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CLINICAL PRACTICE UPDATES

AGA Clinical Practice Update on Pregnancy-Related Gastrointestinal and Liver Disease: Expert Review

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DESCRIPTION: The purpose of this American Gastroenterological Association (AGA) Institute Clinical Practice Update is to review the available published evidence and expert advice regarding the clinical management of patients with pregnancy-related gastrointestinal and liver disease. **METHODS:** This expert review was commissioned and approved by the AGA Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership and underwent internal peer review by the Clinical Practice Updates Committee and external peer review through the standard procedures of *Gastroenterology*. This article provides practical advice for the management of pregnant patients with gastrointestinal and liver disease based on the best available published evidence. The Best Practice Advice statements were drawn from a review of the published literature and from expert opinion. Because formal systematic reviews were not performed, these Best Practice Advice statements do not carry formal ratings regarding the quality of evidence or strength of the presented considerations.

BEST PRACTICE ADVICE STATEMENTS

BEST PRACTICE ADVICE 1: To optimize gastrointestinal and liver disease before pregnancy, preconception and contraceptive care counseling by a multidisciplinary team should be encouraged for reproductive-aged persons who desire to become pregnant. **BEST PRACTICE ADVICE 2:** Procedures, medications, and other interventions to optimize maternal health should not be withheld solely because a patient is pregnant and should be individualized after an assessment of the risks and benefits. **BEST PRACTICE ADVICE 3:** Coordination of birth for a pregnant patient with complex inflammatory bowel disease, advanced cirrhosis, or a liver transplant should be managed by a multidisciplinary team, preferably in a tertiary care center. **BEST PRACTICE ADVICE 4:** Early treatment of nausea and vomiting of pregnancy may reduce progression to hyperemesis gravidarum. In addition to standard diet and lifestyle measures, stepwise treatment consists of symptom control with vitamin B6 and doxylamine, hydration, and adequate nutrition; ondansetron, metoclopramide, promethazine, and intravenous glucocorticoids may be required in moderate to severe cases. **BEST PRACTICE ADVICE 5:** Constipation in pregnant persons may result from hormonal, medication-related, and physiological changes. Treatment options include dietary fiber, lactulose, and polyethylene glycol–based laxatives. **BEST PRACTICE ADVICE 6:** Elective endoscopic procedures should be deferred until the postpartum period, whereas nonemergent but necessary procedures should ideally be performed in the second trimester. Pregnant patients with cirrhosis should undergo evaluation for, and treatment of, esophageal varices; upper endoscopy is suggested in the second trimester (if not performed within 1 year before conception) to guide consideration of nonselective β-blocker therapy or endoscopic variceal ligation. **BEST PRACTICE ADVICE 7:** In patients with inflammatory bowel disease, clinical remission before conception, during pregnancy, and in the postpartum period is essential for improving outcomes of pregnancy. Biologic agents should be continued throughout pregnancy and the postpartum period; use of methotrexate, thalidomide, and ozanimod must be stopped at least 6 months before conception. **BEST PRACTICE ADVICE 8:** Endoscopic retrograde cholangiopancreatography during pregnancy may be performed for urgent indications, such as choledocholithiasis, cholangitis, and some cases of gallstone pancreatitis. Ideally, endoscopic retrograde cholangiopancreatography should be performed during the second trimester, but if deferring the procedure may be detrimental to the health of the patient and fetus, a multidisciplinary team should be convened to decide on the advisability of endoscopic retrograde cholangiopancreatography. **BEST PRACTICE ADVICE 9:** Cholecystectomy is safe during pregnancy; a laparoscopic approach is the standard of care regardless of trimester, but ideally in the second trimester. **BEST PRACTICE ADVICE 10:** The diagnosis of intrahepatic cholestasis of pregnancy is based on a serum bile acid level >10 μmol/L in the setting of pruritus, typically during the second or third trimester. Treatment should be offered with oral ursodeoxycholic acid in a total daily dose of 10–15 mg/kg. **BEST PRACTICE ADVICE 11:** Management of liver diseases unique to pregnancy, such as pre-eclampsia; hemolysis, elevated liver enzymes, and low platelets syndrome; and acute fatty liver of pregnancy requires planning for delivery and timely evaluation for possible liver transplantation. Daily aspirin prophylaxis for patients at risk for pre-eclampsia or hemolysis, elevated liver enzymes, and low platelets syndrome is advised beginning at week 12 of gestation. **BEST PRACTICE ADVICE 12:** In patients with chronic hepatitis B virus infection, serum hepatitis B virus DNA and liver biochemical test levels should be ordered. Patients not on treatment but with a serum hepatitis B virus DNA level $>200{,}000$ IU/mL during the third trimester of pregnancy should be considered for treatment with tenofovir disoproxil fumarate. **BEST PRACTICE ADVICE 13:** In

patients on immunosuppressive therapy for chronic liver diseases or after liver transplantation, therapy should be continued at the lowest effective dose during pregnancy. Mycophenolate mofetil should not be administered during pregnancy.

Keywords: Pregnancy; Liver Disease; Endoscopy; Vomiting; Inflammatory Bowel Disease.

Preconception and Contraceptive Counseling

Best Practice Advice 1: To optimize gastrointestinal and liver disease before pregnancy, preconception and contraceptive care counseling by a multidisciplinary team should be encouraged for reproductive-aged persons who desire to become pregnant.

