23 Gastrointestinal diseases and pregnancy

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INTRODUCTION

Pregnancy has a significant effect on the normal physiology of the gastrointestinal tract, and gut-related symptoms are extremely common during gestation. In this chapter, a review is presented of the common gastrointestinal disorders in pregnancy, which may present difficult management problems. The treatment of these disorders in the nonpregnant as well as the pregnant patient is discussed, so that the reader will become familiar with the special diagnostic and therapeutic considerations during pregnancy.

GASTROESOPHAGEAL REFLUX DISEASE AND REFLUX ESOPHAGITIS

Gastroesophageal reflux disease (GERD) results from the inappropriate backwash of gastric contents into the esophagus. Although this process occurs frequently in asymptomatic individuals, it can also result in heartburn and regurgitation. Reflux esophagitis is defined as the presence of typical symptoms of GERD in conjunction with endoscopic and pathologic changes in the esophagus.

Epidemiology

The prevalence of symptoms of GERD is quite high in the general population. Large-scale surveys have revealed that approximately 33% to 44% of adult Americans experience reflux symptoms on a twice weekly to monthly basis (1). However, the great majority of this group does not seek medical attention. Of those individuals who go to a doctor, 40% to 70% will show endoscopic evidence of esophagitis. Gastroesophageal reflux symptoms are extremely common during pregnancy and are an important cause of morbidity in pregnancy. Reflux symptoms are reported by 40% to 85% women during pregnancy (2,3). The incidence of true reflux esophagitis is difficult to determine, because large-scale endoscopic studies of pregnant women have not been performed.

Defense Mechanisms for Prevention of Gastroesophageal Reflux

There are several defense mechanisms that act to limit contact with and damage to the esophagus by gastric contents (Table 1).

1. *Lower esophageal sphincter (LES)*: The LES is probably the major protective barrier, preventing reflux of food, acid, and secretions from the stomach into the esophagus. The LES relaxes in response to hormones, foods, and drugs. Some patients with reflux esophagitis have decreased resting LES pressures or a completely incompetent

LES; reflux events also occur in patients with normal LES pressures, presumably owing to transient LES relaxation (4,5).

2. *Esophageal motility and gravity*: Contact of the esophageal mucosa with damaging substances is limited by esophageal peristalsis and gravity, which promote clearing. Aperistalsis, as found in scleroderma, contributes substantially to the development of esophagitis in these patients (in addition to an incompetent LES).
3. *Saliva*: Saliva has also been shown to neutralize acid.
4. *Intrinsic epithelial defense*: The esophageal epithelial layer has intrinsic defense systems including cell membrane and intercellular components, which prevent influx of hydrogen ions as well as intracellular proteins, which function as buffers.

Pathophysiology

The pathophysiology of GERD and reflux esophagitis in pregnant patients is incompletely understood. It may be multifactorial, involving both mechanical and hormonal factors.

1. *LES*: Some analyses have shown that resting LES pressure decreases in pregnancy, in both early and late gestations (6,7). In other studies, LES pressure was normal in early pregnancy but hypofunction of the LES was detected, as measured by decreased responsiveness to drugs that increase sphincter pressure (8). Decreased LES pressure probably results from elevated serum estrogen and especially progesterone levels during pregnancy (6).
2. *Intra-abdominal pressure*: Although increased intra-abdominal pressure has been postulated to produce reflux, a study of men with tense ascites as a model of pregnancy (9) showed an increase in LES pressure and no demonstrable acid reflux. Thus, the contribution of increased abdominal girth in reflux esophagitis is unclear, but the relevance of this model may be questioned. Intragastric pressures appear to be increased even in early pregnancy, and patients with heartburn have lower mean barrier pressures (LES pressure–gastric pressure) than asymptomatic pregnant individuals (10).
3. *Esophageal motility*: Normal esophageal motility, which helps clear potentially damaging material from the esophagus, is altered in pregnancy; peristaltic wave speed and amplitude are both reduced (11).

Table 1 Esophageal Mucosal Defense Mechanisms

Mechanism	Effect
Lower esophageal sphincter	Barrier
Esophageal motility	Promotes clearing
Gravity (when upright)	Promotes clearing
Saliva	Acid neutralization
Intrinsic epithelial defense	Cell membrane, inter- and intracellular components

Clinical Features

The clinical features of GERD during pregnancy do not differ from those in the general adult population. Classic symptoms of GERD include heartburn (retrosternal burning pain) and regurgitation. In patients with long-standing reflux esophagitis, strictures may result, producing dysphagia or difficulty swallowing. Severe reflux esophagitis may produce painful swallowing (odynophagia), although this is more likely to be associated with infectious causes of esophagitis. Acid reflux may lead to esophageal dysmotility and atypical noncardiac chest pain. Extra-esophageal symptoms may include hoarseness, chronic cough, laryngitis, asthma, and recurrent aspiration.

Complications

A variety of complications can result from reflux esophagitis:

1. Stricture formation
2. Bleeding
3. Pulmonary aspiration
4. Barrett’s esophagus—Chronic esophageal inflammation is thought to lead to Barrett’s esophagus, in which the normal squamous esophageal epithelium is replaced by specialized columnar epithelium. This diagnosis is made by endoscopy with biopsy; routine surveillance with periodic endoscopic examination and biopsies is indicated because of an increased risk of esophageal cancer.

Diagnosis

During pregnancy, initial diagnosis of GERD is based on symptoms, and an empiric trial of therapy may be initiated.

1. *Barium radiography:* Barium studies are less sensitive compared with upper endoscopy for diagnosis of reflux esophagitis. They should be avoided during pregnancy because of risk of radiation exposure to the fetus.
2. *Upper endoscopy:* Endoscopy allows direct visualization of the epithelium, and biopsies can be taken for histologic analysis. Endoscopy can be safely performed during pregnancy for evaluation of intractable symptoms refractory to a trial of standard medical therapy or complications such as gastrointestinal bleeding. Please refer to the section on “Endoscopy and procedural sedation in pregnancy” for further discussion.
3. *Esophageal manometry and pH monitoring:* These studies are rarely used in patients with atypical or refractory symptoms to detect reflux and correlate symptoms with reflux events.

Table 2 Medications Used in Pregnancy for Gastroesophageal Reflux Disease

Drug name	FDA category
<i>Antacids</i>	
Aluminum-, calcium-, or magnesium-containing antacids	None
<i>H2RAs</i>	
Cimetidine	B
Ranitidine (preferred)	B
Famotidine	B
Nizatidine	B
<i>Mucosal protectant</i>	
Sucralfate	B
<i>Proton pump inhibitors</i>	
Omeprazole	C
Lansoprazole (preferred)	B
Rabeprazole	B
Pantoprazole	B
Esomeprazole	B
<i>Promotility agents</i>	
Metoclopramide	B

Abbreviations: FDA, Food and Drug Administration; H2RAs, histamine-2 receptor antagonists.

Management with Maternal–Fetal Consideration

1. *Lifestyle modifications:* Initial management of GERD usually consists of conservative measures such as lifestyle modifications and dietary changes. Avoidance of smoking, late-night meals, and substances that decrease LES pressure such as high-fat foods, caffeine, alcohol, and chocolate often provide some relief. Patients should remain upright after meals to minimize reflux of acidic contents, allowing gravity to aid esophageal clearance. Elevation of the head of the bed by shock blocks helps maintain the beneficial effect of gravity at night.
2. *Medications:* Various medications are used for the management of GERD (Table 2).

Antacids: Antacids are generally considered safe in pregnancy (12) and are used by 30% to 50% of women for relief of reflux symptoms during pregnancy (13). Magnesium-, aluminum-, or calcium-containing antacids are not teratogenic in animal studies (13). There are limited data on the safety and efficacy of antacids during pregnancy. A large retrospective study showed an increased incidence of birth defects in women who used antacids along with many other medications in the first trimester (14); however, no particular antacid was specified, and these data have not been verified in another study. More recent analyses of pregnant women in both the United States and the Netherlands (15,16) indicate that antacid use is common; although no obvious increase in rare birth defects has been noted, small increases in common abnormalities such as spontaneous abortion, cleft palate, or low birth weight would be difficult to detect (15). The major immediate side effects of large doses of antacids include constipation induced by aluminum-containing antacids and diarrhea caused by magnesium-based preparations. The use of a combination of these medications usually resolves

bowel-related problems. Antacids containing sodium bicarbonate should be avoided because it can precipitate metabolic alkalosis and volume overload (17).

Sucralfate: Sucralfate is FDA pregnancy category B. It is a polysulfated salt of sucrose, which binds to exposed proteins found in the base of ulcerated mucosa and produces a protective coating of the ulcer site. In a randomized controlled study, sucralfate-treated pregnant patients (1g three times daily) had a higher frequency of remission of heartburn (90% vs. 43%) and regurgitation (83% vs. 27%) compared with lifestyle and dietary modifications (18). In animal studies, sucralfate was not teratogenic with doses up to 50 times those used in humans (19).

