



Gastric and duodenal ulcers during pregnancy

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Peptic ulcer disease (PUD) in pregnancy should be considered separately from PUD in the general population. First, pregnancy seems to alter the clinical presentation and natural history of PUD in that the frequency, symptoms, and complication rate of PUD decrease during pregnancy. Second, diagnostic tests for PUD that are routine in the general population must be carefully evaluated during pregnancy for fetal safety. For example, an upper gastrointestinal series is contraindicated during pregnancy because of radiation teratogenicity [1,2]. Third, pregnancy influences the drug therapy. For example, misoprostol is used for the prophylaxis and treatment of ulcers induced by nonsteroidal anti-inflammatory drugs (NSAIDs) in the general population but is contraindicated during pregnancy. Fourth, ulcer surgery during pregnancy involves consideration of fetal as well as maternal risks.

The apparently decreased severity and frequency of PUD during pregnancy does not decrease the clinical importance of this subject. The incidence of pyrosis markedly increases during pregnancy [3,4]. Clinicians have to know how to treat pyrosis or dyspepsia of undetermined origin, possibly caused by gastroesophageal reflux disease (GERD) or PUD, during pregnancy empirically because of their reluctance to perform invasive diagnostic tests, such as esophagogastroduodenoscopy (EGD), during pregnancy.

A critical review of PUD during pregnancy is needed to establish what is currently known, to outline the unknown, and to stimulate new research. The literature on PUD during pregnancy suffers from a preponderance of case reports and uncontrolled or poorly controlled studies, a preponderance

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of older studies that predate the identification of the etiologic role of *Helicobacter pylori*, and a paucity of studies with endoscopically proven PUD. This article focuses on how the clinical presentation, natural history, medical therapy, and surgical therapy of PUD differ in pregnancy from that in the general population to help the clinician to evaluate, manage, and treat PUD during pregnancy and to stimulate the researcher to study the role of *H pylori* in ulcerogenesis and to perform controlled endoscopic studies during pregnancy.

Epidemiology

The incidence of PUD during pregnancy is estimated from case reports and retrospective clinical series. These estimates are unreliable. The incidence should be determined by performing EGD on a population of pregnant patients. Studies of roentgenographically proven PUD usually include ulcers diagnosed before or after, and not during, pregnancy. Peptic ulcer disease is a chronic, recurrent problem with remissions and exacerbations [5]; postpartum demonstration of PUD does not necessarily imply that the ulcer existed during pregnancy. Moreover, PUD may be underdiagnosed because patients often treat themselves with nonprescription medications and do not seek medical attention for mild to moderate gastrointestinal symptoms, and physicians may attribute symptoms of abdominal pain, pyrosis, or nausea and vomiting to GERD or nausea and vomiting of pregnancy, more common conditions during pregnancy [6].

Nonetheless, multiple epidemiologic studies support a decreased incidence of PUD during pregnancy [7–11]. Sandweiss and colleagues [23] reported one hospitalization for active PUD among 70,310 consecutive hospitalizations of pregnant patients at five Detroit hospitals in a 10-year period. Sandweiss and colleagues also reported gastrointestinal symptoms were present in only 15 (29%) of 52 pregnancies among 25 women of child-bearing age with chronic PUD followed during the 10-year study period. In a 10-year multicenter study, 6 cases of PUD occurred among approximately 149,500 pregnancies in Milwaukee [12]. Baird [13] found only 11 pregnant women with PUD in a literature review encompassing 233,550 deliveries. A study revealed that among 29,317 pregnant patients admitted to three hospitals, 56 hospitalized pregnant patients (0.19%) had severe upper gastrointestinal complaints [14]. Only 2 of the 20 of these patients undergoing EGD had PUD (both had duodenal ulcers). A study of 17,032 women at 17 family planning clinics in England and Scotland from 1968 through 1974 reported a rate of 0.26 peptic ulcers per 1000 pregnant women, as compared with a rate of 0.67 per 1000 nonpregnant women, but this difference was not statistically significant [15].

Risk factors for PUD in pregnant women, as well as in the general population, include smoking cigarettes, advanced age, NSAID use, alcoholism, genetic predisposition, gastritis, and active *H pylori* infection [16–18].

Symptoms

The symptoms of PUD in pregnant women are similar to those in the general population and include epigastric pain, anorexia, postprandial nausea and vomiting, abdominal distention, and eructation. Pain from an ulcer is usually described as a hungry, gnawing, or burning sensation, but some patients experience only epigastric discomfort. Pain from a duodenal ulcer classically occurs several hours postprandially during the day, occurs nocturnally, and is relieved by eating food or ingesting alkali [19]. Many ulcers, particularly gastric ulcers, however, do not produce this classic pattern of pain, and some ulcers are asymptomatic. Old age, recent antiulcer therapy, and use of NSAIDs are associated with asymptomatic ulcers [20]. Between 15% and 44% of ulcers that persist after a course of medical therapy are asymptomatic [21]. About 20% of complicated ulcers manifest without antecedent symptoms [21].

Although pregnant patients have the same ulcer symptoms as other patients, their symptoms tend to be milder. In a classic study published in 1953, the symptoms of PUD were alleviated or resolved during nearly 90% of 344 pregnancies in patients with chronic PUD [22]. This study used a retrospectively administered questionnaire to correlate symptoms with pregnancy and is, therefore, subject to recall bias. In another study, 11 of 25 women with chronic PUD experienced sudden remission of severe ulcer symptoms with the onset of pregnancy [23]. Symptoms recur in about half of patients within 3 months postpartum [24,25].

Pathophysiology

Several theories explain the apparent decrease in the incidence and symptoms during pregnancy. Most theories are speculative and unsubstantiated (Table 1). First, consider the null hypothesis that the reported decreased incidence during pregnancy is an artifact: the reported increase in GERD [3,4], and decrease in PUD during pregnancy might arise from an overdiagnosis of GERD and an underdiagnosis of PUD because of reliance on symptoms for diagnosis without endoscopic confirmation. Peptic ulcer disease may, however, present with pyrosis, and GERD may present with dyspepsia. Moreover, symptoms from PUD may improve with the same therapy used for GERD. The few published endoscopic studies during pregnancy, however, confirm that GERD is increased and PUD is decreased in incidence during pregnancy. In a study of 83 pregnant patients undergoing EGD, 39 (47%) had GERD, and only 6 (7%) had PUD, including 4 duodenal ulcers and 2 gastric ulcers [26]. Similarly, in a mailed survey of 3300 gastroenterologists that gathered information about 73 EGDs during pregnancy, endoscopic findings included GERD in 34% and PUD in only 11% [27,28]. In an older study involving esophagoscopy and gastroscopy

Table 1
Hypotheses why peptic ulcer disease remits during pregnancy^a

Theory	References
Gestational increase in plasma histaminase levels causes a reduced histamine level and gastric hypochlorhydria during pregnancy	[24,32,33]
Hypochlorhydria caused by gestational hyperestrogenemia	[5]
Increased gastric mucus layer caused by gestational hyperprogesteronemia	[45]
Immunologic tolerance during pregnancy might theoretically permit <i>Helicobacter pylori</i> colonization without immunologic attack and mucosal injury	[233]
Elevated epidermal growth factor plasma level during pregnancy stimulates gastroduodenal mucosal growth	[48]
Maternal avoidance of ulcerogenic factors—including cigarette smoking, alcohol, and NSAIDs—during pregnancy	[49,50]
Reduced psychological stress, greater bed rest, and more nutritious diet during pregnancy	[9]

^a All these theories are unproven.

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

in 15 pregnant patients with upper gastrointestinal symptoms, 10 patients (67%) had GERD, and none had gastric ulcers [29]. Duodenal ulcers could not be detected in this study because of failure to intubate the duodenum using the then available, but now obsolete, endoscopic technology. In a second older study, 5 (42%) of 12 pregnant patients with hematemesis had GERD, and none had PUD [30]. In a third older study, 41 of 43 pregnant patients with pyrosis evaluated by esophagoscopy and esophagoscopy biopsy (without gastroscopy or duodenoscopy) had GERD [3]. These two recent and three older endoscopic studies strongly suggest that the null hypothesis should be rejected and that GERD is increased and PUD is decreased in incidence during pregnancy. The increased incidence of GERD during pregnancy is attributed to esophageal dysmotility caused by gestational hormones and gastric compression by the enlarged gravid uterus [6,30,31]. Gastroesophageal reflux disease during pregnancy is reviewed in another article in this issue.

Second, the decrease in the frequency and the symptoms during pregnancy has been attributed to increased plasma histaminase levels during pregnancy caused by placental histaminase synthesis [32]. This histaminase can metabolize maternal histamine and thereby decrease gastric acid secretion during pregnancy [33]. Gastric acid output was not decreased, however, in the presence of high gestational histaminase levels in a study of nine pregnant patients, including two with duodenal ulcers [24].