In the United States, more than one-half of all pregnancies are unplanned.[1] Unplanned pregnancies are associated with increased risks to the pregnant person and fetus. Pregnant persons with some gastrointestinal (GI) and liver diseases are considered to have high-risk pregnancies, and an unplanned pregnancy increases the risk further. When possible, the patient's health should be optimized before pregnancy. The risk to the pregnancy depends on the underlying GI or liver disease, and pregnancy may affect the course of the GI or liver disease. Therefore, preconception preparation requires collaboration among all of the relevant providers who care for a person of reproductive age. The goal is to reduce potential harm to the mother and fetus by identifying modifiable risk factors and intervening to improve the health of the mother and child while considering the mother's preferences.[2]

A discussion of the patient's reproductive plans should be incorporated into the clinical encounter with a reproductive-aged person with active GI or liver issues that can be affected by pregnancy (and vice versa) and include consideration of contraception if the person is trying to avoid a pregnancy, ways to optimize health before pregnancy occurs, and the optimal timing of pregnancy. Preconception counseling can be done collaboratively with the patient's primary care physician, gastroenterologist, hepatologist, and obstetrician or maternal-fetal medicine (MFM) physician. Issues discussed may include medical and surgical management of the underlying disease, genetic testing, artificial reproductive technologies (if relevant), family planning, and contraceptive care. Preconception visits allow risk stratification and optimization of the management of medical illnesses to achieve a safe pregnancy.

Risk Mitigation

Best Practice Advice 2: Procedures, medications, and other interventions to optimize maternal health should not be withheld solely because a patient is pregnant and should be individualized after an assessment of the risks and benefits.

Pregnancy-related morbidity and mortality are increasing in the United States,[3] particularly for pregnancies that are considered high risk because of chronic or newly diagnosed medical comorbidities. Recognizing a worsening disease course, triaging the level of maternal health, and prescribing appropriate medication and interventions are essential.[4]

Risk mitigation for high-risk pregnancies may include medications, procedures, and other interventions that may have unknown effects on the pregnancy or the fetus. Often, no data exist on teratogenicity and other risks of a specific intervention because of the difficulty conducting large-scale randomized studies in this population. Many interventions will warrant a discussion of safety in the pregnant person and fetus. In general, most interventions, including computed tomography or endoscopic retrograde cholangiopancreatography (ERCP), should not be withheld if deemed necessary.

Coordination of Birth

Best Practice Advice 3: Coordination of birth for a pregnant patient with complex inflammatory bowel disease, advanced cirrhosis, or a liver transplant should be managed by a multidisciplinary team, preferably in a tertiary care center.

Some GI and liver diseases may place patients at an increased risk of adverse pregnancy outcomes, including miscarriages, preterm birth, hypertensive disease of pregnancy, and cesarean birth.[5,6] Patients with moderate- or high-risk GI or liver disease should ideally be managed throughout the pregnancy (ie, prenatal care), during delivery, and in the postpartum period at centers with multidisciplinary teams that have experience treating high-risk diseases in a pregnant person. Pregnant patients with GI and liver diseases should be cared for by subspecialists in gastroenterology, obstetrics, and MFM. Throughout the pregnancy, the team should conduct collaborative discussions related to birth planning, birth location, mode of delivery, and gestational age, as well as medical and surgical interventions that may be needed.

Heartburn, Nausea, and Vomiting

Best Practice Advice 4: Early treatment of nausea and vomiting of pregnancy may reduce progression to hyperemesis gravidarum. In addition to standard diet and lifestyle measures, stepwise treatment consists of symptom control with vitamin B6 and doxylamine, hydration, and adequate nutrition; ondansetron, metoclopramide, promethazine, and intravenous glucocorticoids may be required in moderate to severe cases.

Abbreviations used in this paper: ACOG, American College of Obstetricians and Gynecologists; AFLP, acute fatty liver of pregnancy; anti-TNF, anti-tumor necrosis factor; ERCP, endoscopic retrograde cholangiopancreatography; GD, gallstone disease; GI, gastrointestinal; HBV, hepatitis B virus; HG, hyperemesis gravidarum; IBD, inflammatory bowel disease; IV, intravenous; MFM, maternal-fetal medicine; NVP, nausea and vomiting of pregnancy.

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Table 1. Motherisk Pregnancy-Unique Quantification of Emesis Score

Variable	Motherisk Pregnancy-Unique Quantification of Emesis score[a]				
	1	2	3	4	5
In the past 12 h:					
How long (*h*) have you felt nauseated or sick to your stomach?	Not at all	≤1	2–3	4–6	>6
How many times have you thrown up or vomited?	I have not thrown up at all	1–2	3–4	5–6	≥7
How many times have you had retching or dry heaves without throwing up?	None	1–2	3–4	5–6	≥7

Adapted from Am J Obstet Gynecol, Vol. 186, Iss. 5, Suppl. 2, Koren G, Boskovic R, Hard M, et al, Motherisk–PUQE (pregnancy-unique quantification of emesis and nausea) scoring system for nausea and vomiting of pregnancy, S228–S231, 2002, with permission from Elsevier.
[a]Maximum score = 15; severity: ≤6 = mild, 7–12 = moderate, ≥13 = severe.

Heartburn, nausea, and vomiting are common during pregnancy, with frequency ranging from 30%–90%.[7–9] Nausea and vomiting of pregnancy (NVP) usually begins at 4–6 weeks,[10] peaks at 8–12 weeks, and subsides by week 20.[7] Heartburn is common in the latter part of the pregnancy and resolves after delivery.[11] Heartburn during pregnancy can be attributed to an increase in levels of progesterone, which causes relaxation of the lower esophageal sphincter, thereby facilitating gastroesophageal reflux.[8] NVP, however, is commonly associated with elevated levels of human chorionic gonadotropin and estrogen and changes in GI motility. Progesterone can have an inhibitory effect on GI and small bowel motility and lead to delayed gastric emptying. The severity of vomiting during pregnancy can be quantified with a scoring system, such as the Motherisk Pregnancy Unique Quantification of Emesis score (Table 1).[12]

Diet and lifestyle modification are the initial steps in managing these symptoms in pregnancy. Reducing spicy, fatty, acidic, and fried foods can help to reduce heartburn. Eating small, frequent, and bland meals, for example, the BRAT (bananas, rice, applesauce, and toast) diet, and high-protein and low-fat meals can also be helpful in NVP.[13] Specific triggers, such as certain foods with strong odors or activities, should be identified and avoided. If symptoms are persistent or severe, therapeutic options include ginger (a 250-mg capsule 4 times daily) and vitamin B6 (pyridoxine, 10–25 mg every 8 hours), as recommended by the American College of Obstetricians and Gynecologists (ACOG).[14]