Histamine-2 receptor antagonists: All histamine-2 receptor antagonists (H2RAs) including cimetidine, ranitidine, famotidine, and nizatidine are classified as FDA pregnancy category B. H2RAs have been recently replaced by proton pump inhibitors for treatment of reflux esophagitis in nonpregnant patients; however, in pregnant patients with GERD, H2RAs are the most commonly used and safest medications for those not responding to lifestyle modifications and antacids. Generally, 8 or more weeks of therapy is required to produce complete healing, and recurrences are frequent when medication is discontinued. In a study, efficacy of ranitidine once or twice daily was compared with placebo in pregnant women (20). Only ranitidine 150mg twice daily demonstrated significant relief in symptoms and reduction in the use of antacids. No adverse pregnancy or fetal outcomes were noted. A surveillance study in the United States found no increase in the incidence of congenital anomalies among infants exposed to various H2RAs including ranitidine, cimetidine, and famotidine (21). Ranitidine is usually the preferred H2RA during pregnancy because of the absence of teratogenicity in animal studies and documented efficacy in pregnancy.

Proton pump inhibitors: Proton pump inhibitors (PPIs) including lansoprazole, rabeprazole, pantoprazole, and esomeprazole are classified as FDA pregnancy category B drugs. Omeprazole is the only PPI, which is classified as FDA pregnancy category C because of dose-related embryonic and fetal mortality observed in animal studies. PPIs act as inhibitors of parietal cell H^+/K^+ ATPase (the proton pump responsible for hydrogen ion secretion) and are the most effective inhibitors of gastric acid secretion. These are the drugs of choice in nonpregnant patients for treatment of severe erosive reflux esophagitis and can heal esophageal lesions that are refractory to treatment with H2RAs. However, PPIs have not been extensively used in pregnancy and limited safety data are available for their use during pregnancy. A recent meta-analysis showed no significant increase in the risk of congenital anomalies in pregnant women exposed to various PPIs (22). PPIs should be used only in pregnant women with refractory symptoms who are not responding to H2RAs. Lansoprazole may be the preferred PPI because of its lack of teratogenicity in animal studies and limited safety reports during pregnancy.

Conclusion

GERD and reflux esophagitis in pregnancy should be managed in a step-up approach starting with lifestyle modifications. Medical therapy should be initiated for those who do not

respond to lifestyle and dietary modifications. Antacids and sucralfate are considered as first-line medical agents for GERD and/or reflux esophagitis. H2RAs should be introduced if symptoms persist despite the use of antacids. PPIs should be reserved for pregnant patients with refractory symptoms or complications secondary to GERD. Antireflux surgery is avoided during pregnancy because the symptoms usually resolve after delivery.

PEPTIC ULCER DISEASE

An ulcer is an injury to or interruption of the mucosal lining of the gastrointestinal tract extending through the muscularis mucosa. Peptic ulcer disease (PUD) is an important cause of morbidity and mortality in the general population; however, severity of symptoms and frequency of complications associated with PUD decrease during pregnancy (23–25).

Epidemiology

The incidence of PUD is low in pregnant women (23–25). It is difficult to ascertain the true incidence of PUD in pregnancy because diagnostic testing is generally avoided. Symptoms of PUD may be attributed to GERD or nausea and vomiting of pregnancy with resolution of symptoms upon treatment, thereby precluding further testing (26). Patients may also avoid medical attention by self-treatment with nonprescription medications for mild to moderate gastrointestinal symptoms.

A number of hypotheses have been proposed for the low incidence of PUD in pregnancy. Plasma levels of histaminases are increased during pregnancy due to placental synthesis. The histaminases can metabolize maternal histamine leading to decreased gastric acid secretion during pregnancy (27). Increased estrogen levels can result in hypochlorhydria, and gestational progesterone may increase synthesis of the protective gastric mucous layer (28). Immunologic tolerance during pregnancy may permit growth and colonization of *Helicobacter pylori* without immunologic response and mucosal injury (29,30). Maternal avoidance of ulcerogenic factors, such as smoking, alcohol, and nonsteroidal anti-inflammatory drug (NSAID) use, and reduced psychologic stress may also play a role in the decreased incidence of PUD during pregnancy (31,32).

Etiology and Pathophysiology

The etiology of PUD is complex and multifactorial. The two most common causes of PUD are *H. pylori* infection and use of NSAIDs. *H. pylori* has been implicated in the pathogenesis of PUD. Patients who are colonized with *H. pylori* have histologic evidence of antral gastritis, and eradication of infection leads to resolution of gastritis. *H. pylori* survives in the harsh gastric environment by the production of urease, which neutralizes acid by the generation of ammonia. *H. pylori* also produces protease, which thins the mucous layer and allows penetration and damage of the initial layer of mucosal defense. Almost all patients with duodenal ulcers, and gastric ulcers unassociated with the use of NSAIDs, are infected with *H. pylori*. The healing of ulcers occurs when *H. pylori* is eradicated and, most importantly, relapse of ulcer disease is prevented (33).

Gastric mucosal defenses, including a thick mucous layer and the ability of the mucosa to secrete bicarbonate, can

resist damage by acid, pepsin, and biliary reflux. Impairment or disruption of these protective mechanisms occurs because of inhibition of cyclooxygenase, prostaglandin synthesis, and mucosal mucous and bicarbonate secretion, leading to superficial gastric mucosal injury or gastric ulcer, predominantly in the gastric antrum. NSAIDs, including aspirin, increase the risk of PUD by inhibiting cyclooxygenase and a direct toxic effect on the gastric mucosa. There are several factors that influence the risk of developing PUD in patients using NSAIDs. The risk is more in patients taking higher doses of NSAIDs for a prolonged duration. Other risk factors for PUD include cigarette smoking and alcohol consumption (34). Cigarette smoking has been shown to slow ulcer healing and is associated with a higher rate of ulcer recurrence (35) in smokers compared with nonsmokers.

Clinical Features

Typical symptoms of PUD include epigastric pain, which is relieved by food or antacids. Patients often describe a dull “gnawing” or burning sensation, which may awaken them at night or may occur in the morning before eating or after meals. Because the abdominal pain is often relieved by eating, patients with PUD may gain weight. Other symptoms arise when duodenal or gastric ulcer is complicated by hemorrhage, perforation, penetration, or obstruction (Table 3). If the ulcer bleeds, the patient may develop black or tarry stools (melena) or hematemesis. Ulcer penetration into an arterial blood vessel can lead to massive, brisk bleeding with rapid transit of blood through the gastrointestinal tract and bright red blood per rectum (hematochezia). Abdominal pain that radiates to the back indicates possible penetration of the ulcer posteriorly through the wall of the stomach or duodenal bulb into surrounding organs. Duodenal bulb ulcers may penetrate into the pancreas, whereas gastric ulcers can erode into the liver or colon. The sudden onset of severe pain in conjunction with physical findings of an acute abdomen (rebound tenderness, guarding, absent bowel sounds, and distention) is associated with free perforation of the ulcer, which is a surgical emergency. Finally, prolonged nausea and vomiting can result from gastric outlet obstruction caused by edema and inflammation surrounding an ulcer crater located in the prepyloric or pyloric region. It is important to note that complicated ulcer disease may present with no antecedent history of abdominal pain or other symptoms.

In pregnancy, the signs and symptoms of PUD and its complications may be obscured. First, symptoms that are consistent with PUD may also be associated with GERD, which is quite common in pregnancy. Nausea and vomiting indicating the presence of an obstructing ulcer may be mistakenly considered to be “normal” pregnancy-related symptoms. Because of the morbidity and mortality associated with complicated PUD during gestation, a high index of suspicion should be maintained for those patients who develop nausea, vomiting, and abdominal pain in the second and third trimesters. Finally, in the immediate postdelivery period, signs of perforation such as abdominal rebound or guarding may be absent or decreased due to muscular relaxation, leading to delayed or misdiagnosis.

Diagnosis

During pregnancy, barium radiography is contraindicated because of risk of radiation teratogenesis. Upper endoscopy (esophagogastroduodenoscopy, EGD) is preferred for the diagnosis of PUD in both pregnant and nonpregnant patients because of a higher sensitivity and specificity when compared with barium radiography (30). EGD also has the ability to obtain histologic specimens to test for *H. pylori* infection and to exclude malignant gastric ulcer. In pregnant patients, EGD should be reserved only for patients with symptoms refractory to intensive medical therapy or PUD-related complications such as hemorrhage or gastric outlet obstruction. Since duodenal ulcers are benign, follow-up endoscopy to document complete healing is unnecessary. A significant although small percentage of gastric ulcers are malignant. Therefore, EGD and biopsy of gastric ulcers with follow-up until complete healing is documented is recommended.

In all patients with documented PUD, the presence of *H. pylori* infection should be determined. Upper endoscopy with gastric biopsy for histologic examination is considered the “gold standard” for the detection of active *H. pylori* infection. Histologic examination may also reveal changes in the gastric mucosa indicative of *H. pylori* infection, such as intestinal metaplasia or dysplasia. Gastric biopsy for detection of urease activity (Clotest), an enzyme produced in abundance by *H. pylori*, can also be used for the detection of active infection. Noninvasive methods include serologic detection of IgG antibodies to *H. pylori*, stool antigen assay for *H. pylori*, and urease breath test. Antibiotics, bismuth, and PPIs can affect the sensitivity of the test results. It is recommended to discontinue antibiotics for 4 weeks and hold PPIs for at least 2 weeks prior to testing for *H. pylori* infection.

