20 biosimilar infliximab exposures): similar overall complications (48% vs 35%, *P*=.29); no differences in preterm birth, low birth weight, congenital malformations, or 12-month developmental outcomes[29]	Available data do not demonstrate increased obstetric or neonatal risk with biosimilar exposure. Maintenance of remission remains paramount; insurance-mandated transition should generally proceed with proactive counseling and shared decision-making.
Obstetrics risk reduction		
Low-dose aspirin recommended for pregnant patients with IBD	ASPRE trial showed reduced preterm preeclampsia with low-dose aspirin (aOR, 0.38)[36]; USPSTF meta-analysis: reduced preeclampsia (RR, 0.85) and preterm birth (RR, 0.80)[37] IBD cohorts show no increase in disease activity on low-dose aspirin[38-40]	Low-dose aspirin initiated between 12 and 16 weeks' gestation and continued until delivery may reduce the risk of hypertensive disorders of pregnancy and has not been shown to increase disease activity in IBD.
Infant and neonatal considerations		
Rotavirus vaccination and reassuring safety data after in utero biologic exposure	Over 200 biologic-exposed infants vaccinated across cohorts with no serious adverse events[47] Immunologic studies show normal infant immune profiles despite detectable drug levels[49]	Although current recommendations suggest a 6-month rotavirus vaccine deferral, accumulating immunologic and clinical data may support the safety of vaccination in most biologic-exposed infants.

6-MMP, 6-methylmercaptopurine; 6-TGN, 6-thioguanine nucleotide; aOR, adjusted odds ratio; CD, Crohn's disease; IBD, inflammatory bowel disease; ICP, intrahepatic cholestasis of pregnancy; IUS, intestinal ultrasound; JAK, Janus kinase; PIANO, Pregnancy Inflammatory Bowel Disease and Neonatal Outcomes; RR, risk ratio; TNF, tumor necrosis factor; UC, ulcerative colitis; USPSTF, US Preventive Services Task Force.

vaccine deferral was physician recommendation.

Taken together, a growing body of immunologic, clinical, and population-based data support the safety of rotavirus vaccination in most infants exposed to biologic therapy in utero, including those with detectable circulating drug levels at the time of vaccination.[46] As the evidence base continues to expand, reevaluation of existing guideline recommendations may be warranted to weigh theoretical risks against the potential burden of severe gastroenteritis in unvaccinated infants.

Conclusion

Ongoing research related to imaging, medical therapy, and prevention-focused approaches continues to support evidence-based care that extends from preconception through the postpartum period (Table). The utility of IUS, particularly early in pregnancy, is supported by studies demonstrating strong correlation with established biomarkers and the ability to detect clinically meaningful inflammation, while also providing insight into obstetric risk. Randomized studies support the safety of anti-TNF biosimilars, while early data on newer agents, including IL-23 inhibitors, are reassuring but remain limited. Emerging observational data reinforce the potential associations between thiopurine use and ICP, while JAK inhibitors, based on preclinical and limited human data, continue to be avoided during pregnancy in most cases. Preventive strategies such as low-dose aspirin to reduce the risk of hypertensive disorders of pregnancy, as well as optimization of vaccine timing and safety for infants, particularly as it relates to rotavirus vaccination in biologic-exposed infants, continue to advance a proactive, risk-based approach to care.

Future directions in research may focus on standardizing IUS training and defining its optimal role across pregnancy. Additional investigation is needed to refine therapeutic drug monitoring during pregnancy and to better identify patient- and medication-specific risk factors, including those associated with ICP in patients receiving thiopurines. Further study is also warranted to better stratify which infants with in utero biologic exposure can safely receive live vaccines according to standard schedules, including rotavirus vaccination, and to inform potential updates to current vaccination guidelines as safety data continue to accumulate.

Disclosures

Dr Boyd has no relevant conflicts of interest to disclose. Dr Kane serves as a consultant to Boehringer Ingelheim, Bristol Myers Squibb, Gilead, Janssen, Lilly, and Takeda; is a contributor to Oakstone Publishing; and is the Section Editor for IBD for UpToDate.