H1-receptor antagonists, such as doxylamine, promethazine, and dimenhydrinate, are considered safe first-line pharmacologic antiemetic therapies, if needed. Doxylamine is US Food and Drug Administration–approved and recommended by ACOG for persistent NVP refractory to nonpharmacologic therapy.[14] Doxylamine and pyridoxine are available in 10 mg/10 mg and 20 mg/20 mg combinations and are safe and well tolerated.[15] Early intervention and treatment of NVP may help prevent progression to hyperemesis gravidarum (HG).[14]

H2-receptor blockers are the most used antireflux medications during pregnancy. Cimetidine and famotidine are administered routinely in pregnancy. Proton pump inhibitors, such as omeprazole or pantoprazole, can be considered if lifestyle modifications and antacids fail to alleviate symptoms. In a meta-analysis of 26 studies evaluating the risk of adverse neonatal outcomes associated with maternal intake of proton pump inhibitors, no significant associations between proton pump inhibitor use and abortion, stillbirth, neonatal death, preterm birth, and low birth weight were observed, although a nonsignificant increase in the risk of congenital malformations was reported in 1 study.[16]

Hyperemesis Gravidarum

HG is an intractable form of NVP that can lead to dehydration, weight loss of >5% of prepregnancy weight, and electrolyte imbalances.[17] It can affect 0.3%–2% of pregnant persons. HG usually starts before week 22 of gestation. By week 16, symptoms resolve in >50% of affected persons and by 20 weeks, 80% improve; however, in 10%, symptoms persist throughout pregnancy and occasionally into the postpartum period.

The cause of HG is not fully understood, but HG has been associated with hyperthyroid disorders; elevated levels of human chorionic gonadotropin and estrogen; previous molar pregnancy; psychiatric illness; pre-existing conditions, such as diabetes mellitus and asthma; singleton female pregnancies; and pregnancies with multiple male fetuses.[18] In a meta-analysis, HG was associated with a higher female to male ratio of offspring and a higher frequency of low birth weight, small for gestational age, and premature delivery.[19] In a recent report, higher growth or differentiation factor-15 (a hormone acting on the brainstem that is produced by the fetus) levels in maternal blood were found to be associated with vomiting in pregnancy and HG.[20]

The evaluation of HG involves comprehensive history taking, including any previous pregnancies (patients with HG have a higher risk in subsequent pregnancy) and any pre-existing conditions. Physical examination is focused on an evaluation of signs of dehydration (eg, orthostatic hypotension, decreased skin turgor, and dry mucus membranes) and

malnutrition (weight loss and muscle wasting). Neurologic evaluation for neuropathy or vitamin deficiency should be carried out. Laboratory evaluation is focused on the extent of dehydration, nutritional or vitamin deficiencies, and electrolyte imbalances. Elevated levels of liver enzymes can be seen in 40%–50% of patients with HG.[21] Ultrasonography of the abdomen can help detect multiple or molar pregnancies and adequate fetal growth, and also help to rule out hepatobiliary, vascular, or renal explanations for the symptoms, such as gallstones and portal vein thrombosis.

The goals of management of HG are prevention of dehydration; correction of electrolyte abnormalities; and support of adequate maternal and, thereby fetal, nutrition. Treatment is guided by the severity of symptoms and may require a multidisciplinary team approach involving obstetricians, nutritionists, psychologists, and gastroenterologists. Mental health care professionals can help manage anxiety, depression, and other emotional challenges associated with HG. Supplementation with vitamin B6 (pyridoxine) may be suggested as a first-line treatment for mild cases. Vitamin B1 (thiamine) is given to prevent refeeding syndrome and Wernicke encephalopathy; thiamine therapy should be started at a dosage of 100 mg daily for a minimum of 7 days, followed by a maintenance dosage of 50 mg daily until adequate oral intake is established.

ACOG recommends a step-up approach for patients who do not respond to first-line therapy. Metoclopramide can be given for NVP and HG. In a randomized study comparing promethazine and metoclopramide, both drugs had similar efficacy in patients who were hospitalized for HG; however, drowsiness, dizziness, dystonia, and discontinuation of therapy owing to adverse events were less frequent with metoclopramide.[22] No increased risk of congenital defects has been reported with metoclopramide.[23] Ondansetron is given primarily in severe NVP that requires hospitalization, and has not been associated with an increased risk of stillbirth, spontaneous abortion, or major birth defects; however, some studies have reported cases of congenital heart defects when ondansetron is given in the first trimester, and thus it should only be administered as a second-line therapy.[24] ACOG recommends using ondansetron on a case-by-case basis in patients with persistent symptoms before 10 weeks of pregnancy.[14] In a Cochrane review and meta-analysis of 25 studies, no significant difference was seen in efficacy among the medications administered commonly for HG (ie, metoclopramide, ondansetron, and promethazine).[25] Recently published European Association for the Study of the Liver Clinical Practice Guidelines on the management of liver diseases in pregnancy recommended doxylamine and pyridoxine and phenothiazines as first-line pharmacologic treatment of HG and metoclopramide and ondansetron as second-line therapies. They also noted that drug-induced extrapyramidal adverse effects may be seen with phenothiazines and metoclopramide and recommended that the drug be withdrawn in patients reporting such symptoms.[21]

Methylprednisolone can be given as a last resort in patients with severe HG and reduces the rate of rehospitalization. It is given in a dosage of 16 mg intravenous (IV) every 8 hours for up to 3 days, followed by tapering over 2 weeks to the lowest effective dosage and limiting the maximum duration to 6 weeks.[14] Its administration in the first trimester has been reported to slightly increase the risk of cleft palate when given before 10 weeks of gestation; however, the data have been conflicting and, therefore, it should be administered with caution in the first trimester. Patients with severe symptoms may need hospitalization for IV hydration and replacement of electrolytes, vitamins, and nutrients. If weight loss and symptoms persist, enteral or parenteral nutrition may be required.

Constipation

Best Practice Advice 5: Constipation in pregnant persons may result from hormonal, medication-related, and physiological changes. Treatment options include dietary fiber, lactulose, and polyethylene glycol–based laxatives.