Management of PUD

Acid secretion by the parietal cell is controlled by neural, paracrine, and endocrine influences. Receptors for histamine (H2 receptors) and gastrin are present on the surface of the parietal cell; exposure to either histamine or gastrin leads to acid secretion. Cholinergic neural signals interact with muscarinic receptors to produce acid secretion. In response to these and other stimuli, vesicles containing the proton pump, or H⁺/K⁺ ATPase, fuse to the cell membrane and H⁺ ions are secreted into the gastric lumen. Treatment of PUD in the general population is primarily directed at blocking the interaction of histamine with its receptor. The treatment of PUD focuses on (i) healing of the ulcer crater and (ii) permanently eradicating *H. pylori* if present. Healing of the ulcer crater can be achieved by 4 to 8 weeks of therapy with antacids, H2RAs, or PPIs.

Table 3 Complications of Peptic Ulcer Disease

Gastrointestinal bleeding (melena, hematemesis, hematochezia if brisk bleeding)
Perforation (acute abdomen with abdominal distention, rebound, guarding, absent bowel sounds)
Penetration (intractable abdominal pain, pancreatitis, gastrocolic fistula)
Obstruction (nausea, vomiting, early satiety)

Management with Maternal–Fetal Consideration

Antacids are preferred as the first line of therapy for PUD during gestation. Most antacids are considered safe in pregnancy, particularly those containing magnesium or aluminum, because they are not well absorbed systemically after oral ingestion. Recommended doses of antacids are 15 to 30 mL 1 hour after meals and at bedtime. Iron malabsorption may result from antacids, and because iron deficiency is common during pregnancy, antacids should be administered at a different time than iron supplements to avoid this possible drug complication (36).

Sucralfate is FDA pregnancy category B and is a good alternative to antacids in pregnancy. It is a preferred drug for PUD during pregnancy because it is not absorbed systemically and has not been shown to be teratogenic in animal studies (12).

H2RAs are highly effective in the treatment of PUD. About 80% of duodenal ulcers in the general population heal after treatment with H2RAs (37). All H2RAs including cimetidine, ranitidine, famotidine, and nizatidine are classified as FDA pregnancy category B. A recent meta-analysis revealed that H2RAs are not associated with an increased risk of congenital malformations (38). Use of H2RAs in pregnancy is recommended for refractory PUD, which does not respond to antacids or sucralfate, and for complicated ulcer disease (e.g., gastrointestinal bleeding, obstruction). Ranitidine is the preferred H2RA because of a better documented safety profile in humans.

PPIs effectively suppress gastric acid secretion by inhibiting the H⁺/K⁺ ATPase on the surface of the parietal cell. PPIs are highly effective in the treatment of PUD. Omeprazole is rated as category C during pregnancy because of embryotoxicity without teratogenicity in animal studies (19). All other PPIs, including lansoprazole, rabeprazole, pantoprazole, and esomeprazole, are classified as FDA pregnancy category B drugs. Lansoprazole is the preferred PPI during pregnancy because of lack of clinical data regarding the safety of newer PPIs. Treatment with PPIs during pregnancy should be reserved only for patients with refractory or complicated PUD, which does not respond to alternative medical therapies, including H2RAs.

Eradication of *H. pylori* Infection

Treatment of *H. pylori* infection is recommended in the general population because the risk of ulcer recurrence is lower after *H. pylori* eradication (39). Triple drug regimen consisting of antibiotics and PPI therapy is usually used for treatment of *H. pylori* infection. The recommended antibiotics for eradication of *H. pylori* infection during pregnancy include amoxicillin (FDA category B), clarithromycin (FDA category C), and metronidazole (FDA category B). However, administration of antibiotics for treatment of *H. pylori* infection should be avoided during pregnancy. Therapy is usually deferred until postpartum because of low risk of complications from untreated *H. pylori* infection during pregnancy and to avoid potential fetal risk from exposure to antibiotics.

HYPEREMESIS GRAVIDARUM

Definition

Hyperemesis gravidarum (HG) is a severe and disabling condition with potentially life-threatening complications. One of the most widely quoted definitions of HG is that proposed by Fairweather (40) in 1968, who described this syndrome as

“vomiting occurring in pregnancy, appearing for the first time before the twentieth week of gestation and of such severity as to require the patient’s admission to the hospital, the vomiting being unassociated with such coincidental conditions as appendicitis, pyelitis, etc.” HG is defined as nausea and vomiting in pregnancy, typically in the first trimester, resulting in dehydration, weight loss, and electrolyte imbalances severe enough to interfere with the nutritional and metabolic status of the patient and requiring admission.

Epidemiology

Nausea or vomiting is a common symptom occurring in up to 80% of women during pregnancy (41). HG is a much rarer disorder, affecting only 0.3% to 1.5% of pregnancies (42). HG is the most common cause of hospitalization during the first half of pregnancy. There is an increased risk of recurrence, with the risk of HG about 15% in a woman with a previous history of HG during pregnancy, compared with 0.7% with no prior history of HG (43). Several epidemiologic risk factors have been identified (Table 4).

Pathophysiology

Although nausea and vomiting in pregnancy and hyperemesis have been studied for many years, the etiology of these disorders remains obscure. A variety of pathophysiologic mechanisms for HG have been proposed. Etiology of HG is probably multifactorial, with both physiologic and psychologic components.

Hormonal

Because of its presentation early in the first trimester, a hormonal etiology has been suggested. Serum and urinary human chorionic gonadotropin (hCG) levels have been compared in emetic, hyperemetic, and non-emetic pregnancies; the results of these studies are inconsistent. Some groups have found no correlation between hCG levels and nausea and vomiting (44,45), whereas others report higher levels in emetic vs. non-emetic patients (46). However, increased free beta subunit of hCG has been found in the sera of hyperemetic patients compared with normal pregnant controls (47).

Analyses of serum estradiol levels also conflict. Depue and coworkers (44) found that estradiol levels and sex hormone binding globulin capacity were elevated in hyperemetic patients in the first trimester. Others did not show a correlation between

Table 4 Epidemiologic Risk Factors and Associated Conditions in Hyperemesis Gravidarum (HG)

HG is more common in Western countries
Ethnicity: Higher incidence in Asians and Africans
Young age (<20 years): HG is more common in younger maternal age
Family history of HG: Increased likelihood of HG
Parity and multiple gestations: HG is more common in nulliparous and multiple pregnancy
Body mass index (BMI): Low prepregnancy BMI is associated with HG
Coexisting medical conditions: HG is associated with molar pregnancy, hyperthyroidism, psychiatric illness, diabetes, and asthma
Prior history of HG: 15% recurrence risk

estradiol levels and nausea and vomiting, but these analyses did not include many hyperemetic patients (46).

There is a strong association between HG and abnormal thyroid function tests. Transient hyperthyroidism is frequently observed in hyperemetic patients (48). In one series, 73% of hyperemetic pregnant patients showed an increased free thyroxine (T4) index (48). Hyperthyroxinemic patients demonstrated tachycardia and weight loss but no other symptoms of Graves’ disease. The hyperthyroid state tends to be short-lived, resolving by the third trimester, and usually does not require treatment. The mechanisms underlying transient hyperthyroidism in patients with hyperemesis are unknown. hCG has been implicated due to the structural similarity between hCG and thyroid-stimulating hormone (TSH), which may lead to hCG stimulating thyroid activity. Thyroxine and TSH levels in early pregnancy have been correlated with the severity of HG symptoms and electrolyte abnormalities (49).

Gastric Dysmotility

Decreased gastric motility is found to cause nausea. Measurement of gastric myoelectric activity in women with and without nausea in pregnancy revealed a much higher incidence of abnormal electrical patterns in nauseated patients compared with non-nauseated pregnant women (50); the physiologic significance of these findings is unclear.

Psychogenic

Psychologic factors have been considered for many years in the pathogenesis of hyperemesis. Analyses of the maternal relationships of pregnant hyperemetic women have revealed a variety of disturbances including over-strong maternal attachments (51) or negative maternal relationships (52). Persistence of hyperemesis into the third trimester was significantly associated with psychiatric symptoms (52).

Clinical Signs and Symptoms

Although vomiting may begin before the first missed menstrual period, persistent vomiting requiring hospitalization usually peaks between 8 and 12 weeks of gestation (40,51). Majority of the symptoms resolve by 20 weeks. Patients usually describe typical “morning sickness,” which then becomes more severe and persists throughout the day. Intractable vomiting may lead to development of complications including dehydration and oliguria. Weight loss of more than 5% of prepregnancy weight is usually one of the diagnostic criteria. Physical examination may reveal signs of dehydration with poor skin turgor and tachycardia. Jaundice is occasionally present and the odor of ketones may be noted in the patient’s breath. Neurologic symptoms include changes in mental status ranging from drowsiness to coma, and evidence of peripheral neuropathy due to vitamin B₆ or B₁₂ deficiency.