References

1. Torres J, Chaparro M, Julsgaard M, et al. European Crohn's and Colitis Guidelines on sexuality, fertility, pregnancy, and lactation. *J Crohns Colitis*. 2023;17(1):1-27.
2. Prentice RE, Flanagan EK, Wright EK, et al. Active inflammatory bowel disease on intestinal ultrasound during pregnancy is associated with an increased risk of adverse pregnancy and neonatal outcomes independent of clinical and biochemical disease activity. *Gastroenterology*. 2025;169(4):647-662.
3. De Voogd F, Joshi H, Van Wassenaer E, Bots S, D'Haens G, Gecse K. Intestinal ultrasound to evaluate treatment response during pregnancy in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2022;28(7):1045-1052.
4. Tan WL, Khoo E, Khaing MM, et al. Point-of-care intestinal ultrasound impacts inflammatory bowel disease care and reduces the need for additional investigations. *J Gastroenterol Hepatol*. 2025;40(10):2472-2481.
5. Mahadevan U, Seow CH, Barnes EL, et al; Global Consensus Group for Pregnancy and IBD. Global consensus statement on the management of pregnancy in inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2025;23(11S):S1-S60.
6. Jabehdar Maralani P, Kapadia A, Liu G, et al. Canadian Association of Radiologists recommendations for the safe use of MRI during pregnancy. *Can Assoc Radiol J*. 2022;73(1):56-67.
7. Madsen GR, Wilkens R, Boysen T, et al. The knowledge and skills needed to perform intestinal ultrasound for inflammatory bowel diseases-an international Delphi consensus survey. *Aliment Pharmacol Ther*. 2022;56(2):263-270.
8. Mahadevan U, Long MD, Kane SV, et al; Crohn's Colitis Foundation Clinical Research Alliance. Pregnancy and neonatal outcomes after fetal exposure to biologics and thiopurines among women with inflammatory bowel disease. *Gastroenterology*. 2021;160(4):1131-1139.
9. Meyer A, Taine M, Drouin J, Weill A, Carbonnel F, Dray-Spira R. Serious infections in children born to mothers with inflammatory bowel disease with in utero exposure to thiopurines and anti-tumor necrosis factor. *Clin Gastroenterol Hepatol*. 2022;20(6):1269-1281.e9.
10. Selinger CP, Rosiou K, Broglio G, et al. Antenatal thiopurine exposure in women with IBD is associated with intrahepatic cholestasis of pregnancy. *Expert Opin Drug Saf*. 2023;22(11):1091-1097.
11. Nguyen NV, Sandström A, Dominicus A, et al; SWIBREG study group. Thiopurines and intrahepatic cholestasis of pregnancy in systemic lupus erythematosus and inflammatory bowel disease pregnancies. *Am J Gastroenterol*. 2025;121(5):1183-1191.
12. Prentice R, Flanagan E, Wright E, et al. Thiopurine metabolite shunting in late pregnancy increases the risk of intrahepatic cholestasis of pregnancy in women with inflammatory bowel disease, and can be managed with split dosing. *J Crohns Colitis*. 2024;18(7):1081-1090.
13. Jena A, Neelam PB, Telaprolu H, et al. Effectiveness and safety of thioguanine as a maintenance therapy of inflammatory bowel disease: systematic review, meta-analysis and meta-regression. *Clin Res Hepatol Gastroenterol*. 2023;47(7):102155.
14. Crouwel F, Simsek M, de Boer MA, et al. Exposure to thioguanine during 117 pregnancies in women with inflammatory bowel disease. *J Crohns Colitis*. 2023;17(5):738-745.
15. Wieringa JW, van der Woude CJ. Effect of biologicals and JAK inhibitors during pregnancy on health-related outcomes in children of women with inflammatory bowel disease. *Best Pract Res Clin Gastroenterol*. 2020;44-45:101665.
16. Mitrova K, Julsgaard M, Augustijns P, Cerna K, Mahadevan U, Duricova D; Pregnancy Study Group. Tofacitinib in pregnancy: assessing pregnancy and infant outcomes, cord blood, and breast milk concentrations. *Clin Gastroenterol Hepatol*. 2025;23(1):163-165.e3.
17. Monfared N, Gold M, Carbery I, Laube R, Selinger CP. Reproductive safety issues of novel small molecules for the treatment of inflammatory bowel disease: a systematic review. *J Clin Med*. 2023;13(1):34.
18. Mahadevan U, Levy G, Gensler L, et al. Pregnancy outcomes in patients treated with upadacitinib: analysis of data from clinical trials and postmarketing reports. *Drug Saf*. 2024;47(10):1039-1049.
19. Mahadevan U, Dubinsky MC, Su C, et al. Outcomes of pregnancies with maternal/paternal exposure in the tofacitinib safety databases for ulcerative colitis. *Inflamm Bowel Dis*. 2018;24(12):2494-2500.
20. Julsgaard M, Mahadevan U, Vestergaard T, Mols R, Ferrante M, Augustijns P. Tofacitinib concentrations in plasma and breastmilk of a lactating woman with ulcerative colitis. *Lancet Gastroenterol Hepatol*. 2023;8(8):695-697.
21. Panaccione R, Feagan BG, Afzali A, et al; GALAXI 2 & 3 Study Group. Efficacy and safety of intravenous induction and subcutaneous maintenance therapy with guselkumab for patients with Crohn's disease (GALAXI-2 and GALAXI-3):