Third, female gestational sex hormones might cause a decrease in PUD by suppressing gastric acid secretion [34]. Peptic ulcer disease occurs equally frequently in prepubescent girls and boys, as demonstrated in a review of 101 cases in young children [12], but occurs less frequently in adult women

than in men. Johnsen and coworkers [35] reported the lifetime incidence of PUD in adult men was 5.3% compared with 2.1% in adult women [36]. In a review of 408 perforated duodenal ulcers in adults at the Radcliffe Infirmary, men had a 20-fold higher rate than women [5]. These observations led to the hypothesis that estrogen may decrease gastric acidity. Truelove [5] reported that male subjects administered stilbesterol, an estrogen analogue, had significantly fewer clinical relapses of PUD than male controls administered placebo. This study suffered from a lack of endoscopic or radiologic confirmation of PUD recurrence and from an unusually high relapse rate of PUD in the control group. Hunt and Murray [37] reported that gastric acid secretion declines slightly during the first 30 weeks of gestation. Rooney and associates [38] showed a small and statistically insignificant decline in serum gastrin levels during this same period and argued that the lower gastrin level could cause gastric hypochlorhydria during pregnancy.

Contradictory results have been published. In a small study, O'Sullivan and Bullingham [39] reported no significant difference in basal gastric acidity between pregnant women in the third trimester and nonpregnant women. Participating women had no history of PUD. Van Thiel and colleagues [40] also reported no differences in basal or peak gastric acid secretion between pregnant versus postpartum women in a study of four patients. Similarly, dogs do not develop gastric hypochlorhydria during gestation [41]. Two abnormalities that could produce gastric hypochlorhydria, depression of serum gastrin or serum group I pepsinogen levels, do not normally occur during pregnancy [42,43]. These conflicting gastric acid studies suggest that even if pregnancy results in gastric hypochlorhydria, this effect is small and is unlikely to account for the reported large decrease in incidence of PUD during pregnancy.

Fourth, female gestational sex hormones might cause a decrease in PUD by increasing gastric mucus synthesis [44]. Montoneri and Drago [45] found pregnant female rats were resistant to cysteamine-induced gastroduodenal ulcers. This effect might be related to increased mucus synthesis, induced by gestational progesterone, because administering progesterone to nonpregnant female or male rats mimicked this effect.

Fifth, immunologic tolerance during pregnancy, which permits the growth of a fetus that contains foreign antigens, might permit *H pylori* to colonize gastric mucosa without immunologic attack, resulting in reduced gastric inflammation, injury, and symptoms. Immunologic attack against the hepatitis E and poliomyelitis virus is blunted during pregnancy [46,47]. This theory is speculative and unsubstantiated.

Sixth, in a recent experimental study, reported only in abstract form, ulcer healing was attributed to elevated serum epithelial growth factor (EGF) levels during pregnancy. Epithelial growth factor stimulates gastroduodenal mucosal growth. In this study, pregnant rats had accelerated healing of gastroduodenal ulcers that was abolished by sialoadenectomy, which prevented the gestational rise in plasma EGF levels [48].

Seventh, maternal avoidance of ulcerogenic factors—including cigarette smoking, alcohol, and NSAIDs—during pregnancy could contribute to the observed decreased incidence [49,50]. These ulcerogenic factors are generally proscribed and normally avoided during pregnancy because of potential fetal harm. Maternal smoking of cigarettes is correlated, in a dose-dependent pattern, with low neonatal birth weight [51]. Maternal alcoholism is highly associated with the fetal alcohol syndrome [52]. Pregnant women tend to avoid medications because of potential drug teratogenicity.

Eighth, the decreased incidence of PUD during pregnancy has been attributed to reduced psychologic stress, greater bed rest, and a better diet during pregnancy [9]. These factors, however, are currently believed to play only a limited role in PUD.

Other physiologic changes during pregnancy play an important role in promoting GERD but seem to play an insignificant role in preventing PUD during pregnancy. During pregnancy the stomach is displaced rostrally, and the pylorus is displaced posteriorly by the enlarged gravid uterus; intragastric pressure is increased because of gastric compression by the enlarged gravid uterus; and lower esophageal sphincter tone decreases and gastric emptying may be slowed, results believed to be caused by gestational hormones, particularly progesterone [10,53].

Differential diagnosis

The symptoms of PUD are mimicked by other common gastrointestinal problems during pregnancy. The differential diagnosis of dyspepsia or pyrosis of pregnancy includes

- Peptic ulcer disease
- Gastroesophageal reflux disease
- Nausea and vomiting of pregnancy
- Hyperemesis gravidarum
- Pancreatitis
- Acute cholecystitis
- Viral hepatitis
- Appendicitis
- Acute fatty liver of pregnancy (in late pregnancy)
- Irritable bowel syndrome

Gastroesophageal reflux disease is extremely common in pregnancy, particularly in the last trimester [3,4]. The diagnosis of GERD, rather than PUD, is suggested by pain radiating to the neck; pain exacerbated by drinking acidic citrus drinks and by recumbency; symptoms of water brash or regurgitation; and presence of extraintestinal manifestations, including nocturnal asthma, hoarseness, laryngitis, or periodontal disease. About 20% of patients with PUD experience nausea and vomiting. Nausea and vomiting

occurs in 50% to 80% of pregnancies [54,55]. Nausea and vomiting of pregnancy is common in the first trimester of pregnancy and uncommon beyond the twentieth week of gestation, whereas the symptoms of PUD seem to become worse during the third trimester [56]. Nausea and vomiting of pregnancy is classically most intense in the morning, whereas PUD symptoms are most intense nocturnally or postprandially during the day. Hyperemesis gravidarum is a severe and intractable form of nausea and vomiting of pregnancy. It begins early in pregnancy and causes weight loss with dehydration, electrolyte disturbances, or nutritional deficiencies. It has an incidence of about 2 of 1000 pregnancies [6]. It is most common in primigravidas but tends to recur during subsequent pregnancies in patients with prior hyperemesis gravidarum.

Pancreatitis occurs in about 1 of 8000 pregnancies [57]. Pancreatitis, rather than PUD, is suggested by pain exacerbated with eating; pain radiating to the back; presence of leukocytosis or pyrexia; and a history of alcoholism, gallstones, or prior pancreatitis. Levels of serum biochemical parameters of liver function are often elevated with gallstone pancreatitis. Pancreatitis is distinguished from PUD by determination of serum amylase or lipase levels. Pancreatitis is reliably diagnosed when the amylase level is three or more times the normal serum level. Serum amylase and lipase levels are not significantly affected by pregnancy [58,59].

Acute cholecystitis occurs in about 1 of 4000 pregnancies. This diagnosis is favored by a history of fatty food intolerance, right upper quadrant pain, pyrexia, Murphy's sign on physical examination, leukocytosis, and neutrophilia. Abdominal ultrasound evaluation may help distinguish cholecystitis from PUD. Acute viral hepatitis, rather than PUD, is suggested by pain localized to the right upper quadrant, a short history of symptoms, hepatomegaly, jaundice, and elevated levels of serum biochemical parameters of liver function. Acute hepatitis A, B, and C are diagnosed serologically. Appendicitis occurs in approximately 1 of 1500 pregnancies [60]. Appendicitis during pregnancy can cause epigastric or right upper quadrant pain that mimics PUD, because the growing gravid uterus pushes the appendix rostrally during pregnancy [61,62]. Appendicitis, rather than PUD, is suggested by a short 1- to 2-day history of abdominal pain, severe abdominal pain, presence of rebound tenderness, pyrexia, leukocytosis, and neutrophilia.

Acute fatty liver of pregnancy is uncommon. It usually occurs after the thirty-sixth week of gestation and presents early on with abdominal pain, vomiting, and headache [63]. Clinical findings that favor the diagnosis of acute fatty liver of pregnancy, rather than PUD, include hyperbilirubinemia, elevated serum hepatic aminotransferase levels, hyperuricemia, lactic acidosis, and neutrophilia [64]. Before the onset of jaundice, early acute fatty liver of pregnancy may be difficult to differentiate from PUD.

Rarely, a gastric ulcer may be caused by gastric adenocarcinoma or lymphoma. Differentiation of a malignant from a benign gastric ulcer is

considered later. Other diagnoses, including obstetric and gynecologic disorders, may be considered in the differential depending on the clinical presentation. Abdominal pain during pregnancy is reviewed in another article.

Peptic ulcer disease occasionally presents with hematemesis. The differential diagnosis of hematemesis during pregnancy includes GERD or a Mallory-Weiss tear from nausea and vomiting of pregnancy, as well as PUD [26,65].

Diagnosis

Physical examination

The evaluation of a patient with suspected PUD begins with a complete history and physical examination. The type and severity of symptoms should be determined, including agents that exacerbate and relieve symptoms. Past history of NSAID use, alcoholism, and cigarette smoking should be noted. When a patient reports a history of PUD, it is important to inquire about the diagnostic technique, because a symptomatic diagnosis is unreliable.

During the physical examination, the abdominal and rectal examination should be carefully performed, including evaluation of abdominal tenderness, voluntary or involuntary guarding, pitch and frequency of bowel sounds, and presence of fecal occult blood. Uncomplicated PUD tends to produce minimal or no physical signs, whereas complicated PUD frequently produces physical findings as described under the individual complications [66,67]. For example, bleeding from an ulcer can cause fecal occult blood.

Laboratory tests

Standard laboratory tests should be performed, including a hemogram, routine serum electrolytes, serum biochemical parameters of liver function, and serum amylase level. Mild anemia may be caused by physiologic changes in pregnancy of hemodilution produced by gestational hormones and of iron extraction by the developing fetus [68].