Diagnosis

The diagnosis of HG is based on the presence of symptoms of intractable nausea and vomiting, and any of the several indicators of severity including weight loss of more than 5%, ketonuria, signs of dehydration, and serum electrolyte imbalances. Evidence of major organ dysfunction may be present in more severe cases, including neurologic symptoms (Wernicke’s

encephalopathy (53) and peripheral neuropathy (54)), renal failure, liver dysfunction, or retinal hemorrhage.

Elevated levels of blood urea nitrogen and creatinine, abnormal thyroid and liver function tests, ketosis and ketonuria, hyponatremia, hypochloremia, and hypokalemia are common laboratory abnormalities. HG is a diagnosis of exclusion. It is important to exclude other causes of nausea and vomiting such as pyelonephritis, gastroenteritis, and acute intra-abdominal conditions including pancreatitis, appendicitis, and cholecystitis (51).

Management

Treatment for HG is supportive because the condition is mostly self-limiting. The principles of management of HG include control of nausea and vomiting, correction of dehydration and electrolyte abnormalities, psychologic support, and prevention and treatment of complications.

Control of Nausea and Vomiting

Because of reluctance to use medications, especially in the first trimester, patients with uncomplicated nausea and vomiting are generally advised lifestyle modifications including small meals and avoid ingesting large amounts of liquid; specific therapy is usually not required. By contrast, the management of HG is challenging and often frustrating. Recurrent admissions are common and occur more often in nulliparous women (55).

Antiemetics are commonly used for the management of nausea and vomiting during pregnancy, but there are little data regarding their safety and efficacy in HG (Table 5). Antihistamines and phenothiazines are considered the most effective antiemetic medications. In general, antihistamines are considered to have the lowest teratogenic risk. A meta-analysis showed no evidence of teratogenicity or other serious maternal or fetal adverse outcomes associated with the use of antihistamines for nausea and vomiting during pregnancy (56). Phenothiazines include prochlorperazine and chlorpromazine. Isolated case reports have reported cleft palate, skeletal, limb, and cardiac abnormalities in association with

Table 5 Common Antiemetics Used in Nausea and Vomiting of Pregnancy

Drug class	Dosage
<i>Antihistamines</i>	
Promethazine	12.5–25 mg orally, i.m., or rectally every 4 hours
Dimenhydrinate	50–100 mg orally every 4–6 hours or 50 mg i.m. or i.v. every 4–6 hours (total dose should not exceed 400 mg/day, 200 mg/day if also taking doxylamine)
Doxylamine	12.5 mg orally three to four times daily
<i>Dopamine antagonists</i>	
Prochlorperazine	5–10 mg orally or i.v. every 6 hours (Max dose 40 mg/day)
Metoclopramide	5–10 mg orally, i.m., or i.v. every 8 hours
<i>5HT₃ antagonist</i>	
Ondansetron	4–8 mg orally or i.v. every 8 hours

Abbreviations: i.m., intramuscularly; i.v., intravenously.

the use of phenothiazines; however, there is no evidence of adverse fetal effects in clinical studies (57). No adverse fetal outcomes have been found with the use of metoclopramide in animals or humans (57). Recently 5HT₃ antagonists (ondansetron) have been shown to have efficacy for nausea and vomiting during pregnancy, and their use seems to be increasing (58). No adverse effects in animal studies and no reported increase in birth defects have been found with the use of ondansetron during pregnancy (58).

Correction of Dehydration and Electrolyte Abnormalities

Initial therapy should focus on repletion of fluids, usually by an intravenous route, and resolution of electrolyte imbalances. Chronic or severe hyponatremia must be corrected slowly and cautiously to avoid the complication of cerebral pontine myelinolysis (54,59). An increase in serum sodium of no more than 12 mmol/L/day is recommended.

Repletion of vitamin deficiencies including thiamine is critical since prolonged vomiting may lead to severe depletion. Thiamine deficiency resulting in Wernicke's encephalopathy should be considered in pregnant patients with mental status changes and other neurologic symptoms. All women with HG symptoms should be prescribed thiamine supplementation (thiamine 50 mg orally or 100 mg intravenously daily) if their symptoms are prolonged for 3 weeks or more. Women with HG should take folic acid 5 mg daily, once oral intake has resumed because of deficiency induced by vomiting.

When nausea and vomiting have resolved after treatment with intravenous fluids, oral hydration is begun slowly and diet is advanced from liquid to solid as tolerated (51,60). The cessation of vomiting and commencement of normal weight gain are the therapeutic endpoints to be achieved. In severe cases, in-hospital and even home-based parenteral hyperalimentation can be used if nutrition cannot be maintained orally (61).

Psychologic Support

Psychologic support is offered by nursing staff and physicians depending upon the needs of the patient. Intervention by a psychiatrist is recommended if there is evidence of an obvious psychiatric disorder (51) or occasionally for patients with third-trimester vomiting, which may indicate more serious psychologic problems (52).

Management of Complications

In the past, HG was regarded as a dreaded complication of pregnancy. Maternal mortality was high and primarily caused by severe metabolic disturbances. Improvements in fluid and electrolyte management have dramatically reduced the mortality rate of HG to virtually zero (51). Although uncomplicated nausea and vomiting in pregnancy may be an indicator of a favorable fetal outcome (62), the effects of hyperemesis on the fetus are unclear. A study of hyperemetic pregnancies associated with abnormal thyroid function indicated a higher than expected rate of premature labor and an increased incidence of low birth weight (49). Whether these effects were due to hyperemesis or hyperthyroxinemia is unclear. Analyses of the birth weights of babies born to hyperemetic mothers have been confounded by a varied patient population. Fairweather (40) found no change in birth weight when he reviewed birth records of a large group of

women with hyperemesis. However, others (62,63) have subclassified hyperemetic patients into mild versus severe disease based on maternal weight loss, heavy ketonuria, elevated urea nitrogen or creatinine, and electrolyte disturbances; those with severe hyperemesis gave birth to babies with significantly lower weights. Also more growth-retarded babies were found in the groups of mothers with hyperemesis and weight loss, or hyperemesis requiring multiple admissions (55). The risk of congenital anomalies may also be increased. One study suggested an increase in minor integumentary defects including webbed toes and an extra finger, and skin tags. However, the number of patients was small and the possible influence of anti-emetic medication was not clarified.

INFLAMMATORY BOWEL DISEASE

The inflammatory bowel diseases (IBDs) include two disorders, Crohn's disease (CD) and ulcerative colitis (UC). Both illnesses are characterized by inflammation of the gastrointestinal tract. Clinical manifestations commonly include diarrhea and abdominal pain, and patients may suffer multiple exacerbations and remissions. In CD, a transmural inflammatory process occurs, which can affect any part of the gastrointestinal tract from mouth to anus. On the other hand, the inflammatory process of UC is mucosal and is limited to the colon and rectum. IBD commonly affects women during the childbearing years; therefore, problems in the management of these disorders during pregnancy are frequently encountered by both the obstetrician and the gastroenterologist. In this section, the effect of IBD on fertility and pregnancy outcome, and the impact that pregnancy has on the course of IBD are discussed, and an approach to the management of these disorders in pregnancy is presented.

Epidemiology

The incidence of CD is now approximately equivalent to UC in North America and Europe. In North America, incidence rates range from 2.2 to 14.3 cases per 100,000 person years for UC and 3.1 to 14.6 cases per 100,000 person years for CD (64). Combined prevalence of CD and UC is approximately 100 per 100,000 population. The incidence of IBD has a bimodal distribution, with the peak age of onset between 15 and 30 years of age (65). A second peak in the incidence of IBD occurs between the ages of 50 and 80. There is marked geographic variation in the incidence of IBD. IBD is more common in developed nations compared with countries with poor sanitation. The regions with the highest incidence of UC include the United States, Northern Europe, and Israel. There is no gender specificity; however, within the United States, there is racial and ethnic variation. Incidence rates are increased in Jews and in white versus non-white populations, although the incidence in black populations may in fact be increasing (66).

Etiology

The etiology of IBD is at present unknown, but is thought to be multifactorial (67). A number of infectious agents have been postulated to be pathogenic. A bacterium similar to *Mycobacterium paratuberculosis* was isolated from the intestine of patients who underwent surgical resection for active CD, yet in the majority of patients, this organism cannot be cultured. Other potential agents involved in eliciting an immune

response have been postulated to include cow's milk proteins, other foods, water, viruses, and smoking, yet none has been definitively linked to either disease. Intestinal permeability has been shown to be altered in CD; a "leaky bowel" may allow translocation of antigens that elicit an immune response. Although the antigen that triggers the gut's immunologic response is unknown, there is active research directed at understanding the intestinal mucosal immune system in normal and affected individuals. The contribution of autoimmunity, cytokines, mucosal B and T cells, as well as neutrophil function is being actively examined in IBD.

Genetic factors play an important role as indicated by family studies. First-degree relatives of patients with IBD are approximately 3 to 20 times more likely to develop the disease than the general population (68). In one report, children in whom both parents had IBD (CD or UC) had up to a 33% chance of developing IBD by age 28 (68). Stronger familial association has been shown for CD than for UC. Twin studies showing disease concordance in monozygotic but not dizygotic twins further strengthen the evidence that genetic influences play a role in the pathogenesis of CD (67). In a study that included 80 twins with IBD, the concordance rate for monozygotic twins was markedly higher in CD than UC (58% vs. 6%) (69).