Constipation may be experienced by 20%–40% of pregnant persons.[26,27] It usually improves in the postpartum period.[28] Hemorrhoids occur in approximately 80% of pregnant persons, more commonly during the third trimester due to compression of the rectum by the gravid uterus. Constipation during pregnancy can be attributed to physiological, medication, anatomic, dietary, metabolic, and hormonal changes.[29] The increased levels of progesterone can slow GI motility. Evaluation involves detailed history taking regarding the frequency and consistency of bowel movements, presence of pain or bleeding during bowel movements, and severity of symptoms. Hemorrhoids can present with itching, pain, or bleeding.

Dietary fiber intake during pregnancy in the United States is low[30] and, therefore, increasing dietary fiber intake (eg, fruits, vegetables, whole grains, and legumes) to the recommended daily amount of approximately 30 g/d can help promote regular bowel movements and prevent constipation. Consumption of an adequate amount of fluids, particularly water, can help soften stools and ease bowel movements. Bulk-forming agents, such as psyllium husk or methylcellulose, are safe to administer in pregnancy because of the lack of systemic absorption. Soluble fiber, like psyllium husk, improves stool viscosity and transit time in addition to increasing bulk compared with insoluble fiber, which is exclusively bulk-forming. Osmotic laxatives, such as polyethylene glycol or lactulose, can also be administered safely during pregnancy.[31] Excessive fiber and osmotic laxatives like lactulose can cause maternal bloating. Stimulant laxatives should be avoided because safety data on these medications are conflicting. In a prospective study of 204 patients treated with hydrocortisone foam for hemorrhoids in the third trimester, no adverse events were seen compared with placebo.[32] Encouraging pregnant women to avoid straining during bowel movements by providing ample time, using relaxation techniques, and adjusting diet and hydration is helpful.

Endoscopy

Best Practice Advice 6: Elective endoscopic procedures should be deferred until the postpartum

period, whereas nonemergent but necessary procedures should ideally be performed in the second trimester. Pregnant patients with cirrhosis should undergo evaluation for, and treatment of, esophageal varices; upper endoscopy is suggested in the second trimester (if not performed within 1 year before conception) to guide consideration of nonselective β-blocker therapy or endoscopic variceal ligation.

GI endoscopy is considered to be safe; however, when performed during pregnancy, endoscopy necessitates additional considerations. Routine screening or surveillance colonoscopy should be deferred until after delivery, but in cases with a strong suspicion of a colonic mass or severe diarrhea, sigmoidoscopy or colonoscopy may be considered. Because esophageal varices can worsen during pregnancy, pregnant patients with cirrhosis or noncirrhotic portal hypertension should undergo evaluation for, and treatment of, esophageal varices. Upper endoscopy is suggested in the second trimester (if not performed within 1 year before conception) to guide consideration of nonselective β-blocker therapy or endoscopic variceal ligation.

Endoscopy is contraindicated in cases of placental abruption, imminent birth, ruptured membranes, or hypertensive disease of pregnancy.[33] The use of sedation or anesthesia during endoscopy raises risks of adverse effects on the fetus. Placental blood flow is linked directly to maternal blood pressure and oxygenation, and oversedation causing maternal hypotension and/or hypoxia can lead to decreased placental blood flow and fetal hypoxia, leading to fetal distress and possible demise. Propofol, fentanyl, and midazolam have not been associated with congenital malformations. An ACOG guidance has stated that there is no anesthetic agent used currently that has been found to have any teratogenic effect when given in standard concentrations at any gestational age.[34] When moderate sedation is required, the American Society for Gastrointestinal Endoscopy recommends meperidine as the preferred agent, followed by small doses of midazolam as needed, but attempts should be made to limit the use of midazolam during the first trimester. When deep sedation is needed, administration by an experienced anesthesiologist is advised.[33] ACOG also advises fetal heart rate monitoring, depending on gestational age, facility type, and nature of the surgery, as monitoring may assist in maternal positioning and cardiopulmonary management.

Most sedatives are short-acting and safe for use during lactation. Once a postpartum patient has recovered from sedation and is alert and awake, breastfeeding can be resumed without the need to pump and discard.[35]

Nonurgent but nonelective endoscopic procedures can generally be postponed until after the first trimester. Elective procedures should be delayed until after delivery to limit maternal and fetal risks. If the condition poses a significant risk to the mother, or if emergent endoscopic intervention is required, endoscopy can be performed at any gestational age. Patients should be kept in the left pelvic tilt or left lateral position to facilitate uterine displacement to the left side and minimize aortocaval compression, decrease the risk of hypotension, and maintain cardiac return.[36] A gravid uterus can lead to compression of the aorta or inferior vena cava and decrease venous return, causing placental hypoperfusion and fetal hypoxia ("supine hypotension syndrome").[36] After 20 weeks of gestation, patients should not lie supine during an endoscopic procedure.[33] When cautery is used during an endoscopic procedure, the grounding pad should be placed on the leg or on the right shoulder or arm to prevent the conduction of electrical current through the amniotic fluid. Bipolar cautery is preferable to prevent currents from reaching the fetus.

Inflammatory Bowel Disease

Best Practice Advice 7: In patients with inflammatory bowel disease, clinical remission before conception, during pregnancy, and in the postpartum period is essential for improving outcomes of pregnancy. Biologic agents should be continued throughout pregnancy and the postpartum period; use of methotrexate, thalidomide, and ozanimod must be stopped at least 6 months before conception.