Abdominal ultrasound evaluation is useful to exclude cholelithiasis and gallstone pancreatitis. Abdominal roentgenograms are generally relatively contraindicated in pregnancy but are indicated to evaluate suspected intestinal perforation, as described later. An electrocardiogram is indicated when the pain is acute, severe, or substernal, to exclude myocardial ischemia or infarction, even though myocardial infarction is rare in premenopausal women. Urinalysis and urine culture are useful to exclude urinary tract infection.

Diagnostic esophagogastroduodenoscopy

In the general population, an upper gastrointestinal series or EGD is routinely performed for moderate to severe dyspepsia or pyrosis to evaluate

possible PUD. Esophagogastroduodenoscopy, however, is generally preferable to an upper gastrointestinal series because of a higher sensitivity, a higher specificity, and an ability to obtain histologic specimens to test for *H pylori* infection and to exclude malignant gastric ulcer.

An upper gastrointestinal series is contraindicated during pregnancy because of radiation teratogenesis. Radiation is particularly fetotoxic during the first trimester during organogenesis [1,2,69]. Aside from maternal safety, EGD during pregnancy raises the unique issue of fetal safety. Esophagogastroduodenoscopy could potentially cause fetal complications because of medication teratogenicity [70,71], placental abruption or fetal trauma during endoscopic intubation [72], cardiac arrhythmias [73–75], systemic hypertension or hypotension [76], and transient hypoxia [77–79]. The fetus is particularly sensitive to maternal hypotension and hypoxia [80,81].

Several studies suggest that EGD during pregnancy is relatively safe for the fetus and for the pregnant mother. In the largest study, a case-controlled study of 83 EGDs during pregnancy, the mean week of gestation was 20 weeks. Indications for EGD included gastrointestinal bleeding in 37, abdominal pain in 28, vomiting in 14, and other indications in 4 patients [26]. Endoscopic medications included meperidine in 47 patients (mean dose, 57.9 ± 21.0 mg), midazolam in 21 (mean dose, 2.8 ± 1.4 mg), diazepam in 18 (mean dose, 7.1 ± 4.3 mg), and others in 4 patients. Esophagogastroduodenoscopy did not cause any maternal complications. Esophagogastroduodenoscopy did not induce labor. Excluding 6 voluntary abortions and 3 unknown pregnancy outcomes, 70 (95%) of 74 patients delivered healthy infants. Nine infants were born prematurely, of whom one died of severe prematurity. In this study, the 4 bad pregnancy outcomes, including 3 stillbirths or deaths from severe prematurity and 1 involuntary abortion, occurred in high-risk pregnancies and were unrelated to EGD temporally or etiologically. No live-born infant had a congenital malformation noted in the neonatal nursery.

The pregnancy outcome of the 83 pregnant patients undergoing EGD was compared with the pregnancy outcome in an age-matched, racially matched, and hospital-matched control group comprising 48 pregnant patients matched for EGD indications who did not undergo EGD because of the pregnancy. The pregnancy outcome in study patients—including the mean Apgar scores at 1 and 5 minutes postpartum and the frequency of low birth weight, infant deaths, congenital defects, and delivery by cesarean section—was not statistically different from the mean scores or rates in the study controls. For example, 95% of pregnant patients undergoing EGD delivered healthy infants, compared with 94% for the study controls not undergoing EGD. The study patients undergoing EGD had as good a pregnancy outcome as the study controls even though the study patients generally were sicker and had a stronger indication for EGD than the controls [14,26]. This study suggested that EGD is at least as safe as not performing EGD in pregnant patients with a strong indication for EGD.

The study analyzed separately the safety of EGD performed for gastrointestinal bleeding. Excluding 2 unknown pregnancy outcomes and 4 voluntary abortions, the fetal outcome in the 31 patients undergoing EGD for acute bleeding included 30 healthy infants (97%) and 1 stillbirth. Again, this pregnancy outcome was at least as good as that for the pregnant study controls who did not undergo EGD for acute gastrointestinal bleeding.

Similar results were reported in a study of 73 pregnant patients undergoing EGD analyzed by a mailed survey of 3300 gastroenterologists [27,28]. In the mailed survey, 71 (97%) of 73 patients undergoing EGD during pregnancy delivered healthy infants, with 2 miscarriages, at 1 and 5 months after EGD, for reasons unrelated to EGD [27,28]. A mailed survey, however, is subject to recall bias because of the retrospective nature of the study and to selection bias because of voluntary reporting by physicians of endoscopic complications.

Two historical studies further support the safety of EGD during pregnancy. In 1961 McCall and colleagues [29] published a pioneering study on flexible esophagoscopy and gastroscopy (without duodenoscopy) in 15 pregnant patients performed at 5 to 9 months of gestation. All patients received 100 mg of meperidine and 0.4 mg of atropine hypodermically before endoscopy. Fourteen patients (93%) delivered at term. There were 9 spontaneous vaginal deliveries, 5 low forceps deliveries, and 1 cesarean section. Although the study did not specifically address the fetal outcomes, apparently 2 infants had distress at birth: one had a mother with chronic hypertension, and 1 had a mother with hyperemesis gravidarum and hematemesis during pregnancy. Neither neonatal complication seemed to be temporally or etiologically related to EGD. Additionally, no direct maternal or fetal complications from EGD were reported in case reports of 17 pregnant patients undergoing EGD during pregnancy [26,72]. In a study of GERD during pregnancy published in 1967, Castro [3] reported on esophagoscopy and esophagoscopy biopsy performed in 43 pregnant patients from the third to ninth months of gestation. He noted a high rate of endoscopic and pathologic findings of reflux esophagitis in patients with pyrosis but did not specifically report or analyze the safety of esophagoscopy during pregnancy. The safety of endoscopy during pregnancy is considered in detail in another article.

Esophagogastroduodenoscopy is recommended during pregnancy for suspected PUD when symptoms are severe and refractory to intensive medical therapy, when complications including hemorrhage or gastric outlet obstruction occur, or when gastric adenocarcinoma or lymphoma is suspected. The following measures are recommended to improve the safety of EGD during pregnancy: avoidance of diazepam as an endoscopic premedication because of unconfirmed reports of diazepam teratogenicity [71,82,83]; preferential use of meperidine over midazolam as an endoscopic premedication because of a better-documented safety profile [84,85]; restriction of meperidine dosage to 50 mg or less during EGD because fetal sedation is dose-related [86,87]; administration of supplemental oxygen by nasal cannula during EGD to

reduce the likelihood of hypoxia from endoscopic sedation or tube impingement of the airway [77,88]; and maternal monitoring by continuous pulse oximetry and intermittent sphygmomanometry because the fetus poorly tolerates maternal hypoxia or hypotension [80,89]. Fetal cardiac monitoring is often used during abdominal surgery in late pregnancy and should be considered for EGD during late pregnancy to detect fetal distress rapidly [26]. The physician should recognize that meperidine administration during EGD is a common cause of decreased fetal beat-to-beat cardiac variability detected by fetal cardiac monitoring. Although diminished fetal beat-to-beat cardiac variability generally indicates fetal distress, this fetal effect, when produced by a single moderate dose of meperidine, is transient, reversible, and not a poor prognostic indicator [85].

Esophagogastroduodenoscopy should be performed after consultation with an attending obstetrician. Attendance of an anesthesiologist during EGD in a pregnant patient should be considered to monitor the patient closely and to minimize fetal risks from administered endoscopic medications. Esophagogastroduodenoscopy is contraindicated when a patient presents with suspected perforation from a peptic ulcer because endoscopic intubation can convert a contained perforation into a free intraperitoneal perforation, and endoscopic insufflation can promote intraperitoneal spillage of contaminated intestinal contents.