The inflammatory process of UC is confined to the colon. This disease may affect the rectum alone, the rectum plus the left colon, or it may be pancolonic. By contrast, in CD, inflammation can be found anywhere throughout the gastrointestinal tract, from mouth to anus. The commonest sites of involvement are small bowel alone (predominantly distal ileum) (30%), colon alone (15–25%), or ileocolon (40–55%). Perianal and perirectal disease is commonly encountered, manifested by fissures, fistulae, and abscesses.

In UC, mucosal lesions predominate; the muscularis propria is rarely involved. Crypt abscesses, in which collections of neutrophils invade crypt epithelium and may even be present in the crypt lumen, are characteristic of UC, yet may also be seen in CD. Evidence of chronic inflammation is also apparent with lymphocytic, plasma cell, and eosinophilic involvement of the lamina propria. Marked edema, hemorrhage, and pseudopolyps are often found in active UC. By contrast, the presence of granulomas and transmural inflammation with deep ulcerations that extend to the muscularis propria are more characteristic of CD. "Skip areas" (intervening normal mucosa) or rectal sparing are consistent with CD.

Clinical Signs and Symptoms

There are both similarities and differences in the presentation of UC and CD. Patients afflicted with either disorder may present with abdominal pain, diarrhea, weight loss, fevers, and malaise. Multiple extraintestinal manifestations accompany both illnesses.

UC

The inflammatory process characteristic of UC is confined to the colon. Some patients initially present with inflammation confined to the rectum (ulcerative proctitis); the disease may progress during subsequent exacerbations to other areas of the colon or may remain in the rectum. Other patients suffer from more extensive colitis and may have disease up to and

including the cecum. Due to rectal involvement, patients often complain of urgency and frequency of bowel movements as well as tenesmus. Rectal bleeding and diarrhea are the hallmarks of this disease. Abdominal pain is usually mild but may be severe in fulminant colitis. In mild cases, physical examination may be unremarkable, whereas patients with more active disease develop fevers, tachycardia, diffuse abdominal tenderness, and occasionally distention. A serious complication of acute UC, which may be heralded by the appearance of abdominal distention, is toxic megacolon. Massive dilatation of the inflamed colon may progress to perforation; this is a surgical emergency and requires immediate colectomy. A significant long-term complication of UC is the development of colon cancer. Patients are at an increased risk for carcinoma after 8 to 10 years of disease and are screened with yearly colonoscopy.

CD

CD is a chronic indolent disorder characterized by multiple remissions and exacerbations. Patients commonly present with abdominal pain, diarrhea, weight loss, anal pain, and drainage. On physical examination, abdominal tenderness and inflammatory masses particularly in the right lower quadrant and pelvis can be palpated. Because the inflammatory lesion is transmural, perianal fissures, internal fistulae between the bowel and skin, bladder, or vagina, as well as free perforation with abscess formation are common complications.

Extraintestinal Manifestations

Both UC and CD are associated with a wide variety of extraintestinal manifestations. The "colitis-related" manifestations include skin, eye, and joint diseases, which present in parallel with recrudescence of disease activity. Skin manifestations such as erythema nodosum and pyoderma gangrenosum, and oral lesions including diffuse aphthous ulcerations may be severe enough to require treatment with corticosteroids. Arthritic complaints include ankylosing spondylitis, sacroiliitis, and peripheral large joint arthritis. Ocular diseases such as uveitis, iritis, and episcleritis may be present in approximately 15% to 20% of patients and may be the initial symptom that prompts a visit to a physician. Nonspecific complications of CD include a variety of liver diseases such as fatty liver, pericholangitis, primary sclerosing cholangitis, hepatic granulomas, and abscesses. In patients who have had extensive small bowel resection, malabsorption may result in deficiency of vitamin D and calcium, leading to osteoporosis. Increased absorption of oxalate from the gut lumen may lead to enhanced urinary excretion and the development of oxalate stones.

Diagnosis in the Nonpregnant Patient

In the nonpregnant patient, endoscopy has a pivotal role in establishing a diagnosis of IBD. The presence and extent of disease tend to be underestimated when radiographic studies are compared with direct endoscopic visualization, since subtle mucosal abnormalities can only be detected with endoscopy. The addition of biopsy adds considerably to the sensitivity and specificity of endoscopy in the diagnosis of IBD. Radiographic studies are now considered an adjunctive rather than a primary diagnostic tool. Small bowel barium radiograms may demonstrate terminal ileal narrowing, strictures, and enteric fistulae.

This may be useful in the evaluation of stricturing or fistulizing CD, and if patients are unable to undergo colonoscopy due to medical comorbidities. However, other imaging modalities such as small bowel wireless capsule endoscopy, CT, or MRI have supplanted the barium radiographic studies for evaluation of small bowel involvement in CD.

Endoscopic evaluation including upper endoscopy (for patients who have upper abdominal symptoms suggestive of CD), flexible sigmoidoscopy, and colonoscopy provides direct visualization of the gut's mucosa. Characteristic findings of ulcerative and Crohn's colitis include erythema, edema, granularity, ulceration, and friability of the colonic epithelium. Strictures may result from chronic inflammation. However, it is important to emphasize that these findings, while consistent with IBD, are not diagnostic, since they may also be found in a variety of infectious and other colitides. Abnormalities such as aphthous ulcerations and erythema may also be found in the upper gastrointestinal tract in CD. Biopsies taken during endoscopy may show the presence of granulomas or crypt abscesses and may help confirm the clinical impression.

Diagnosis in Pregnancy

There are limited data regarding the safety of endoscopic procedures during pregnancy. In those patients with undiagnosed abdominal pain, diarrhea, or rectal bleeding in whom IBD is suspected, flexible sigmoidoscopy under either minimal or no sedation appears to be safe (70). Complete colonoscopy usually requires a greater degree of sedation and is avoided when possible, although it is safe with appropriate monitoring of vital signs and oxygenation. In the pregnant patient, all efforts should of course be made to avoid fetal exposure to radiation, and radiologic procedures are not recommended. However, in emergent situations (when bowel perforation, abscess, or toxic megacolon are being considered), radiologic examinations may be necessary; there is some evidence to suggest that a very low dose of irradiation may have no long-term harmful effects (71).

Stool studies for routine bacterial pathogens (including *Clostridium difficile*) are extremely important in the initial evaluation of a patient in whom IBD is suspected. Infectious colitides such as those caused by salmonella, shigella, yersinia, *Campylobacter fetus*, *Giardia lamblia*, and amebae may present with an identical picture and demonstrate similar endoscopic findings. In patients infected with human immunodeficiency virus, organisms such as *Mycobacterium avium-intracellulare*, cryptosporidiosis, isospora, and cytomegalovirus can be ruled out with stool cultures and histologic examination of biopsies.

Management with Maternal-Fetal Consideration

Critical issues in the management of IBD during pregnancy include (i) the effects of pregnancy on the course of IBD and (ii) the impact of IBD and its therapy on fertility, pregnancy, and fetal outcome.

Effects of Pregnancy on the Course of IBD

Early studies in the 1950s and 1960s indicated that pregnancy had an adverse effect on the course of UC, yet more recent studies dispute these findings. Part of the reason for this discrepancy is the realization that the spontaneous risk of exacerbation of UC in the nonpregnant patient is similar to the

rate of relapse reported for pregnant patients with this illness. Pregnant women with IBD are as likely to flare (34% per year) as nonpregnant women with UC (32% per year) (72). With the advent of more effective medical therapy for UC, it has become apparent that pregnancy does not adversely affect the course of this disease. Those patients with quiescent disease will usually remain inactive (73,74), whereas those with active colitis will demonstrate persistent disease or worsen during pregnancy (75).

Patients with quiescent CD are probably not at increased risk for precipitating active disease when pregnant (76,77). Again, in those patients who are already active, approximately two out of three will continue to be ill or will worsen during pregnancy (75,77,78). Therefore, patients with IBD are usually counseled to avoid pregnancy when in a phase of moderate to severe disease activity.

Effects of IBD on Fertility, Pregnancy, and Fetal Outcome

Patients with UC demonstrate fertility rates that are comparable with those of the general population (76,78), although there are few case-controlled studies. In considering CD, there are conflicting reports; some groups have shown that as many as 50% of women of child-bearing age are subfertile, correlating with disease activity, whereas others have shown no difference in fertility rates when compared with the general population (76,79–81). Many studies did not account for disease activity, the patient's desire to become pregnant, or other risk factors that could decrease fertility. In fact, a recent report revealed that fertility may not be impaired in women who wished to conceive; there was a voluntary decrease in the number of pregnancies, arising from a desire to avoid pregnancy because of illness (79). Men with IBD who take sulfasalazine may show diminished fertility due to direct toxic effect on sperms (82).