Inflammatory bowel disease (IBD) usually affects young persons of reproductive age; approximately 50% of patients are diagnosed before aged 30 years. Pregnancy can impact the clinical course of IBD, and management of IBD during pregnancy requires multidisciplinary care and close collaboration among the gastroenterologist, obstetrician, and patient. The importance and benefit of achieving adequate disease control before and during pregnancy and the potential risks of medications should be discussed. The AGA IBD Parenthood Project Working Group has recommended consultation with an MFM specialist, if available, for every pregnant patient with IBD.[6]

Persons with IBD have an increased risk of preterm birth, low birth weight, fetal growth retardation, hypertensive disease of pregnancy, and cesarean birth in the setting of active disease.[37,38] Conception in the setting of disease remission has similar outcomes and relapse rates as those for nonpregnant persons with IBD. Fertility rates of patients with ulcerative colitis without prior intestinal surgery are similar to those in persons who do not have IBD.[39] In patients who have undergone total colectomy with a J-pouch ileoanal anastomosis, fertility can be affected by pelvic adhesions, which cause fallopian tube obstruction. Therefore, persons waiting to complete their families are advised to either avoid pelvic dissection or undergo subtotal colectomy with a Hartmann pouch and end-ileostomy or ileorectal anastomosis.

The Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes registry reported a higher rate of exacerbation during pregnancy in patients with ulcerative colitis than in those with Crohn's disease.[40] During pregnancy, symptoms of IBD can overlap with those seen routinely in pregnancy, and the evaluation of IBD during pregnancy involves a multidisciplinary approach. The evaluation may include endoscopic procedures, such as unsedated flexible sigmoidoscopy (which is preferred to colonoscopy), to assess disease activity and extent in patients with ulcerative colitis. These procedures should be considered if they are critical to medical decision making.

Screening for active disease in all pregnant women with IBD can be performed by checking fecal calprotectin level at preconception, during each trimester, and after delivery.[41] A fecal calprotectin cutoff level of 200 μg/mg has a positive predictive value of 67%–74% for disease activity.[42] Ultrasonography or magnetic resonance imaging without gadolinium (gadolinium should be avoided during pregnancy) may be needed to rule out other causes of the patient's symptoms. Intestinal ultrasound is a new, safe, and noninvasive modality that can be used to assess disease extent and activity and evaluate treatment response in pregnant patients with IBD. It has been reported to distinguish active from quiescent disease with 84% sensitivity and 98% specificity. It is feasible throughout pregnancy; however, visualization of the terminal ileum and sigmoid colon decreases in the third trimester.[43]

The approach to managing an IBD flare during pregnancy is similar to that for nonpregnant persons. Individualized medication plans should be developed, considering the risks and benefits of various treatment options. Conception during remission and maintaining remission through pregnancy and postpartum period are essential. The use of mesalamine is considered safe during pregnancy. Sulfasalazine use should be supplemented with 1 mg folic acid taken 2 times daily 3 months before conception and during pregnancy to avoid fetal neural tube defects. Results of a meta-analysis evaluating mesalamine, sulfasalazine, balsalazide, and olsalazine during pregnancy showed that the medications were not associated with an increased risk of congenital malformations, premature births, stillbirths, spontaneous abortions, or low birth weight.[44]

More recent studies have reported that 6-mercaptopurine and azathioprine are safe for use in pregnancy, and no major congenital anomalies have been reported with their use; however, 60% of newborns can have anemia.[40,45] Methotrexate is contraindicated for use in pregnancy and, given its long half-life, its use should be discontinued at least 6 months before conception.[46]

Biologic agents, such as anti-tumor necrosis factor (anti-TNF) agents, during pregnancy can be continued to maintain remission. Infliximab and adalimumab cross the placenta after 20 weeks of gestation and thus do not interfere with organogenesis. Certolizumab does not cross the placenta. If patients have received anti-TNF medications (eg, infliximab and adalimumab) after 20 weeks of gestation, then the newborn should not receive any live vaccines for the first 6 months due to immunosuppression from the medications that may have crossed the placenta. Anti-TNF medications do not increase the risk of pregnancy complications and have been found to lead to fewer neonatal complications, thereby supporting the need for maintaining remission of disease during pregnancy. Data on the safety of vedolizumab are limited. Various studies and the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes registry have not reported an increased risk of congenital anomalies, delayed infant growth, developmental problems, or miscarriage with anti-TNF medication use.[40,46,47] The dose of a biologic agent, especially infliximab, does not change with pregnancy and is continued based on prepregnancy weight to maintain the patient in remission. Results of a recent meta-analysis showed that the frequency of adverse outcomes among pregnant patients with IBD on biologics was comparable with that in the general population.[48] Metronidazole can be given in cases of pouchitis, perianal Crohn's disease, or intra-abdominal abscesses resulting from fistulizing Crohn's disease. Amoxicillin-clavulanic acid is safe and can also be administered during pregnancy. Glucocorticoids are given frequently for IBD flares and, in contrast to prior reports, newer studies and the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes registry have reported that glucocorticoids do not pose a teratogenic risk of orofacial cleft in the fetus.[40,49] Nevertheless, glucocorticoids have been reported to increase the risk of preterm birth, small for gestational age, low birth weight, intrauterine growth restriction, and neonatal intensive care unit admission, and should be given with caution in the first trimester.[50] Thalidomide and ozanimod should be avoided during pregnancy due to potential adverse effects.

Pregnant persons with IBD may require additional nutritional support, particularly if intestinal malabsorption or nutrient deficiencies are present. Consultation with a registered dietitian specializing in IBD can help ensure adequate nutrient intake. Most IBD medications are safe for use during breastfeeding.

The mode of delivery of the fetus should be planned. Vaginal birth should be avoided in patients with active perianal Crohn's disease, perianal abscess, or active rectal disease. Patients with prior complex fistulizing disease and a J-pouch should also be considered for cesarean birth to minimize the risk of instrumentation of the perineal region, avoid injury to the anal sphincter, and preserve continence.[42,51]

Endoscopic Retrograde Cholangiopancreatography

Best Practice Advice 8: Endoscopic retrograde cholangiopancreatography during pregnancy may be performed for urgent indications, such as choledocholithiasis, cholangitis, and some cases of gallstone pancreatitis. Ideally, endoscopic retrograde cholangiopancreatography should be performed during the second trimester, but if deferring the procedure may be detrimental to the health of the patient and fetus, a multidisciplinary team should be convened to decide on the advisability of endoscopic retrograde cholangiopancreatography.