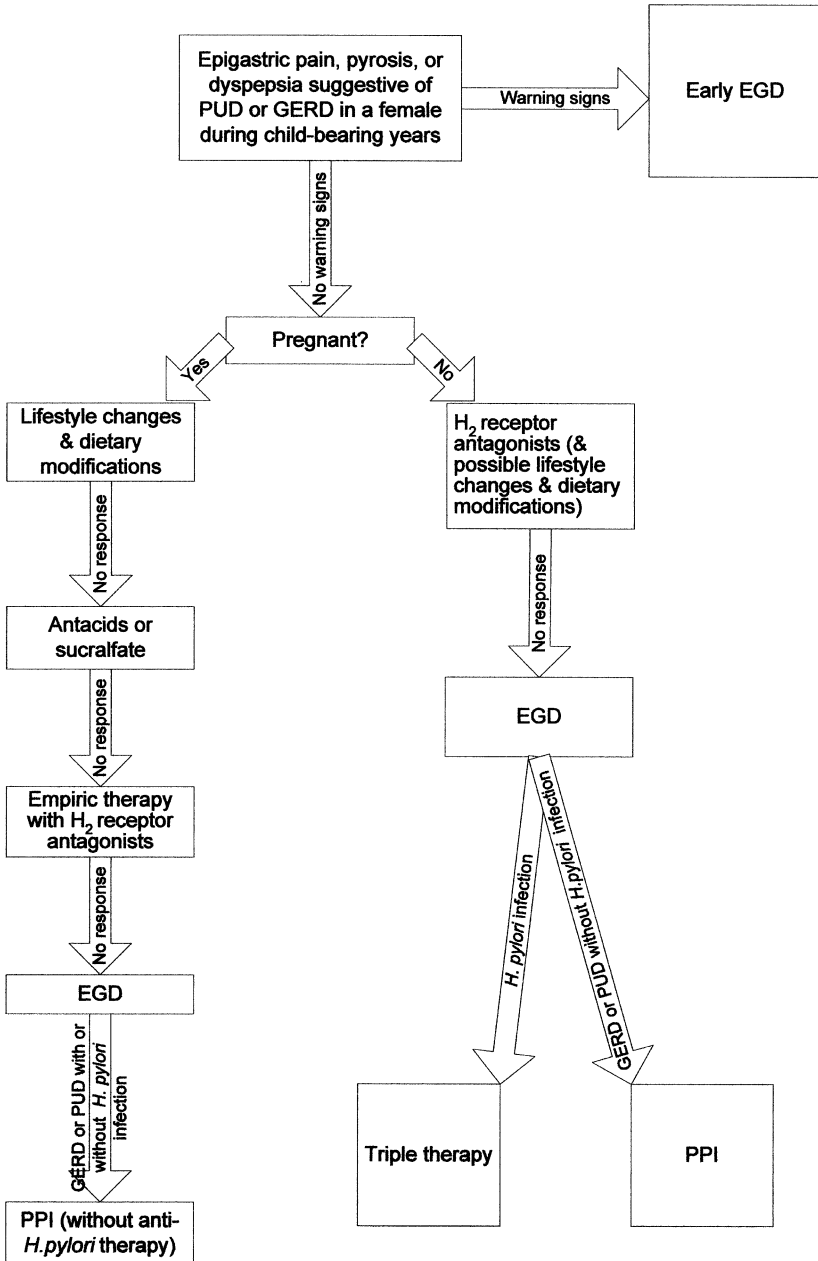
Medical therapy

Lifestyle and diet

The physician often encounters pregnant patients with dyspepsia or pyrosis. Rather than immediately performing invasive diagnostic tests to differentiate between GERD, PUD, or other conditions, it is reasonable to treat the patient empirically with dietary and lifestyle changes and safe drugs (Fig. 1). Fortunately, differentiation between GERD and PUD is not essential before instituting therapy, because symptomatic medical therapy is similar for the two diseases. Only after failure of symptomatic or histamine₂ (H₂) receptor antagonist therapy should the physician consider invasive tests, such as EGD, and proton-pump inhibitor (PPI) therapy during pregnancy. A stepwise therapeutic approach during pregnancy is advisable (Fig. 1) because PPIs have a less-established fetal safety profile than the older, less potent medications, and pyrosis and dyspepsia are usually self-limited during pregnancy.

The patient should receive a normal healthy and nutritious diet. Fatty foods, acidic citrus drinks, caffeine, chocolate, salicylates and other NSAIDs, alcohol, and cigarette smoking should be avoided; other gastrointestinal stimulants or irritants that aggravate the patient's symptoms should be avoided; and stress, anxiety, and nighttime snacks should be avoided [90,91]. Elevation of the head of the bed during recumbency retards

gastroesophageal reflux. When symptoms are refractory to these lifestyle and dietary changes, patients are prescribed the medications described here. The fetal safety of individual drugs is reviewed before considering general recommendations.



Antacids

Antacids are commonly used nonprescription medications in the general population [92]. A meta-analysis of 13 endoscopically controlled studies reported that 75% of duodenal ulcers in the general population healed after 4 weeks of high-dose antacid therapy [93,94]. Ching and Lam [93] found no reports of teratogenic effects of antacids in laboratory animals. Antacids, however, can cause iron malabsorption because gastric alkalinity retards iron absorption. This effect is important, because iron deficiency is common and oral iron supplementation is routine during pregnancy. Antacids should be administered at a different time of day than iron supplements to avoid this drug interaction [95]. Antacids containing bicarbonate are best avoided during pregnancy because they can induce maternal and fetal metabolic alkalosis and fluid overload [49,93]. Magnesium-containing antacids should be avoided at or near term, despite little systemic absorption after oral ingestion, because systemically absorbed magnesium could theoretically cause tocolysis and dystocia [84]. Aluminum-containing antacids seem to be safe during the second and third trimesters of pregnancy because of little systemic absorption [49]. In one study, magnesium trisilicate, or alginate and aluminum hydroxide, relieved pyrosis after 2 weeks in about 50% of pregnant women, without apparent fetal toxicity [96]. One older, retrospective study noted an increase in congenital anomalies following in utero exposure to any antacid during the first trimester, but the association was not statistically significant for any specific antacid [97].

Most antacids are considered safe in pregnancy, particularly magnesium-containing antacids during the second and early third trimesters and aluminum-containing antacids during the second and third trimesters [53,98]. Up to half of pregnant women, therefore, take antacids during late pregnancy for pyrosis or dyspepsia [99]. As in nonpregnant patients, more potent acid-suppressive therapies seem to control these symptoms more effectively during pregnancy [100,101].



Fig. 1. Typical evaluation and treatment algorithm for symptoms suggestive of peptic ulcer disease (PUD) or gastroesophageal reflux disease (GERD) for pregnant versus nonpregnant women of childbearing age. Nonpregnant women are initially treated with potent acid-suppressive medications and undergo early esophagogastroduodenoscopy (EGD) for a definitive diagnosis. Pregnant women are initially treated with less potent medications, lifestyle changes, and dietary modifications because of the better-documented fetal safety profile of these therapies and undergo EGD later in the evaluation, particularly during the first trimester of pregnancy, because of potential slight fetal risks from EGD. The algorithm represents a personal clinical preference, and physicians may reasonably modify this algorithm according to clinical judgment in individual circumstances. Warning signs, including dysphagia, involuntary weight loss, and gastrointestinal bleeding, are indications for early EGD. Triple-drug therapy for *Helicobacter pylori* infection usually includes two antibiotics (or one antibiotic plus bismuth subsalicylate) and one potent acid-suppressive medication. This algorithm omits routine laboratory tests because they are identical for pregnant and nonpregnant women in the evaluation of symptoms. (Abbreviations: H₂, histamine₂; PPI, proton-pump inhibitors)

Sucralfate

Sucralfate, a sulfated polysaccharide complex with aluminum oxide, attaches to the proteinaceous surface of an ulcer and protects the mucosa against further injury by acid, pepsin, and bile salts [102]. Sucralfate also seems to suppress *H pylori* infection [103]. It is an effective therapy for duodenal ulcers. For example, about 75% of acute duodenal ulcers healed after 4 weeks of sucralfate therapy [102].

Orally administered sucralfate is safe in the general population [104]. The potential fetal toxicity of sucralfate comes from its aluminum content: aluminum constitutes about 20% of sucralfate [105]. Parenteral aluminum is fetotoxic: parenteral administration in pregnant laboratory animals caused increased perinatal mortality and impaired memory in surviving pups [106,107]. Parenteral aluminum may also cause osteopenia in premature infants [108] and dialysis-associated encephalopathy and osteodystrophy in uremic patients [105].

Aluminum toxicity arises solely from parental administration, however, and orally administered sucralfate seems to be safe during pregnancy because of negligible absorption of the orally administered aluminum component in sucralfate [105]. Sucralfate is not teratogenic in laboratory animals at doses up to 50 times the maximal recommended dose in humans [109]. Eighty-eight pregnant women exposed to aluminum accidentally added to the water supply had no increase in congenital defects in their offspring, except, perhaps, for an increased rate of talipes (clubfoot) in that 4 infants had this defect (Table 2) [110]. In a surveillance study of pregnant Michigan Medicaid recipients, no teratogenic effects were observed in 183 newborns exposed in utero to sucralfate during the first trimester [84]. Sucralfate was safe, effective, and not teratogenic in a randomized, controlled trial of 66 pregnant patients with heartburn [111]. The Food and Drug Administration (FDA) rates sucralfate as a category B drug during pregnancy [109]. Sucralfate is, therefore, a preferred drug for PUD during pregnancy [112].

Histamine₂ receptor antagonists

Until the discovery of *H pylori* and the introduction of PPIs, H₂ receptor antagonists were the premier therapy for PUD. Drugs in this category have similar actions but differ in bioavailability, pharmacokinetics, and side effects. About 80% of duodenal ulcers in the general population heal after a course of H₂ receptor antagonist therapy [113]. Despite their common use, the safety of H₂ receptor antagonists in pregnancy is inadequately proven (Table 3). All commercially available H₂ receptor antagonists, including cimetidine, ranitidine, famotidine, and nizatidine, cross the human placenta, probably by passive transport [114–117].

Cimetidine

Cimetidine, the first H₂ receptor antagonist, has a good safety profile in the general population. Studies in animals have generally revealed no teratogenicity [109]. For example, studies on pregnant rats and rabbits using high doses revealed no harmful effects in the offspring [109,118,119]. Other investigators, however, reported impairment in sexual development and sexual behavior in male rat offspring because of weak antiandrogenic effects of cimetidine [120,121]. The testes, prostatic glands, and seminal vesicles of male rats decreased in size after in utero exposure to cimetidine [122]. This finding is controversial. Other investigators have reported insignificant effects on sexual development in male laboratory animals after in utero cimetidine exposure [123,124].