48-week results from two phase 3, randomised, placebo and active comparator-controlled, double-blind, triple-dummy trials. *Lancet*. 2025;406(10501):358-375.
22. Peyrin-Biroulet L, Chapman JC, Colombel JF, et al; SEQUENCE Study Group. Risankizumab versus ustekinumab for moderate-to-severe Crohn's disease. *N Engl J Med*. 2024;391(3):213-223.
23. Rabinowitz LG, Gade A, Deyhim T, Feuerstein JD. Safety and use of IBD therapies during pregnancy and lactation. *Expert Rev Gastroenterol Hepatol*. 2026;20(2):81-92.
24. Lin C, Geldhof A, Ballina M, Patel H, Li H. Pregnancy outcomes in women exposed to guselkumab: review of cases reported to the manufacturer's global safety database [ACR abstract 0447]. *Arthritis Rheumatol*. 2024;76(suppl 9).
25. Mahadevan-Velayos U, Long M, Julsgaard M, et al. P1042 Pregnancy outcomes in maternal exposure to guselkumab: review of cases reported to the Company Global Safety Database. *J Crohns Colitis*. 2026;20(suppl 1):jjaf231.1223.
26. Winter RW, Tao LY, Friedman S, Ma KS. Pregnancy and maternal outcomes after exposure to risankizumab during pregnancy: a multi-center experience in the United States. *Inflamm Bowel Dis*. 2026;32(4):820-823.
27. Casanova MJ, Nantes Ó, Varela P, et al. Real-world outcomes of switching from adalimumab originator to adalimumab biosimilar in patients with inflammatory bowel disease: the ADA-SWITCH study. *Aliment Pharmacol Ther*. 2023;58(1):60-70.
28. Jørgensen KK, Olsen IC, Goll GL, et al; NOR-SWITCH study group. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet*. 2017;389(10086):2304-2316.
29. Long MD, Kane S, Beaulieu D, Abraham B, Zhang X, Mahadevan U. Use of biosimilars to infliximab during pregnancy in women with inflammatory bowel disease: results from the pregnancy in inflammatory bowel disease and neonatal outcomes study. *Clin Transl Gastroenterol*. 2024;15(12):e00795.
30. Scott R, Parker H, Mccartney S, Harrow P, Williams D, Giles I. Outcomes following biosimilar TNF inhibitor use for inflammatory-mediated immune disorders in pregnancy. *Obstet Med*. 2022;15(2):104-107.
31. Chícharo AT, Lopes AR, Barreira S, Pinto L, Cruz-Machado AR, Capela S. Maternal and perinatal outcomes in pregnant women with rheumatic diseases treated with biosimilar TNF inhibitors. *Rheumatol Adv Pract*. 2024;8(2):rkae044.
32. Bhat S, Kane SV. Clinical guide to navigating the landscape of biosimilars for inflammatory bowel disease. *Gastroenterol Hepatol (N Y)*. 2024;20(7):376-382.
33. D'Amico F, Solitano V, Magro F, et al. Practical management of biosimilar use in inflammatory bowel disease (IBD): a global survey and an international Delphi consensus. *J Clin Med*. 2023;12(19):6350.
34. Haghnejad V, Le Berre C, Dominique Y, Zallot C, Guillemin F, Peyrin-Biroulet L. Impact of a medical interview on the decision to switch from originator infliximab to its biosimilar in patients with inflammatory bowel disease. *Dig Liver Dis*. 2020;52(3):281-288.