Gallstone disease (GD) affects a substantial proportion of women during pregnancy. Ultrasonography is the imaging modality of choice for gallstones. Although computed tomography can be performed when medically indicated, computed tomography does involve radiation and is not typically needed for gallstone evaluation. In cases of suspected choledocholithiasis, magnetic resonance cholangiopancreatography, which does not require contrast, can be performed. Endoscopic ultrasound can also be done in cases of suspected choledocholithiasis if the patient cannot undergo magnetic resonance cholangiopancreatography to confirm the absence of a bile duct stone and can obviate the need for ERCP. Optimal management of bile duct obstruction by gallstones requires a multidisciplinary team that

includes an advanced endoscopist experienced in ERCP, MFM physician, neonatologist, obstetrician, and anesthesiologist. Initial management may include IV hydration, symptom control, antibiotics, and nutritional support.

When indicated, ERCP can be performed during pregnancy to manage choledocholithiasis, cholangitis, and acute biliary pancreatitis with a retained bile duct stone. Minimizing fetal radiation and pre- and postprocedure fetal monitoring is required. A Nationwide Readmission Database reported that pregnant patients with acute biliary pancreatitis were less likely to undergo laparoscopic cholecystectomy or ERCP compared with nonpregnant age-matched cohorts, and ERCP, when performed, reduced the odds of early readmission by 60%.[52] In a study of 68 ERCPs in pregnant women, technical outcomes were uniformly favorable; however, patients undergoing ERCP in the first trimester had relatively poor fetal outcomes, including a low rate of term pregnancies (73.3%), high rate of low-weight newborns (21.4%), and high risk of preterm delivery (20%).[53] Therefore, the American Society for Gastrointestinal Endoscopy guidelines recommend deferral of endoscopy to the second trimester, whenever possible.[33]

Pregnancy has been reported to be an independent risk factor for post-ERCP pancreatitis. A 2016 national cohort study comparing pregnant women with a large control group of nonpregnant women undergoing ERCP found that, although there was no significant difference in the frequencies of ERCP-related complications (perforation, infection, or hemorrhage), the rate of post-ERCP pancreatitis was greater in pregnant women (12% vs 5%; $P < .001$).[54] Also the risk of post-ERCP pancreatitis was higher in nonteaching vs teaching hospitals (14.6% vs 9.6%; $P < .001$), therefore, if possible, these patients should be transferred to a tertiary care setting for treatment management by an experienced endoscopist and for multidisciplinary care.

Another major concern with ERCP in a pregnant person is minimizing fetal radiation exposure. Total fetal radiation exposure can be influenced by gestational age, body size, and fetal exposure and results mainly from radiation scatter within the pregnant patient's body. Fetal and gonadal shielding is no longer recommended by the American Association of Physicists in Medicine because the benefits of shielding are minimal and it may compromise the study if the shield enters the examination field.[55] The fetal teratogenic threshold dose is considered to be 50 mGy, and detrimental outcomes are usually seen with a dose >100 mGy.[33] Various measures should be taken to minimize radiation exposure to mother and fetus (Table 2).[56] During ERCP, the patient can be placed in the supine or prone position in the first trimester; however, in the second and third trimesters, the patient should be kept in the left pelvic tilt or left lateral position to avoid compression of the aorta or inferior vena cava. Thromboprophylaxis and antibiotic prophylaxis should be administered, when indicated.

Table 2. Measures to Minimize Fetal Radiation During Endoscopic Retrograde Cholangiopancreatography

Measure
1. A multidisciplinary team with obstetrician, perinatologist or MFM, radiation safety officer, obstetrical anesthesiologist, and endoscopist with experience performing ERCP and use of radiation in pregnant persons
2. Use of a modern fluoroscopy unit with collimation ability and pulsed fluoroscopy
3. Use of last image hold feature and short taps of fluoroscopy
4. Avoidance of spot films and use of magnification
5. Use of image intensifier as close to the patient as possible with the patient kept away from the radiation source
6. Use of low radiation dose protocols and low frame rates
7. Use of the bile aspiration technique, cholangioscopy, or endoscopic ultrasound to reduce radiation during cannulation and clearance during ERCP
8. If large stones are present in the in bile duct, consideration of placing a stent and planning lithotripsy and stone clearance after delivery
9. Avoidance of pelvic and gonadal shielding because radiation from newer fluoroscopy machines may penetrate lead and thereby inadvertently increase radiation exposure

Gallstone Disease

Best Practice Advice 9: Cholecystectomy is safe during pregnancy; a laparoscopic approach is the standard of care regardless of trimester, but ideally in the second trimester.

GD is the second leading cause (after acute appendicitis) of nonobstetric acute abdominal pain during pregnancy and can cause significant morbidity and mortality.[57–59] The timing of surgical intervention should be evaluated carefully. Elective surgery is usually avoided in the first and third trimesters and is ideally performed in the second trimester to reduce the risk of spontaneous abortion and preterm labor, respectively. The traditional approach to management of GD in pregnancy has been conservative, with supportive care consisting of IV hydration; symptom control; and avoidance of dietary triggers, such as high-fat meals; however, studies have reported that recurrent biliary symptoms develop in 60% of pregnant patients with GD treated conservatively, leading to a high number of emergency department visits and hospitalizations.[60] Patients treated conservatively are more likely to undergo cesarean birth. To minimize the risk of complications, laparoscopic cholecystectomy is considered superior to conservative management in the first or second trimester for patients with symptomatic cholelithiasis.[61] Same-admission cholecystectomy in pregnant patients with acute biliary pancreatitis has been found to reduce the odds of early readmission by 85%.[52] For biliary pain presenting late in the third trimester, postponing surgical intervention until delivery may be reasonable, if postponement does not pose a risk to maternal or fetal health.