In a surveillance study of 229,101 Michigan Medicaid recipients, 20 (4.4%) of 460 newborns exposed to cimetidine in utero during the first trimester had major congenital defects; the frequency of major congenital defects was the same in unexposed infants (Table 3) [84]. In the Swedish Medical Birth Registry study, 2 (5.7%) of 35 infants exposed to cimetidine in utero during early pregnancy had congenital defects [125]. In a large English and Italian study, 11 (4.7%) of 234 infants exposed to cimetidine in utero during the first trimester had congenital malformations, as compared with a rate of 4.1% in unexposed control infants [126]. The relative risk for cimetidine exposure was 1.3 (95% confidence interval [CI], 0.7–2.6). Several small studies report cimetidine administration during pregnancy in humans without adverse fetal effects [99,127].

Cimetidine is frequently administered at term to prevent maternal pneumonia from gastric acid aspiration during delivery; numerous studies demonstrate no adverse fetal effects from administration at term [84]. The manufacturer in postmarketing surveillance of cimetidine has received three isolated reports of congenital defects after in utero exposure, including congenital heart disease, mental retardation, and talipes [84]. One published case report noted a possible association between neonatal hepatitis and cimetidine exposure during the last month of gestation [128], but this finding has not been confirmed [129,130]. Cimetidine might be contraindicated in infants receiving tolazoline for pulmonary hypertension because of a deleterious drug interaction [131]. The FDA rates cimetidine as a category B drug during pregnancy (Table 4) [109].

Ranitidine

Ranitidine was administered to pregnant rats and rabbits at doses up to 160 times the maximal recommended human dose without impaired fertility or fetal harm [132]. In contrast to cimetidine, ranitidine has no demonstrable antiandrogenic activity in laboratory animals or humans [121]. Ranitidine does not adversely affect the sexual functioning of adult male rats after in utero exposure [121].

Table 2
Clinical studies of fetal safety of Anti-*Helicobacter pylori* and miscellaneous drugs used to treat peptic ulcer disease or its symptoms

Drug	First author and year of publication [Reference]	Incidence of major malformations	Database/type of study	Conclusions
Amoxicillin	Heinonen 1977 [168]	Low rate ^a	Collaborative Perinatal Project	Not teratogenic ^a
	Rosa 1993 ^b	317/8,538 (3.7%)	Michigan Medicaid Program	Not teratogenic
Clarithromycin	Schick 1992 [169]	1/21 (4.8%)	Teratogen Information Service	5 unknown fetal outcomes
	Einarson 1998 [170]	3/123 (2.4%)	Prospective controlled multicenter	Unlikely teratogenic
	Jacoby 1999 [171]	0/3	Case reports	Inconclusive
Bismuth subglate	Heinonen 1977 [168]	0/13 (0%)	Collaborative Perinatal Project	Inconclusive
Tetracycline	Rosa 1993 ^b	47/1004 (4.7%)	Michigan Medicaid Program	Known minor teratogen ^c
	Heinonen 1977 [168]	Low rate of major anomalies	Collaborative Perinatal Project	Possibly increased risk of minor malformation (inguinal hernia)
Metronidazole	Beget 1972 [184]	Low rate	Case series of 20 years experience	Not teratogenic
	Rosa 1987 [185]	63/1,083 (5.9%)	Michigan Medicaid Program	Not teratogenic
	Rosa 1993 ^b	100/2445 (4.1%)	Michigan Medicaid Program	Not teratogenic
	Piper 1993 [186]	96/1318 (7.3%)	Tennessee Medicaid Program	Not teratogenic
	Czeizel 1998 [187]	CCS	Hungarian case controlled study	Not teratogenic
	Sorensen 1999 [188]	CCS	Danish cohort study	Not teratogenic
	Beard 1979 [189]	5/20 (25%)	Mayo Clinic study	Inconclusive ^d
	Heinonen 1977 [168]	4/31 (12.9%)	Collaborative Perinatal Project	Inconclusive
Misoprostol ^e	Fonseca 1991 [198]	5/5	Case reports of rare cranial defect	Teratogen
	Gonzalez 1993 [199]	12/12	Case reports-vascular disruption defects	Teratogen
	Pastuszak 1998 [200]	CCS	Causes Mobius' syndrome	Teratogen
	Gonzalez 1998 [201]	CCS	Causes vascular disruption anomalies	Teratogen
	Vargas 2000 [202]	CCS	Causes vascular disruption anomalies	Teratogen
	Orioli 2000 [204]	CCS	Causes vascular disruption anomalies	Teratogen

Simethicone	Rosa 1993 ^b	14/248 (5.6%)	Michigan Medicaid recipients	Unlikely teratogen
Sucralfate (oral aluminum)	Golding 1991 [110]	4/88 (4.5%)	Aluminum exposure in water supply	Unlikely teratogen
	Rosa 1993 ^b	5/183 (2.7%)	Michigan Medicaid Program	Not teratogenic
	Ranchet 1990 [111]	low risk	Prospective controlled trial	Unlikely teratogen

^a For all penicillin derivatives.

^b As cited by Briggs et al, 2002 (84).

^c Causes minor congenital defect of yellow-brown staining of teeth and may rarely cause maternal fatty liver.

^d Possible confounding genetic factors.

^e Misoprostol is a known abortifacient.

Abbreviation: CCS, case-control study, in which the rate of drug exposure in infants with congenital defects is compared with the rate of drug exposure in healthy infants.

Table 3
Clinical studies of fetal safety of histamine₂ receptor antagonists and proton-pump inhibitors

Drug	First author and year of publication [Reference]	Rate of major malformations	Database/type of study	Conclusions
<i>Histamine₂ receptor antagonists</i>				
Cimetidine	Rosa 1993 ^a	20/460 (4.3%)	Michigan Medicaid recipients	Not teratogenic
	Kallen 1998 [125]	2/35 (5.7%)	Swedish medical birth registry	Unlikely teratogenic
Ranitidine	Ruigomez 1999 [126]	11/234 (4.7%)	British and Italian databases	Unlikely teratogenic
	Rosa 1993 ^a	23/516 (4.5%)	Michigan Medicaid recipients	Not teratogenic
	Kallen 1998 [125]	6/156 (3.8%)	Swedish medical birth registry	Not teratogenic
	Magee 1996 [133]	3/142 (2.1%)	Teratology Information Service	Not teratogenic
Famotidine	Ruigomez 1999 [126]	20/330 (6.1%)	British and Italian databases	Not teratogenic
	Rosa 1993 ^a	2/33 (6.1%)	Michigan Medicaid recipients	Unlikely teratogenic
<i>Proton-pump inhibitors</i>				
Omeprazole	Kallen 1998 [125]	8/262 (3.1%)	Swedish medical birth registry	Not teratogenic
	Lalkin 1998 [154]	4/78 (5.1%)	Multicenter prospective controlled	Unlikely teratogenic
	Nielsen 1999 [156]	3/38 (7.9%)	Danish prescription and birth registry	Inconclusive
	Brunner 1998 [155]	0/9 (0%)	Clinical series	Unlikely teratogenic
	Ruigomez 1999 [126]	5/139 (3.7%)	British and Italian databases	Not teratogenic
Lansoprazole	Wilton 1998 [157]	0/6 (0%)	British observational cohort study	Inconclusive
	Kallen 1998 [125]	2/13 (15.4%)	Swedish medical birth registry	Inconclusive
	Nielsen 1999 [156]	3/38 (7.9%)	Danish prescription and birth registry	Inconclusive

^a As cited by Briggs et al, 2002 [84].

Table 4
Fetal safety of medications used to treat peptic ulcer disease

Drug	FDA pregnancy category	Comments
Antacids	Unrated	Generally safe, see discussion
Simethicone	C	
Sucralfate	B	
Histamine ₂ receptor antagonists		
Cimetidine	B	
Ranitidine	B	
Famotidine	B	
Nizatidine	B	
Proton-pump inhibitors		
Omeprazole	C	
Lansoprazole	B	
Rabeprazole	B	
Pantoprazole	B	
Esomeprazole	B	
Misoprostol	X	Abortifacient and teratogen ^a
Drugs active against <i>Helicobacter pylori</i>		
Amoxicillin	B	
Clarithromycin	C	
Bismuth subsalicylate	C	
Tetracycline	D	Causes yellow-brown staining of neonatal teeth
Metronidazole	B ^b	

FDA category definitions [257]:

B—Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

C—Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

D—There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

X—Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

^a Causes congenital malformations because of vascular reduction, including Mobius' syndrome and limb reduction.

^b American College of Obstetricians and Gynecologists discourages use of drug during the first trimester.

Abbreviation: FDA, Food and Drug Administration.

In a study of 229,101 pregnant Michigan Medicaid recipients, no teratogenic effects were attributed to ranitidine in 516 newborns exposed in utero during the first trimester [84]. In a prospective study, 3 of 142 infants exposed to H₂ receptor antagonists in the first trimester, of whom 71% were exposed to ranitidine, had congenital defects, a rate similar to that in an unexposed control group [133]. In this drug trial, however, the H₂ receptor antagonist exposure was very brief, with a duration as short as 1 week [134]. In the Swedish Medical Birth Registry study, 6 (3.8%) of 156 infants exposed in utero to ranitidine had congenital defects, for an odds ratio of about 0.9 as compared with unexposed control infants [125]. In a study of English and Italian databases, 20 (6.1%) of 330 infants exposed in utero to ranitidine had congenital malformations, as compared with a risk of 4.1% in nonexposed control infants, for an odds ratio of 1.5 (95% CI, 0.9–2.6) [126]. No adverse neonatal effects were attributed to ranitidine after maternal ranitidine administration during labor to prevent maternal aspiration of gastric acid during delivery [135,136]. Ranitidine is rated a class B drug during pregnancy.