The risk of spontaneous abortion in patients with quiescent CD or UC is probably no higher than that in the general population (75), but in several studies it has been shown to be increased as much as twofold in those patients with active disease (72,83,84). Reports indicate that IBD predisposes patients to a significant risk of preterm delivery (79), as defined by birth before 37 weeks of gestation. Therefore, vigilant monitoring of patients in the third trimester is recommended. Fortunately, once pregnancy occurs, the likelihood of a normal fetal outcome is identical to that in the general population. In almost all studies, the incidence of small-for-gestational-age babies and congenital defects was not increased, even in those patients on multiple medications such as steroids and sulfasalazine.

Management of IBD in Pregnancy

To improve the likelihood of a favorable outcome, patients are generally encouraged to avoid pregnancy during periods of disease activity if this is at all possible. Numerous retrospective analyses have ascertained that patients with IBD can be successfully treated without adverse effect to the mother or fetus. Medications should be reduced to the minimal amount required. In reports in which low birth weight or congenital anomalies were detected, it was often difficult to ascertain whether the severity of the bowel disease or the medications used were the major contributor.

Aminosalicylates are one of the cornerstones of medical therapy of IBD and are considered low risk for use in pregnancy. Most are pregnancy category B (sulfasalazine, mesalamine, and balsalazide) with the exception of olsalazine, which is category C. Sulfasalazine contains a sulfapyridine residue linked to 5-aminosalicylic acid (5-ASA), the active moiety. Its mechanism of action is unknown, but it has been shown to inhibit production of leukotriene B₄, an important mediator of inflammation, block prostaglandin production, and inhibit immunoglobulin secretion by mononuclear cells. Sulfasalazine crosses the placenta (85) and is found in breast milk, although in low concentrations. Serum levels of sulfasalazine in newborns are the same as in the mother (86). This drug is thought to be safe during pregnancy (87). There are a few case reports of congenital defects in infants of treated patients; however, a population-based study did not find a significant increase in congenital abnormalities in children of women treated with sulfasalazine (88). Its efficacy in maintaining remission in UC makes its continuation during pregnancy an important consideration. Patients are usually tapered to the lowest dose that is effective in suppressing disease activity. Sulfasalazine has anti-folate effects, and it is recommended that women take folate supplementation of at least 2 mg daily during the prenatal period and pregnancy.

Because of multiple side effects associated with the presumably inactive sulfapyridine moiety, both topical and oral agents that contain only 5-ASA have been developed. Topical therapy with 5-ASA (mesalamine) enemas is an effective treatment for acute proctitis or proctitis with left-sided colitis. In addition, several oral forms of 5-ASA (Pentasa®, Asacol®, and Dipentum®) have been released for treatment of both CD and UC. These drugs contain 5-ASA in formulations that prevent their premature absorption from the gastrointestinal tract. A number of studies have established the safety of oral and topical aminosalicylates in pregnancy (89–91). A meta-analysis of mesalamine formulations used during pregnancy demonstrated no increased risk for congenital malformations, stillbirths, spontaneous abortions, preterm delivery, or low birth weight with the use of mesalamine (92). Thus sulfasalazine and 5-ASA drugs can be used during pregnancy as in nonpregnant women with IBD.

Corticosteroids, including budesonide, are pregnancy category C. Steroid therapy is frequently used in the treatment of moderate to severe and fulminant UC, and moderate to severe active CD. In severely ill, hospitalized patients, high doses of intravenous steroids are employed to control bowel inflammation. Corticosteroid enemas are important topical agents for the treatment of proctitis and left-sided colitis. The major side effects associated with long-term corticosteroid therapy (such as cataracts, osteoporosis, diabetes, and hypertension) make it imperative that patients be tapered off this medication as soon as possible. Unfortunately, some patients with IBD require long-term corticosteroid use to treat persistently active disease; in these patients, a trial of an immunosuppressive agent such as 6-mercaptopurine (6-MP) or azathioprine (AZA) may be used to facilitate steroid tapering.

Evidence suggests that steroids should be used with caution in the first trimester because of an association with an increased risk of oral clefts (93). A number of studies showed no adverse effects on fetal outcome in women who took

corticosteroids during pregnancy (94,95). A meta-analysis of five studies of oral corticosteroid use did not reveal a major teratogenic risk of major malformations in the offspring of exposed patients at therapeutic doses (95). A significant increase was noted in risk of oral clefts (OR 3.69; 95% CI, 2.15–6.32); however, the increased risk appeared to be in women taking steroids for non-IBD diseases such as asthma. A case series of eight patients receiving budesonide during pregnancy demonstrated no increase in maternal adverse events (96). Corticosteroids also appear to be safe during breast-feeding (97). As in their nonpregnant counterparts, pregnant patients should be taken off steroids if at all possible, yet treatment during pregnancy can be safely initiated or continued as needed to control disease activity.

Immunosuppressive agents such as 6-MP and its prodrug AZA are primarily used to maintain remission in UC and CD. These agents are often used as steroid-sparing agents to facilitate discontinuation or dose reduction of steroids. 6-MP and AZA are pregnancy category D. Animal studies show teratogenicity with increased rates of cleft palate and skeletal anomalies (98). However, in these studies, animals were exposed to significantly higher doses than those used in humans. Limited data exist regarding the long-term adverse effects that may result from the use of these medications in IBD. However, regarding usage in pregnancy, there is a large body of data from the transplant population, which indicate that treatment with these agents is surprisingly well tolerated. The doses used for treatment of UC and CD are much lower than that used in transplant patients. Few studies also indicate their relative safety in pregnant IBD patients (99,100). It is reasonable to continue these drugs during pregnancy in patients who cannot be managed with other alternative medications.

AZA and 6-MP are detectable at low levels in breast milk. 6-MP excretion in breast milk occurs within the first 4 hours after intake (101). Mothers taking these medications should be discouraged from nursing; however, there is no absolute contraindication to breast-feeding. Lactating mothers are advised to wait 4 hours after dosing to feed.

Methotrexate is a pregnancy category X drug. Methotrexate is a folic acid antagonist and should not be used in women considering conception. It is contraindicated in pregnancy because of its mutagenic and teratogenic effects. Methotrexate is associated with multiple congenital anomalies including craniofacial malformations and central nervous system abnormalities, including anencephaly and mental retardation (102).

Antibiotics are frequently used in the treatment of CD. Particularly, metronidazole is useful in the treatment of perianal complications such as fistulae or abscesses. Metronidazole is pregnancy category B. A number of studies have demonstrated that metronidazole is not associated with an increased risk of birth defects or cancer in humans (103,104). However, long-term use in pregnancy remains controversial due to its teratogenic and carcinogenic potential. Breast-feeding should be withheld for 12 to 24 hours if a single dose of metronidazole is given. Long-term use of metronidazole should be avoided during breast-feeding due to potential toxic effects.

Biologic therapy has opened a new era in the treatment of IBD. All three biologic agents including infliximab, adalimumab, and certolizumab are pregnancy category B. These agents inhibit

the activity of tumor necrosis factor and are used for induction and maintenance of remission in IBD patients. Data on the safety of infliximab in pregnancy are limited; however, no maternal toxicity, embryotoxicity, or teratogenicity to infliximab has been observed. The two largest studies are the Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) registry and the Infliximab Safety Database (105,106). The TREAT registry is a prospective, multicenter study of CD patients. Of more than 6200 patients enrolled, 117 of 168 pregnancies were exposed to infliximab. No fetal malformations were seen. Miscarriage and neonatal complication rates were not statistically significant between the infliximab-exposed and unexposed group (105). The Infliximab Safety Database is a retrospective database that records voluntary adverse event reports associated with infliximab use. The expected versus observed outcomes among women exposed to infliximab were reported no different than those of the general population (106). In a recent case series, infliximab remained undetectable in breast milk while maternal levels remained in the therapeutic range (107). Case reports have also described successful use of adalimumab in women with CD and pregnancy (108–110).

Special Considerations—Surgical Management, Pregnancy with Ileostomy, or Ileoanal Anastomosis

Despite advances in the medical management of IBD and improved therapy during pregnancy, surgical treatment is occasionally necessary. Emergent colectomy may be indicated for fulminant colitis unresponsive to medical therapy or for complications of UC such as toxic megacolon and colonic perforation. Morbidity and mortality rates for both fetus and mother are unknown; although there are scattered case studies of successful surgical intervention, fetal deaths have been reported.

Fertility and fecundity (rate of conception per menstrual cycle) are decreased after surgery for CD and colectomy with ileal pouch anal anastomosis for UC (111,112). Ileostomy may predispose to intestinal obstruction, which may be difficult to recognize, since abdominal pain may be mistakenly attributed to uterine contractions. An increased frequency of nocturnal stooling was noted in patients with ileoanal pouches (113). Patients may undergo vaginal or cesarean delivery and fetal outcome seems unaffected by the presence of an ileostomy or ileoanal anastomosis.

PANCREATITIS

Acute inflammation of the pancreas, or pancreatitis, is rare in pregnancy, ranging in incidence from 1 case per 1000 to 1 in 10,000 pregnancies occurring usually late in the third trimester or early in the postpartum period (114–116). Acute pancreatitis can cause significant fetal and maternal morbidity and mortality including premature delivery, shock, sepsis, and multiorgan dysfunction syndrome. Management of this disorder in pregnancy is often complicated and requires careful monitoring of the mother and fetus.