In patients with acute cholecystitis, initial management includes IV hydration, symptom control with analgesia and antiemetics, and antibiotics. The standard approach is laparoscopic cholecystectomy. In a study of 1245 pregnant women with biliary pancreatitis, a significantly higher 30-day readmission rate was seen in patients who did not undergo index cholecystectomy (33.7% vs 5.3%; $P < .01$);

there was no significant difference in the risk of premature delivery and abortion in the cholecystectomy group, and patients who underwent cholecystectomy during the index hospitalization had a significantly lower mean number of cumulative hospitalizations.[62] If a patient is hemodynamically unstable, not responding to medical management, or at high risk for surgery, percutaneous cholecystostomy tube placement or percutaneous gallbladder aspiration can be used as "bridging" therapy in the first (to the second) trimester or in the third trimester to the postpartum period, when cholecystectomy can be performed.[63,64] Despite the longstanding belief that laparoscopic cholecystectomy is safest during the second trimester with regard to fetal loss and risk of anesthesia, increasing evidence has supported the safety of laparoscopic cholecystectomy in the first and third trimesters, and the Society of American Gastrointestinal and Endoscopic Surgeons guidelines stated that laparoscopy can be performed safely during any trimester of pregnancy.[65] The Society of American Gastrointestinal and Endoscopic Surgeons guidelines recommended that after the first trimester of pregnancy, patients should be placed in the left lateral or partial left lateral decubitus position for laparoscopy to minimize compression of the inferior vena cava.

Liver Diseases in Pregnancy

Liver diseases in pregnancy represent not only preexisting liver conditions, but also those acquired and those that are unique to pregnancy. In this Clinical Practice Update, we will briefly review liver disease in pregnancy. For detailed information on the management of these diseases, various society guidelines are available and should be reviewed.[21,66]

Intrahepatic Cholestasis of Pregnancy

Best Practice Advice 10: The diagnosis of intrahepatic cholestasis of pregnancy is based on a serum bile acid level >10 μmol/L in the setting of pruritus, typically during the second or third trimester. Treatment should be offered with oral ursodeoxycholic acid in a total daily dose of 10–15 mg/kg.

Mild elevations in alkaline phosphatase levels are common in pregnancy during the second and third trimester.[66–68] Intrahepatic cholestasis of pregnancy is diagnosed on the basis of clinical presentation of pruritus in the second and third trimester with a total serum bile acid level >10 μmol/L. Most cases present in the third trimester with mild to moderately elevated serum aspartate aminotransferase and alanine aminotransferase levels (up to 10–20 times the upper limit of normal), and a serum total bilirubin level <6 mg/dL. If serum bile acid levels are normal, testing should be repeated after other causes of pruritus are excluded, including biliary obstruction, viral hepatitis, and chronic liver disease. Serum bile acid levels correlate with the risk of intrauterine fetal demise, with the highest risk in patients with levels ≥100 μmol/L.[69] Treatment should begin with ursodeoxycholic acid in a daily divided dosage to total of 10–15 mg/kg/d. Ursodeoxycholic acid has been reported to improve pruritus, serum bile acid levels, and serum alanine aminotransferase levels, and in a recent meta-analysis were found to decrease adverse outcomes, including preterm birth and stillbirth.[70,71] Additional treatment of pruritus can be attempted with cholestyramine and rifampicin. Delivery is advised to be based on serum total bile acid levels. When ≥100 μmol/L, the Society for Maternal-Fetal Medicine recommends delivery at 36 weeks or at diagnosis if after 36 weeks. If levels are <100 μmol/L, delivery is recommended at 36 or 39 weeks of gestation if diagnosed later. As per the European Association for the Study of the Liver guidelines, consider early delivery in patients with bile acids >100 μmol/L, as the risk of stillbirth increases in this group after 35 weeks.[21] Management should be individualized, and delivery at term should be considered for those with total bile acid levels <40 μmol/L.[72,73] Pruritus typically resolves after delivery, but if it persists after 6 weeks, further evaluation for underlying chronic liver disease should be pursued.

Other Liver Diseases Unique to Pregnancy

Best Practice Advice 11: Management of liver diseases unique to pregnancy, such as pre-eclampsia; hemolysis, elevated liver enzymes, and low platelets syndrome; and acute fatty liver of pregnancy requires planning for delivery and timely evaluation for possible liver transplantation. Daily aspirin prophylaxis for patients at risk for pre-eclampsia or hemolysis, elevated liver enzymes, and low platelets syndrome is advised beginning at week 12 of gestation.

For liver diseases unique to pregnancy, specifically preeclampsia; hemolysis, elevated liver enzymes, and low platelets syndrome; acute fatty liver of pregnancy (AFLP); and intrahepatic cholestasis of pregnancy, management converges on appropriate and expeditious childbirth. Distinguishing among these conditions can be difficult, and the clinician can focus on supportive care and management of concomitant comorbidities, such as hypertension; coagulopathy; seizures; and other symptoms, while preparing the patient for childbirth. Liver biopsy to make a specific diagnosis is rarely needed and should not be obtained unless it will affect management. Liver transplantation evaluation should be considered in patients who progress to acute liver failure, especially those with suspected AFLP who have already given birth but do not improve clinically.[66–68,74]

Systematic studies and meta-analyses have reported the benefit of low-dose aspirin on lowering the risks of fetal growth restriction and fetal demise in patients with preeclampsia.[75,76] Aspirin in a dosage of 81 mg/d beginning at weeks 12–16 of gestation and continuing until delivery should be considered in patients with risk factors for preeclampsia (ie, prior pre-eclampsia, multiple gestation, diabetes mellitus, hypertension, chronic kidney disease, or autoimmune disease).[77] The diagnosis of AFLP is suggested by the Swansea criteria[78,79]; however, the Swansea criteria have limitations in differentiating AFLP from other causes of liver diseases unique to pregnancy and acute liver failure of any cause. Additional detailed information is available in

recent European Association for the Study of the Liver guidelines.[21] Table 3 compares various features of intrahepatic cholestasis of pregnancy; hemolysis, elevated liver enzymes, and low platelets syndrome; and AFLP.[80,81]

Chronic Viral Hepatitis

Best Practice Advice 12: In patients with chronic hepatitis B virus infection, serum hepatitis B virus DNA and liver biochemical test levels should be ordered. Patients not on treatment but with a serum hepatitis B virus DNA level >200,000 IU/mL during the third trimester of pregnancy should be considered for treatment with tenofovir disoproxil fumarate.