35. Clarke LM, Hsu S, Pant D, et al. The risk of hypertensive disorders of pregnancy in inflammatory bowel disease [published online October 23, 2025]. *Am J Gastroenterol*. doi:10.14309/ajg.0000000000003818.
36. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med*. 2017;377(7):613-622.
37. Henderson JT, Vesco KK, Senger CA, Thomas RG, Redmond N. Aspirin use to prevent preeclampsia and related morbidity and mortality: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2021;326(12):1192-1206.
38. Memel Z, Yu A, Fenton C, et al. The effect of low-dose aspirin on disease activity in pregnant individuals with inflammatory bowel disease. *Am J Gastroenterol*. 2025;120(11):2603-2610.
39. DeBolt CA, Gottlieb ZS, Rao MG, et al. Low-dose aspirin use does not increase disease activity in pregnant patients with inflammatory bowel disease. *Dig Dis Sci*. 2024;69(5):1803-1807.
40. Patel P, Gao G, Gulotta G, et al. Daily aspirin use does not impact clinical outcomes in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2021;27(2):236-241.
41. Dall'Asta A, D'Antonio F, Saccone G, et al. Cardiovascular events following pregnancy complicated by pre-eclampsia with emphasis on comparison between early- and late-onset forms: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2021;57(5):698-709.
42. Roberts JM, King TL, Barton JR, et al. Care plan for individuals at risk for preeclampsia: shared approach to education, strategies for prevention, surveillance, and follow-up. *Am J Obstet Gynecol*. 2023;229(3):193-213.
43. Troeger C, Khalil IA, Rao PC, et al. Rotavirus vaccination and the global burden of rotavirus diarrhea among children younger than 5 years. *JAMA Pediatr*. 2018;172(10):958-965.
44. Benchimol EI, Tse F, Carroll MW, et al. Canadian Association of Gastroenterology clinical practice guideline for immunizations in patients with inflammatory bowel disease (IBD)-part 1: live vaccines. *Gastroenterology*. 2021;161(2):669-680.e0.
45. Goulden B, Chua N, Parker E, Giles I. A systematic review of live vaccine outcomes in infants exposed to biologic disease modifying anti-rheumatic drugs in utero. *Rheumatology (Oxford)*. 2022;61(10):3902-3906.
46. Ernest-Suarez K, Murguía-Favela LE, Constantinescu C, et al. Live rotavirus vaccination appears low-risk in infants born to mothers with inflammatory bowel disease on biologics. *Clin Gastroenterol Hepatol*. 2025;23(5):835-845.
47. Schell TL, Fass L, Hitchcock ME, et al. Safety of rotavirus vaccination in infants that were exposed to biologics in utero: a systematic review. *Inflamm Bowel Dis*. 2025;31(7):1789-1796.
48. Bendaoud S, Nahon S, Beaugerie L, et al. Risk of anti-TNF therapy on pregnancy, breastfeeding, live vaccines and related information in patients with inflammatory bowel disease: real-world data from a nationwide study. *Dig Liver Dis*. 2024;56(12):2038-2044.
49. Beaulieu DB, Ananthakrishnan AN, Martin C, Cohen RD, Kane SV, Mahadevan U. Use of biologic therapy by pregnant women with inflammatory bowel disease does not affect infant response to vaccines. *Clin Gastroenterol Hepatol*. 2018;16(1):99-105.