Etiology and Pathogenesis

The etiology and pathogenesis of acute pancreatitis are similar to those in the nonpregnant population (Table 6). Cholelithiasis is the most frequent cause of acute pancreatitis during pregnancy accounting for more than 70% cases (117). Weight gain and hormonal changes during pregnancy predispose to

Table 6 Etiologies of Pancreatitis

Gallstones (most common)
Hypertriglyceridemia
Alcohol
Obstruction (tumors, strictures)
Drugs (diuretics, azathioprine, sulfonamides, metronidazole, estrogens, valproic acid)
Trauma (blunt or penetrating abdominal injury, ERCP, surgery)
Viruses (mumps, hepatitis B, Coxsackie)
Metabolic (hypercalcemia, hyperparathyroidism)
Pre-eclampsia/eclampsia
Idiopathic (20% cases)

gallstone formation (118). Cholesterol secretion in bile increases during pregnancy leading to a supersaturated bile. Changes in serum hormonal levels may also result in bile stasis, which in turn favor stone development. Acute pancreatitis may be precipitated when gallstones become impacted at the ampulla of Vater or pass into the duodenum initiating premature activation of intracinar trypsinogen to trypsin (119). Release of activated digestive enzymes into the pancreatic parenchyma may result in autodigestion and injury.

Hypertriglyceridemia (serum triglyceride levels >1000mg/dL) is the second most common cause of acute pancreatitis during pregnancy. Hyperlipidemic pancreatitis accounts for 4% to 6% of cases with the majority of cases being associated with either type I or V familial hyperlipoproteinemia (117). During pregnancy, triglyceride levels elevate due to increase in estrogen-induced synthesis (120). In women with familial hyperlipidemias, further elevation of serum lipid levels during pregnancy leads to an even higher risk of pancreatitis. In patients with hypertriglyceridemia, it is postulated that pancreatic lipase becomes activated and releases fatty acids into the pancreas, producing inflammation, or that vascular obstruction results from blockage of vessels by fat globules (121).

Alcohol causes pancreatitis probably due to a direct toxic effect. Patients who have pancreatic duct obstruction from strictures, tumors, or other lesions may develop pancreatitis because of backflow of pancreatic juices into the gland, although the mechanism of enzyme activation in the pancreas is unclear. Pre-eclampsia or eclampsia is a rare cause of pancreatitis with its microvascular abnormalities that may affect the hepatic, splanchnic, renal, and placental circulation (117).

Clinical Signs and Symptoms

Acute pancreatitis can be divided into mild and severe or necrotizing pancreatitis. The presenting signs and symptoms of pancreatitis in pregnant patients are similar to those in the nonpregnant population. Characteristic symptoms include acute abdominal pain radiating to the back and associated with nausea and vomiting. Abdominal pain may worsen while lying flat or improve after assuming a forward or fetal position. Obstruction of the common bile duct as it courses through the head of the pancreas can lead to jaundice. Fever, pleuritic pain, and shock may result from peripancreatic fluid collection and pancreatic parenchymal hemorrhage. Physical examination may reveal epigastric tenderness, guarding and rebound, decreased, or absent bowel sounds, ecchymosis of the flank (Grey-Turner's sign) or periumbilical region (Cullen's sign) and ascites. Several other diseases such as duodenal ulcer

perforation, cholecystitis, hepatitis, bowel obstruction, diabetic ketoacidosis, and pre-eclampsia may share a similar presentation (122).

Diagnosis

Typical symptoms of severe acute epigastric pain radiating to the back, nausea, and vomiting in conjunction with elevated serum amylase and/or lipase levels strongly suggest the diagnosis of pancreatitis. Pregnancy does not affect serum amylase or lipase levels; therefore, marked elevations in amylase and lipase levels are reliable markers of acute pancreatitis during pregnancy (117). However, there are many other pathologic states in which these enzymes may be elevated, since organs other than the pancreas synthesize and release amylase. Bowel ischemia or obstruction, perforated viscus, ovarian/tubal diseases such as salpingitis or ruptured ectopic pregnancy, cholecystitis, and a variety of salivary gland and pulmonary diseases (mumps, pneumonia) may also lead to elevations in serum amylase and lipase. Elevation of serum alanine aminotransferase to more than three times the upper limit of normal is a high sensitivity for biliary pancreatitis (123).

The severity of pancreatitis can be predicted to a certain extent by using Ranson's criteria, a series of biochemical parameters (124). Poor prognostic signs include (at presentation) age greater than 55 years, white blood cell count greater than $16,000/\text{mm}^3$, glucose concentration greater than 200mg/dL , lactate dehydrogenase level greater than 350IU/L , and serum glutamic-oxaloacetic transaminase level greater than 250IU/L . Within 48 hours of presentation, a decrease in hematocrit of more than 10%, a drop in serum Ca^{++} level below 8mg/dL , arterial oxygen pressure less than 60mmHg , base deficit greater than 4mEq/L , rise in blood urea nitrogen level of greater than 5mg/dL , or fluid sequestration of more than 6 liters may also indicate more severe disease.

Ultrasonography, without fetal radiation, is the initial test of choice to detect gallstones with a high accuracy during pregnancy. However, if common bile duct stones or biliary sludge are suspected based on ultrasound examination or biochemical abnormalities, a more invasive test may be required such as endoscopic ultrasonography (EUS) or magnetic resonance cholangiopancreatography (MRCP), which can provide an adequate view of the bilio-pancreatic duct anatomy. EUS and MRCP do not involve radiation and are often the tests of choice for detecting CBD stones. Computer tomography (CT) scan is not recommended during pregnancy as it carries a small radiation risk to the fetus. Endoscopic retrograde cholangiopancreatography (ERCP) is no longer widely used as a diagnostic study due to its post-procedure pancreatitis risk, radiation exposure, and the availability of newer and safer techniques such as EUS and MRCP (119). Performing diagnostic EUS or MRCP helps to identify patients who require therapeutic ERCP.

Complications

Maternal Complications

Patients with pancreatitis may develop hypovolemia and shock due to fluid sequestration and prolonged nausea and vomiting. Hypocalcemia may occur, possibly owing to entrapment of calcium in necrotic pancreatic tissue. Other metabolic abnormalities include hypochloremic alkalosis resulting from

vomiting. Severe pancreatitis may result in disseminated intravascular coagulation and adult respiratory distress syndrome.

Pancreatic pseudocyst is a collection of pancreatic fluid within a fibrous cavity; its presence may be heralded by persistent abdominal pain or chronically elevated amylase levels. Infected pancreatic necrosis must be considered if patient develops fever and leukocytosis. A CT scan or ultrasonogram (the latter is preferable in the pregnant patient) may reveal the presence of fluid and necrosis in the pancreas, but cannot determine whether or not there is concomitant infection. The diagnosis of infected pancreatic necrosis is therefore usually made on clinical grounds. Hemorrhagic pancreatitis due to necrosis and blood vessel rupture may lead to massive bleeding. Pancreatic ascites results from rupture of pancreatic ducts with leakage of amylase-rich fluid into the peritoneum.

Over the years, the maternal mortality rate associated with pancreatitis has significantly decreased. Older reviews reported a very high mortality rate of up to 37% (125); however, more recent studies have shown no maternal mortality attributed to acute pancreatitis (126,127). The improvement in the outcome of pregnant patients with pancreatitis is mainly due to earlier diagnosis with better imaging and less invasive therapeutic options including ERCP and laparoscopic cholecystectomy.

Fetal Complications

Premature labor is the main cause of adverse fetal outcomes in pancreatitis during late pregnancy (116). The rates of preterm delivery ranged between 15% and 19% (128). Fetal growth restriction can occur but may in part be avoided by the use of total parenteral nutrition (TPN). Fetal loss rate of 4.7% has also been reported (119).

Management with Maternal-Fetal Consideration

The treatment of acute pancreatitis in pregnancy follows the same guidelines as in the nonpregnant patient. The management is primarily supportive and aimed at correcting any underlying predisposing factors. Close observation is imperative, keeping in mind that multiple organ systems may be affected. The treatment of gallstone and hyperlipidemic pancreatitis in pregnancy deserves special consideration and is discussed separately.

General Measures

The general management of uncomplicated acute pancreatitis is mainly supportive including bowel rest, fluid resuscitation, correction of electrolyte and metabolic abnormalities, and pain control. Volume depletion is frequently encountered due to vomiting and fluid sequestration into the retroperitoneum. Aggressive intravenous fluid replacement is necessary to prevent pancreatic necrosis and systemic complications. Patients are given nothing by mouth for bowel rest. Fluid and electrolyte balance is closely observed; in particular, correction of hypocalcemia and hypomagnesemia may be necessary. Abdominal pain is a prominent feature in acute pancreatitis and may be severe requiring analgesics. Intravenous opiates may be used cautiously for pain control during pregnancy. Meperidine and fentanyl are the preferred analgesics during pregnancy (129).

Prophylactic antibiotics are not routinely recommended in uncomplicated pancreatitis if there is no evidence of infection (130). Although therapeutic delivery has been considered in the past, recent literature suggests that termination of pregnancy does not affect the outcome of acute pancreatitis and is not recommended (131).