Famotidine

Famotidine is a more potent H₂ receptor antagonist than cimetidine or ranitidine. No significantly impaired fertility or fetal harm was found in studies of high-dose administration of famotidine in laboratory animals [119,137,138]. The manufacturers, however, report sporadic abortion occurring in pregnant rabbits subjected to decreased food intake and administered 250 times the maximal recommended human dose. Famotidine lacks antiandrogenic activity in man [139].

In a surveillance study of 229,101 pregnant Michigan Medicaid recipients, 2 (6.1%) of 33 newborns whose mothers had taken famotidine during the first trimester had congenital defects, as opposed to 1 expected [84]. The exposed population is too small to draw any conclusions. Famotidine is rated a category B drug during pregnancy [109].

Nizatidine

No fetal harm occurred after pregnant rats received 40 times the recommended maximal human dose and pregnant rabbits received 15 times the maximal recommended human dose of nizatidine [140]. Nizatidine does not seem to have antiandrogenic effects such as those observed with cimetidine in male laboratory animals [141,142], or humans [143]. One woman exposed to nizatidine during the early second trimester delivered a healthy male infant [84]. A literature review revealed no other cases of nizatidine use during pregnancy in humans. Nizatidine is rated a category B drug during pregnancy [109].

Proton-pump inhibitors

Proton-pump inhibitors effectively suppress gastric acid secretion by inhibiting the H⁺, K⁺-ATPase on the surface of the parietal cell. Five PPIs

are currently available: omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole. These agents are highly effective in the treatment of reflux esophagitis, erosive esophagitis, and gastroduodenal ulcers [144] and are often incorporated into a multidrug regimen for eradication of *H pylori* infection [145]. Omeprazole crosses the placenta to the fetus [84]. The other PPIs are also likely to cross the placenta because their chemical structure and molecular weight are similar to omeprazole [84]. Although PPIs are probably safe during pregnancy, their safety is currently unproven because of scant clinical data (see Table 3).

Omeprazole

Omeprazole crosses the placenta in sheep [146], and humans [147]. Animal reproductive studies using 172 times the maximal recommended human dose in rabbits and 345 times the maximal recommended human dose in rats revealed no teratogenicity, but embryoletality, fetal resorption, and pregnancy disruptions were found in both species [84,109].

In multiple human studies, oral administration of omeprazole during labor to prevent aspiration of gastric acid during delivery was safe and effective in the mother, without neonatal teratogenicity [147–152].

In the Swedish Medical Birth Registry study, 8 (3.1%) of 262 infants exposed to omeprazole in utero during early pregnancy had congenital defects [125]. A more recent and larger study from the same registry confirmed this finding of no drug teratogenicity [153]. In a prospective, controlled study, 4 (5.1%) of 78 infants with first trimester in utero exposure to omeprazole had congenital anomalies, as compared with 2 (3.0%) of 66 control infants exposed to nonteratogenic agents such as dental radiation or acetaminophen [154]. In another study, all nine infants whose mother had taken omeprazole during pregnancy were born without complications or congenital abnormalities [155]. Three (7.9%) of 38 infants exposed in utero to omeprazole during the first trimester had major congenital anomalies, including 2 cardiovascular anomalies, in a Danish study linking a prescription database with a birth registry [156]. Exposed infants had a relative risk of 1.6 of congenital malformations compared with a control group of infants whose mothers had not obtained a prescription during gestation. In a study of English and Danish databases, five (3.7%) of 139 infants whose mothers had taken omeprazole during pregnancy had congenital malformations [126]. The relative risk of congenital malformations was 0.9 as compared with infants whose mothers had no drug exposure during pregnancy.

Most case reports and small clinical series likewise support fetal drug safety. In an English study four of four infants exposed to omeprazole during the first trimester were delivered at term without congenital anomalies [157]. Several pregnant women received omeprazole early in pregnancy and delivered healthy infants [158–160]. In addition, one infant whose mother received omeprazole during the third trimester had transient bradycardia

at birth that eventually resolved with normal neurologic development at 1 year of age [161]. Eleven isolated congenital abnormalities, including anencephaly in 4 infants, have been reported to the FDA after in utero exposure to omeprazole [84]. One woman had two consecutive terminations of pregnancy for congenital malformations of anencephaly or talipes after gestational use of omeprazole [162]. The accumulated data indicate that omeprazole is not teratogenic when administered at term, but fetal safety of drug administration during early pregnancy is not established [163]. Omeprazole is rated a category C drug during pregnancy because of embryotoxicity, without teratogenicity, in laboratory animals [109].

Lansoprazole

Teratology studies performed in pregnant rats at 40 times the maximal recommended human dose and in pregnant rabbits at 16 times the maximal recommended human dose revealed no evidence of fetal harm from lansoprazole [109,164].

In an English study, none of six newborns whose mothers had taken lansoprazole during the first trimester had congenital malformations [157]. In the aforementioned Swedish Medical Birth Registry study, 2 of 13 infants exposed in utero in early pregnancy to lansoprazole had congenital defects [35]. In the aforementioned Danish study linking a prescription database with a birth registry, 3 (7.9%) of 38 infants exposed to omeprazole or lansoprazole in utero during the first trimester had birth defects, but the specific drug exposure was not delineated [156]. Lansoprazole is rated a category B drug during pregnancy [109].

Rabeprazole

Pregnant rats exposed to 13 times the recommended maximal human dose and pregnant rabbits exposed to 8 times the recommended maximal human dose of rabeprazole experienced no impaired fertility, and no fetal harm or teratogenicity occurred in their offspring [109]. Briggs and coworkers [84] found no reports of human exposure during pregnancy in a careful recent literature review. The drug is rated as category B during pregnancy [109].

Pantoprazole

No evidence of fetal harm or teratogenicity was found from in utero exposure to 88 times the recommended maximal human dose of pantoprazole in pregnant rats and to 16 times the recommended maximal human dose in pregnant rabbits [109]. Briggs and coworkers [84] found no reports of human exposure during pregnancy in a careful recent literature review. The drug is rated as category B during pregnancy [109].

Esomeprazole

Esomeprazole is the *S*-isomer of omeprazole, a drug that is a racemic mixture of both isomers. It is theoretically more attractive than omeprazole

because it exclusively contains the therapeutically active *S*-isomer without the inactive isomer. Administration of 57 times the maximal recommended human dose in rats and of 35 times the maximal recommended human dose in rabbits revealed no impaired fertility or teratogenicity [109]. Although clinical information about drug safety during pregnancy is lacking, data are available on the closely related drug of omeprazole, as discussed previously. The FDA rates the drug as category B during pregnancy [109].

Drugs active against Helicobacter pylori

In the general population multidrug (often three-drug) therapy, using antibiotics and acid suppressive drugs, is administered for *H pylori* infection associated with duodenal ulcers or causing symptoms because of concern about long-term risks of ulcer relapse and gastric cancer from this infection. The risk of ulcer relapse is much lower after *H pylori* eradication than after conventional acid suppressive therapy [165].

Amoxicillin

Amoxicillin is a penicillin antibiotic. Administration in pregnant mice and rats of 10 times the maximal recommended dose in humans was not teratogenic [109]. A single large dose of amoxicillin has been extensively prescribed to treat bacteriuria during pregnancy without reported teratogenicity [166,167]. In the Collaborative Perinatal Project, no increase in congenital malformations was reported among 3546 first-trimester exposures to penicillin derivatives [168]. In a surveillance study of Michigan Medicaid recipients, 317 (3.7%) of 8538 infants with first-trimester in utero exposure to ampicillin had major birth defects, a rate slightly lower than that in unexposed infants [84]. Amoxicillin seems to be a relatively safe antibiotic during pregnancy and is rated a category B [109].

Clarithromycin

Clarithromycin is a macrolide antibiotic closely related to erythromycin. Four studies in pregnant rats exposed to one to two times the maximal recommended human dose and two studies in pregnant rabbits exposed to two times the maximal recommended human dose revealed no teratogenicity [109]. Two other studies, however, demonstrated a small increase in cardiovascular anomalies in another rat strain administered one to two times the maximal recommended human dose [109]. Pregnant monkeys receiving a dose producing twice the maximal recommended human serum levels exhibited fetal growth retardation.

A teratogen information service reported in an abstract only 1 minor congenital malformation among 21 newborns exposed to clarithromycin during pregnancy, but 5 pregnancy outcomes after prenatal exposure were unknown and unreported [169]. In a prospective, controlled multicenter study, 22 spontaneous abortions and 3 major congenital malformations

occurred among 122 women exposed to clarithromycin during pregnancy, as compared with 11 spontaneous abortions and 2 major congenital malformations among an equal number of matched pregnant controls [170]. Three pregnant women received clarithromycin in a multidrug regimen with successful eradication of *H pylori* infection and with normal pregnancy outcomes [171]. The FDA received six isolated reports of diverse congenital malformations after clarithromycin exposure during pregnancy [84]. Clarithromycin is classified a category C drug during pregnancy [109].

Bismuth subsalicylate

Bismuth subsalicylate is hydrolyzed in the gastrointestinal tract to inorganic bismuth salts and salicylate. Orally administered bismuth may not be teratogenic because of negligible systemic absorption [172]. Bismuth was not teratogenic in a chick embryo model [119]. Chronic administration of bismuth tartarate to four pregnant ewes yielded one stunted, hairless, and exophthalmic newborn lamb, however [173]. In the Collaborative Perinatal Project, 144 infants were exposed in utero to bismuth subgallate, including 13 in the first trimester, without evident teratogenicity, except perhaps for a small increase in the number of inguinal hernias [168].