Pregnant persons with chronic hepatitis B virus (HBV) infection should be assessed for antiviral treatment independent of pregnancy per standard practice guidelines.[82] The risk of mother-to-child transmission of HBV can be reduced by administration of hepatitis B immunoglobulin and initiation of HBV vaccination to the newborn at birth. Further reduction in the risk of mother-to-child transmission can be achieved by identifying pregnant persons with a serum HBV DNA level >200,000 IU/mL and initiating treatment with tenofovir beginning in the third trimester. Treatment can be continued until childbirth or up to 12 weeks postpartum. Tenofovir remains the preferred treatment choice based on its efficacy and safety during pregnancy, although there are growing data to support the use of tenofovoir alafenamide as an alternative. Breastfeeding is not contraindicated in persons with HBV infection, whether or not they are on antiviral therapy.[83] Patients with chronic HBV infection are at risk of HBV flares postpartum and should continue ongoing monitoring after pregnancy.[84,85] Pregnant persons are advised by the Centers for Disease Control and Prevention to be screened for hepatitis C virus infection at each pregnancy.[86] The full results of ongoing trials for treatment of hepatitis C virus during pregnancy are awaited to guide management of hepatitis C virus in this setting. The Infectious Diseases Society of America and the American Association for the Study of Liver Diseases have recommended that direct-acting antiviral treatment may be considered during pregnancy on a case-by-case basis after a discussion of potential risks and benefits.[87]

Table 3. Features of Intrahepatic Cholestasis of Pregnancy; Hemolysis, Elevated Liver Enzymes, and Low Platelets Syndrome; and Acute Fatty Liver of Pregnancy

Feature	ICP	HELLP	AFLP
Frequency in pregnancies, %	0.3–0.5	0.2–0.6	0.01
Onset	Second and third trimester	Third trimester/postpartum	Third trimester/postpartum
Family history	Often	No	Occasionally
Pregnancy characteristics	Multiparity, multifetal pregnancy	Multiparity, aged >35 y	Multifetal pregnancy, male fetus
Symptoms/clinical features	Pruritus, jaundice	Abdominal pain, vomiting, proteinuria, headache, peripheral edema	Abdominal pain, vomiting, polydipsia/polyuria/hepatic encephalopathy, liver failure, DIC
Pre-eclampsia	No	Yes	Seen in approximately 50%
Imaging	Normal	Infarcts, hematoma, rupture, no ascites	Fatty infiltration, sometimes ascites
Laboratory evaluation	Bilirubin <5 mg/dL, elevated ALP and GGT, increased bile acids	Bilirubin <5 mg/dL, hemolysis, low platelets (<100 × 10^9/L), elevated uric acid, ±proteinuria, ALT <500 U/L, elevated LDH	Bilirubin <5 mg/dL, hypoglycemia, elevated creatinine, ±proteinuria and thrombocytopenia, elevated ammonia, ALT<500 U/L, prolonged PT, DIC >75%
Morbidity/mortality	Maternal: predisposed to recurrence in subsequent pregnancy (45%–70%) Fetal stillbirth, fetal mortality 0.4%–1.%	Maternal: seizures, acute renal failure, hepatic rupture, mortality 1%–25% Fetal mortality 11%	Maternal: acute renal failure, mortality 7%–18% Fetal increased mortality 9%–23%

ALP, alkaline phosphatase; ALT, alanine aminotransferase; DIC, disseminated intravascular coagulation; GGT, γ-glutamyl transpeptidase; HELLP, hemolysis, elevated liver enzymes, and low platelets syndrome; ICP, intrahepatic cholestasis of pregnancy; LDH, lactate dehydrogenase; PT, prothrombin time.

Immunosuppressive Therapy

Best Practice Advice 13: In patients on immunosuppressive therapy for chronic liver diseases or after liver transplantation, therapy should be continued at the lowest effective dose during pregnancy. Mycophenolate mofetil should not be administered during pregnancy.

Persons on immunosuppressive therapy for chronic liver disease or prior liver transplantation should undergo counseling for pregnancy planning. Pregnancy is not uncommon in this population, but long-term outcomes data are limited.[88,89] Persons with chronic liver disease, such as autoimmune hepatitis, who require immunosuppressive therapy and who become pregnant face the risks of an autoimmune hepatitis flare (up to 30%); gestational diabetes mellitus; and adverse fetal outcomes, including higher rates of premature birth; small for gestational age; and low birth weight. Treatment with immunosuppressive therapy should be continued at the lowest effective dose to reduce the risk of adverse maternal and fetal outcomes.[66–68,90] Similarly, immunosuppressive therapy should be continued at the lowest effective dose during pregnancy in persons who have previously undergone liver transplantation. In the postpartum period, patients should be monitored closely for disease flare or graft rejection. Mycophenolate mofetil is contraindicated in pregnancy because of a risk of birth defects and its use should be discontinued at least 6–12 weeks before conception planning begins.

Conclusions

The evaluation and treatment of various GI disorders in pregnancy can be challenging and require a multidisciplinary team to manage these patients during pregnancy and the postpartum period. We have summarized approaches to various GI conditions that occur during pregnancy and that need a collaborative strategy to guide the practicing physician. These conditions include disease states unique to pregnancy and common GI conditions that may be present during pregnancy. A paramount goal is to keep both the patient and the fetus safe.

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All authors wrote the paper and critically reviewed the manuscript.

Conflicts of interest
The authors disclose the following: Shivangi Kothari served as a consultant for Boston Scientific and Olympus Medical and is the co-editor of the American College of Gastroenterology pregnancy monograph. Yalda Afshar served as a consultant for Mirvie and Bio-Rad and has conducted investigator-initiated research with Natera. Lawrence Friedman receives financial support from Newton-Wellesley Hospital and receives royalties from Elsevier, McGraw-Hill, and Wiley. Joseph Ahn has served as a consultant for Gilead Sciences.