Nutrition

In mild pancreatitis, oral intake should be initiated when pain subsides and advanced as tolerated. Patients with a prolonged course due to severe pancreatitis or its complications may be unable to eat even after several days of hospitalization. To ensure adequate fetal growth and maintenance of maternal nutrition, TPN can be instituted (132–134). Most of the reported complications of TPN in pregnancy are the same as those found in the nonpregnant patients and are mainly catheter related, including sepsis and thrombosis. The rate of maternal complications such as septic complications secondary to centrally inserted central venous catheters for TPN is greater than that in the nonpregnant patients. Thus, peripherally inserted central venous catheters may be preferable for parenteral nutrition during pregnancy (119,129). There are no reports of adverse fetal outcomes related to TPN in pregnant patients. Enteral nutrition (EN) via nasojunal feeding is preferable compared with TPN (129). EN has been shown to be associated with fewer infectious complications, shorter hospital stay, and reduced surgical interventions in patients with acute pancreatitis (135). EN helps to maintain intestinal barrier and prevents bacterial translocation. Monitoring fetal growth with serial ultrasonograms is generally recommended (132) to ensure that fetal nutritional demands are met.

Management of Complications of Acute Pancreatitis

Patients with *pancreatic pseudocysts* should be monitored with serial ultrasonograms to document resolution of the cysts. Patients should be closely monitored for new symptoms such as abdominal pain, fever, chills, gastric outlet obstruction, or obstructive jaundice. Drainage of pseudocysts should be considered in patients who are symptomatic or have an infected pseudocyst. Endoscopic, percutaneous, or surgical drainage of the pseudocysts may be considered.

The occurrence of *infected pancreatic necrosis* is a leading cause of morbidity and mortality in severe pancreatitis. Infected pancreatic necrosis should be suspected if patient develops unexplained fever, leukocytosis, and/or signs of sepsis in conjunction with a CT scan, which reveals necrosis in the pancreas. Antibiotic therapy with broad-spectrum antibiotics such as imipenem should be initiated if pancreatic infection is suspected. Radiologic-guided fine-needle aspiration of the necrotic area is recommended to determine whether it is sterile or infected. Sterile necrosis is usually managed conservatively; however, infected pancreatic necrosis requires surgical debridement (necrosectomy).

Gallstone Pancreatitis

Because of the risk of recurrent pancreatitis due to cholelithiasis, indications for cholecystectomy during pregnancy should be the same as in the nonpregnant patient. Once pancreatitis resolves, laparoscopic cholecystectomy is ideally

performed in the second trimester because during this period organogenesis is complete and technical problems due to an enlarging uterus are limited (131). A laparoscopic approach is preferable over open cholecystectomy because it is associated with shorter hospital stay, decreased narcotic use, and an earlier resumption of oral intake without affecting maternal or fetal mortality (119). In patients with onset of pancreatitis in the third trimester, postpartum cholecystectomy may be performed. ERCP with sphincterotomy may be useful in patients with severe acute pancreatitis, cholangitis, persistent biliary obstruction, and in those who are not ideal surgical candidates during the first and third trimesters of pregnancy (119). Fetal radiation exposure during ERCP can be kept below the teratogenic doses by limiting fluoroscopy times and shielding the pelvis.

Hyperlipidemic Pancreatitis

The management of hyperlipidemic pancreatitis poses a challenging problem. Attempts at refeeding patients after symptoms of pancreatitis subside may be difficult since even low-fat diets may lead to elevation of triglycerides and recurrent symptomatology (133). In these situations, particularly in patients who are not near term, adequate nutrition must be maintained. TPN has proven to be an efficacious method for delivering an appropriate calorie load without supplementation with fats, leading to improved regulation of triglyceride levels. Other supportive therapies include low-fat diet, antihyperlipidemic therapy, insulin, heparin, and plasmapheresis (134). Planned delivery of patients at term who have pancreatitis due to hyperlipidemia is recommended by some authors (136), and preterm delivery may be considered only in patients whose clinical status deteriorates, since lipid abnormalities are clearly worsened by pregnancy.

ENDOSCOPY AND PROCEDURAL SEDATION IN PREGNANCY

Endoscopy during pregnancy appears to be safe provided the indication for endoscopy is appropriate and adequate precautions are taken. A multidisciplinary team involving an endoscopist, obstetrician, and an anesthesiologist may be required for the management of gastrointestinal diseases in pregnancy requiring endoscopic diagnosis and intervention. Potential risks associated with endoscopy during pregnancy include the following:

1. Fetal hypoxia: Caused by maternal hypotension and hypoxia due to oversedation and may lead to fatal consequences.
2. Exposure of the fetus to potentially teratogenic drugs and radiation.
3. Maternal positioning during endoscopy can cause inferior vena caval obstruction by the pregnant uterus, which can lead to decreased uterine blood flow and fetal hypoxia.

According to the guidelines issued by the American Society for Gastrointestinal Endoscopy for endoscopy in pregnant women (137):

1. Always have a strong indication, particularly in high-risk pregnancies,

2. Defer endoscopy to the second trimester whenever possible,
3. Use the lowest dose of sedative medication,
4. Minimize procedure time,
5. Position the pregnant patient in the left pelvic tilt or left lateral position to avoid vena caval or aortic compression,
6. Presence of fetal heart sounds should be confirmed before sedation is begun and after the endoscopic procedure is completed,
7. Obstetric support should be available in the event of a pregnancy-related complication, and
8. Endoscopy is contraindicated in obstetric complications such as placental abruption, imminent delivery, ruptured membranes, or pre-eclampsia.

EGD

EGD appears to be safe during pregnancy. The indications for considering EGD during pregnancy include significant upper gastrointestinal bleed, dysphagia, odynophagia, severe abdominal pain, and refractory nausea and vomiting. In one study, the diagnostic yield of EGD for upper gastrointestinal bleed was reported to be 95% (138). There were no cases of premature labor or congenital fetal malformation.

Flexible Sigmoidoscopy/Colonoscopy

The common indications for flexible sigmoidoscopy and/or colonoscopy during pregnancy are rectal bleeding, diarrhea with negative evaluation, and strong indication for a colon mass. Sigmoidoscopy may establish diagnosis in majority of patients and should be considered first. Colonoscopy may be required if refractory lower gastrointestinal symptoms persist and sigmoidoscopy was not diagnostic. The safety and efficacy of flexible sigmoidoscopy and colonoscopy were reported in a study in which 48 sigmoidoscopies (46 patients) and 8 colonoscopies (8 patients) were safely performed during pregnancy (70). There were no adverse fetal outcomes, and no evidence that sigmoidoscopy or colonoscopy precipitated the onset of labor. The safety of polyethylene glycol (PEG) electrolyte solutions has not been studied in pregnancy. PEG solutions are classified as category C. Tap water enemas may be used for bowel preparation for flexible sigmoidoscopy. Removal of majority of colon polyps should be deferred until the postpartum period.

ERCP

Pregnancy is associated with an increased risk of gallstone formation due to alterations in the bile composition (139). Therefore, the usual indications for ERCP in pregnant patients include complications related to gallstones including choledocholithiasis, cholangitis, and gallstone pancreatitis. Several studies have reported safety of ERCP during pregnancy with no adverse fetal effects (140,141); however, ERCP should be performed only by an experienced endoscopist preferably at a higher volume tertiary care center. ERCP should be avoided during the first trimester due to radiation exposure. Fluoroscopy and procedure times should be minimized. Radiation exposure should be kept to a minimum by placing lead sheets under the pelvis and lower abdomen. Other diagnostic modalities that do not involve radiation such as MRCP and

Table 7 Common Sedation Medications for Endoscopic Procedures

Drug name	FDA category
Meperidine	B
Fentanyl	C
Midazolam	D
Propofol	B
Glucagon (antiperistaltic agent)	B
Naloxone (opioid reversal agent)	B
Flumazenil (benzodiazepine reversal agent)	C

endoscopic ultrasonography (EUS) should be considered if probability of choledocholithiasis requiring therapeutic intervention is low.

General Precautions

Patient Positioning

Pregnant patients should not be placed in the decubitus or prone position during endoscopic procedures. Position pregnant patients in left pelvic tilt or left lateral position to avoid vena caval or aortic compression. External abdominal pressure should be avoided. If pressure is required, it should be minimal and directed away from the uterus.

Medications for Sedation During Pregnancy and Lactation

EGDs and flexible sigmoidoscopies may be performed without sedation. However, if sedation is required, it should be kept to a minimum. For procedural sedation during pregnancy, meperidine (category B) is preferred. Small doses of midazolam (category D) may be used as needed. If deep sedation is required, then propofol administered by an anesthesiologist should be the preferred choice (Table 7).

Fentanyl is preferred to meperidine for procedural sedation in women who are breast-feeding. The concentrations of fentanyl in breast milk are low, and lactation may be continued after fentanyl administration. Infants should not be breast-fed for at least 4 hours after midazolam administration. After 4 hours, breast milk should be pumped and discarded before reinitiating breast-feeding. Continued breast-feeding after propofol exposure is not recommended, although the period of prohibition is not known (137).

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