The salicylate moiety, however, is mostly absorbed after bismuth subsalicylate ingestion. Salicylates readily cross the placenta [174]. Aspirin, a related salicylate, can cause intracranial hemorrhage when administered near term, probably because of aspirin-induced platelet dysfunction [175], but other salicylates that do not induce platelet dysfunction may lack this toxic effect. Aspirin also promotes premature closure of the ductus arteriosus because it inhibits prostaglandin synthetase [176]. Excessive aspirin use near term can also cause premature births and salicylate intoxication in the newborn [175,177].

Bismuth subsalicylate is rated a category C drug during pregnancy. Although the bismuth moiety of orally administered bismuth subsalicylate presents little theoretic therapeutic risks, data from clinical studies of bismuth are lacking, and the salicylate moiety has theoretic fetal risks, especially when administered in high doses and near term [84].

Tetracycline

Tetracycline crosses the placenta to the fetal circulation [178]. Tetracycline administration during the second half of pregnancy results in yellow-brown staining of newborn teeth resulting from chelation of tetracycline with calcium orthophosphate during the growth of bones and teeth [179]. Tetracycline administration during pregnancy can also cause maternal fatty liver with maternal jaundice [180]. In a surveillance study of 229,101 Michigan Medicaid recipients, 47 (4.7%) of 1004 infants exposed to tetracycline during the first trimester had major congenital defects, about the same as the rate of 4.3% in nonexposed controls [84]. In the Collaborative Perinatal Project in which 341 infants had in utero exposure to tetracycline during the first trimester, tetracycline was not associated with major congenital malformations, but

the rate of minor congenital malformations, such as inguinal hernia, was possibly increased [168]. Four cases of congenital cataracts have been reported in association with tetracycline use during pregnancy or lactation [181]. Tetracycline is rated a category D drug during pregnancy because of the risks of staining of the neonatal teeth and maternal hepatotoxicity. Alternative antibiotics with greater fetal safety are preferred during pregnancy.

Metronidazole

Metronidazole crosses the placenta to the fetus [182]. No fetal harm was observed after administration of up to five times the maximal recommended human dose to pregnant rats [109]. The drug has been analyzed for possible carcinogenicity in humans because it is mutagenic in bacteria and carcinogenic in rodents [84]. In a retrospective cohort study of 328,846 children, 175 residents of Tennessee had developed cancer before age 5 years. The relative risk after in utero exposure to metronidazole was 0.81 for any cancer in these children [183].

Most studies suggest that metronidazole does not cause congenital malformations. In a 1972 review of 1469 pregnant women exposed to metronidazole, including 206 with first trimester exposure, metronidazole was not associated with stillbirths or congenital malformations [119,184]. In the Michigan Medicaid program from 1980 to 1983, 63 of 1083 infants exposed in utero to metronidazole during the first trimester had a congenital defect, for a relative ratio of 0.92 compared with unexposed controls [185]. Furthermore in the same program from 1985 to 1992, 100 (4.1%) of 2445 infants exposed to metronidazole during the first trimester had congenital defects, for a relative risk of 0.97 compared with unexposed controls [84]. Similar evidence of fetal safety was reported in the Tennessee Medicaid Program study [186], the Hungarian Case-Control Surveillance of Congenital Abnormalities study [187], and a Danish study [188].

Two studies, however, raise some concern about general congenital defects. Among 20 births after in utero exposure to metronidazole during the first trimester, 5 congenital malformations occurred, but this study is inconclusive because of the small study population and confounding genetic factors [189]. Also, in the Collaborative Perinatal Project involving 50,282 deliveries, 4 of 31 infants with first-trimester exposure had congenital malformations [168]. Moreover, two studies raise concern about specific fetal risks. The aforementioned Hungarian study [187] noted a possible association of metronidazole exposure with cleft lip or cleft palate. The aforementioned Tennessee study of pediatric cancers noted a 2.60 relative risk for neuroblastoma, but this increased risk was not statistically significant [183].

In summary, most data suggest that metronidazole presents negligible or no fetal risk. The drug is rated a category B during pregnancy, but use during the first trimester is discouraged because a few studies suggest a possibly increased risk of congenital defects and because of an unsubstantiated association with neuroblastoma and cleft lip or palate [190].

Simethicone

Simethicone is a silicon product available without prescription that foams and disperses gas bubbles that accumulate in the gastrointestinal tract. Simethicone is incorporated as part of several popular antacids formulations to relieve the symptoms of abdominal distention, eructation, and dyspepsia that occur with PUD. In a surveillance study of 248 newborns exposed to simethicone during the first trimester, 14 major congenital defects were observed, as compared with 11 expected [84]. This small observed increase was not statistically significant and probably resulted from chance. In a study of 41 neonates, no neonatal complications were attributed to maternal administration of simethicone and antacids 2 hours before elective cesarean section [129]. Briggs and colleagues [84] classify simethicone as a category C drug during pregnancy (Table 4). Although simethicone is probably safe during pregnancy, antacids without simethicone are preferred to treat PUD during pregnancy.

Prostaglandin analogues

Misoprostol, a synthetic prostaglandin E₁ analogue with antisecretory and cytoprotective properties, is approved by the FDA for use in the general population to prevent gastric ulcers in high-risk patients taking NSAIDs. In other countries, this drug is also used to treat idiopathic PUD. The FDA rates misoprostol as a category X drug during pregnancy because it is an abortifacient in humans [99,109]. It produces uterine contractions that can cause uterine bleeding or abortion. Ironically, misoprostol is not mutagenic, teratogenic, or fetotoxic in rats and rabbits at doses much higher than those used in humans [109]. In a study in which misoprostol or placebo was administered to 111 women before planned elective abortion, 6 (11%) of 56 women receiving misoprostol spontaneously aborted within 1 day of drug administration, compared with none among 55 controls receiving placebo [99]. Moreover, 45% of patients receiving misoprostol experienced menorrhagia as compared with 4% receiving placebo [191]. Misoprostol in combination with mifepristone has been used to induce legal [192] and illegal abortion [193]. For example, 18 of 21 women had a complete abortion after administration of 200 to 1000 µg misoprostol and 200 mg mifepristone [192]. This effect was subsequently confirmed in a large clinical trial [194] and in other studies [195]. One case of amniotic fluid embolism, which resulted in maternal and fetal death, was associated with misoprostol administration [195]. Misoprostol administration as an abortifacient can induce heavy vaginal bleeding [196,197].

Misoprostol is also teratogenic. Five infants have been reported with a rare cranial defect of a unilateral circumscribed loss of a patch of cranium and scalp exposing the dura mater after in utero exposure to misoprostol [193,198]. In a surveillance study of Michigan Medicaid recipients involving 229,101 pregnant patients, one of five newborns who had been exposed in

utero to misoprostol during the first trimester had a major birth defect, a cardiac anomaly [84]. A study published in 1993 reported 12 cases of either limb defects or Mobius' syndrome (sixth or seventh nerve palsies) after first-trimester exposure to misoprostol [199]. In a matched case-controlled study, misoprostol was used in 47 (49%) of 96 cases of Mobius' syndrome as compared with 3 (3%) of 96 cases of neural tube defects, for an odds ratio of 29.7 (95% CI, 11.6–76.0) [200]. This high relative risk of Mobius' syndrome has been confirmed [201,202]. Even though the relative risk of Mobius' syndrome is increased 30-fold by misoprostol administration, the absolute risk is still only 1 in 1000 [203]. Misoprostol is believed to cause vascular disruption and cell necrosis because of uterine contractions that deform the fetus and compress fetal blood vessels [84]. Several studies have implicated in utero exposure to misoprostol with other congenital defects associated with vascular disruption, including limb reduction and limb constriction [202,204].

Enprostil is a prostaglandin E₂ analogue not commercially available in the United States. Administration of two doses of enprostil, using twice the usual clinical dosage, did not lead to any abortions within 4 hours after drug administration in a prospective, randomized, placebo-controlled study of 207 women [205]. This study, however, does not preclude a delayed abortifacient effect after prolonged drug administration because patients received only two doses of the drug and were followed for only 4 hours after receiving the second dose, at which time they underwent elective termination of pregnancy. Moreover, in this study, vaginal bleeding occurred in 4% of pregnant patients receiving enprostil as compared with 2% of placebo-treated pregnant patients. In an unpublished study, low-dose enprostil administration did not induce abortion in 100 pregnant women [163]. Prostaglandin analogues are currently contraindicated during pregnancy because of potential abortifacient and teratogenic effects. Physicians should advise women in their childbearing years who take prostaglandin analogues to use effective contraception and to cease taking prostaglandin analogues if they desire pregnancy.

Recommendations for drug therapy during pregnancy

In the general population treatment with PPIs is instituted early and aggressively for documented reflux esophagitis and PUD because of high efficacy and great patient safety. Histamine₂ receptor antagonists are a useful secondary medication, and antacids and sucralfate are useful for symptomatic relief.

In the pregnant patient, therapeutic recommendations are modified because of concerns about fetal safety: drugs with less maternal efficacy are substituted because of better-documented fetal safety (Fig. 1). This principle applies especially to PUD, a generally mild disease during pregnancy. After instituting dietary and lifestyle modifications, pregnant patients are prescribed antacids and sucralfate for dyspepsia or other symptoms of PUD. Antacids containing aluminum and magnesium are recommended during

pregnancy, but magnesium-containing antacids should be avoided near term. Recommended doses of antacids are 15 to 30 mL 1 hour after meals and at bedtime. Patients with severe symptoms can take extra doses 3 hours after meals. Sucralfate is a fine alternative to antacids because of apparent safety during pregnancy. When symptoms are refractory to these therapies, H₂ receptor antagonist therapy is recommended. Histamine₂ receptor antagonists seem to be fairly safe during pregnancy, but their safety is incompletely unproven. Ranitidine is currently the H₂ receptor antagonist of choice during pregnancy: it is preferred over cimetidine because of a theoretic concern about the antiandrogenic effects of cimetidine to the male fetus and is preferred over famotidine and nizatidine because of a much better-documented safety profile in humans. If symptoms persist, institution of PPI therapy is considered. Although PPIs seem to be safe in pregnancy, their safety is unproven because of insufficient data. Currently, lansoprazole is the PPI of choice during pregnancy, because high doses of omeprazole can be lethal to embryos in laboratory animals, and clinical data are unavailable for the newest PPIs. The clinical data on most PPIs during pregnancy are sketchy, however, and prescribing recommendations will be reevaluated as more clinical studies are published. Esophagogastroduodenoscopy should be considered before instituting PPI therapy for refractory symptoms to obtain a precise diagnosis.

Administration of triple-drug therapy, including antibiotics, to eradicate *H pylori* infection is generally discouraged during pregnancy and should be deferred until postpartum because of the low risk of complications from untreated PUD during pregnancy, the usual short-term success of acid-suppressive therapy in controlling PUD, and the potential fetal risks of antibiotics. During pregnancy, the fetal risks from antibiotics are avoided by ulcer treatment with a single conventional antiulcer drug, such as an H₂ receptor antagonist or PPI, with deferral of definitive multidrug therapy until postpartum. Multidrug therapy to eradicate *H pylori* infection associated with a mucosa-associated lymphoid tissue tumor (MALToma) is, however, potentially life-saving and should be administered promptly during pregnancy [206]. The recommended antibiotics to eradicate *H pylori* infection during pregnancy include amoxicillin and clarithromycin or metronidazole. Tetracycline is relatively contraindicated, and misoprostol is absolutely contraindicated during pregnancy. The FDA drug recommendations during pregnancy are summarized in Table 4.

Complications

About 10% of patients with PUD in the general population develop complications of hematemesis, penetration, perforation, or gastrointestinal obstruction. Complications occur infrequently during pregnancy [6,9,207]. Fewer than 100 cases of complicated PUD have been reported during pregnancy [19,208]. Complications that do occur generally occur in the third trimester [25,208] and are associated with eclampsia [50].

Gastric outlet obstruction occurs in about 2% of peptic ulcers in the general population. Obstruction most commonly occurs at or near the pylorus where the lumen is narrowest but can occur at the apex of the bulb. The obstruction can be functional because of impaired motility from mural inflammation and edema or can be mechanical because of scarring. Symptoms include nausea, vomiting, and abdominal pain. Signs include high-pitched bowel sounds, hypoactive bowel sounds, abdominal distention, a succussion splash, and visible peristalsis. Nausea and vomiting from PUD occasionally produces fluid and electrolyte disorders, including hypovolemia, contraction alkalosis, hypokalemia, and hyponatremia [209]. Gastric outlet obstruction should initially be treated with intense medical therapy because functional obstruction remits with resolution of antral inflammation and edema. Medical therapy includes cessation of enteral feeding, nasogastric aspiration to prevent pulmonary aspiration, intravenous fluid hydration with total parenteral nutrition, and potent intravenous acid-suppressive therapy. Mechanical obstruction from scarring generally fails to remit with medical therapy and requires endoscopic balloon dilation or surgery.

Ulcer perforation is rare during pregnancy. Burkitt [210] found only three cases during a 10-year period reported in the English literature. Clinical findings include severe abdominal pain, nausea, vomiting, pyrexia, dehydration, direct abdominal tenderness, rebound tenderness, involuntary guarding, abdominal rigidity, hypoactive bowel sounds, hypotension, leukocytosis, neutrophilia, and increased immature leukocyte forms [211,212]. An abdominal roentgenogram should be performed for suspected gastrointestinal perforation to assess for the presence of pneumoperitoneum because the maternal and fetal benefits from prompt diagnosis and therapy of a perforation clearly outweigh the fetal risks of teratogenicity from a single set of roentgenograms [2,211–213]. Two plain abdominal roentgenograms expose the fetus to about 500 mrad, a level associated with an extremely low risk of congenital malformations [2,213]. Esophagogastroduodenoscopy is contraindicated when gastrointestinal perforation is suspected. Perforation mandates surgery, either patch closure or partial gastrectomy, depending on the operative and clinical findings [211]. Early surgery improves the maternal and fetal prognosis [214].

Acute gastrointestinal bleeding presents with melena, hematemesis, or bright red blood from the rectum. Hypotension, tachycardia, and significant orthostatic changes in blood pressure or pulse indicate hemodynamically significant bleeding that can cause fetal distress. Maternal normotension does not, however, guarantee fetal well-being [89]. Anemia may be caused by the physiologic anemia of pregnancy, as a result of increased intravascular volume produced by gestational hormones and fetal extraction of serum iron [68], as well as by gastrointestinal blood loss. When melena occurs without hematemesis, aspiration of gastric contents helps differentiate between upper and lower gastrointestinal bleeding. Nasogastric aspiration is also important before EGD to prevent pulmonary aspiration during EGD and to clear the

endoscopic field. The actively bleeding pregnant patient should be placed in the left lateral decubitus position because in the supine position the enlarged gravid uterus compresses the inferior vena cava, decreases venous return, and decreases uterine perfusion [68]. The patient with gastrointestinal bleeding should receive a large-bore intravenous line, receive no enteral nutrition, and have blood typed and crossed. Intravenous fluid, including transfusions of packed erythrocytes when indicated, should be aggressively administered in acutely bleeding pregnant patients because of the extraordinary fetal sensitivity to placental hypoperfusion, the difficulty in assessing volume status during pregnancy, and the usually satisfactory cardiac function of pregnant patients. Esophagogastroduodenoscopy should be performed for clinically significant upper gastrointestinal bleeding, requiring transfusion of packed erythrocytes or causing hemodynamic instability [26].

Therapeutic endoscopy

Therapeutic EGD is useful in the general population to stop acute bleeding or to prevent rebleeding from ulcers at high risk of rebleeding, such as ulcers containing stigmata of recent hemorrhage [215]. Little information is known about the risks of endoscopic hemostasis for PUD during pregnancy. Four patients underwent therapeutic EGD during pregnancy, including endoscopic thermocoagulation of a bleeding duodenal ulcer in one patient [26], endoscopic sclerotherapy for bleeding esophageal varices in two patients [26,216], and endoscopic sclerotherapy for bleeding from a Mallory-Weiss tear in one patient [217]. Three of the women delivered healthy infants; the fourth pregnancy was reported as uncomplicated, but the infant's health was not specifically stated [217]. Therapeutic EGD is currently an experimental procedure during pregnancy but seems justifiable when the only alternative is abdominal surgery. Informed and written consent should be obtained, and the patient should be specifically informed about the lack of data concerning fetal safety.

Surgery

The indications for surgery for PUD are generally the same in the pregnant patient as in the general population. A perforated peptic ulcer requires emergency surgery after rapid patient stabilization, which includes correction of electrolyte abnormalities and intensive fluid resuscitation. Surgical delay increases mortality. The patient should receive no enteral nutrition and should be administered broad-spectrum antibiotics. Becker-Andersen and Husfeldt [208] found that surgery resulted in a better maternal and fetal outcome than medical therapy during pregnancy: no pregnant mother undergoing surgery for perforated peptic ulcer died in their clinical series, whereas all pregnant mothers treated medically died. Also, 3 (21%) of 14

infants whose mothers underwent surgery died, whereas 11 (65%) of 17 infants whose mothers were treated medically died.

The indications for surgery for hemorrhage from PUD during pregnancy are continued bleeding after transfusion of six or more units of packed erythrocytes, massive uncontrolled acute bleeding causing sustained hemodynamic instability, and hemodynamically significant rebleeding after bleeding cessation. Becker-Andersen and Husfeldt [208] found that surgery rather than medical therapy for severe bleeding from PUD during pregnancy resulted in better maternal and fetal outcomes: of 14 pregnant patients undergoing surgery, only 2 (14%) died, both of whom were in shock preoperatively [208], whereas 7 (44%) of the 16 pregnant patients treated medically died. Also, 4 of 14 infants whose mothers underwent this surgery died, whereas 7 of 16 infants whose mothers were treated medically died. The fetus is sensitive to maternal hemodynamic compromise, whether from maternal bleeding or gastrointestinal perforation.

Surgery should be performed for gastrointestinal obstruction that fails to improve after an adequate trial of intensive medical therapy. Endoscopic balloon dilation was successful in one case of achalasia during pregnancy [218] but has not been reported for gastric outlet obstruction during pregnancy.

Although older studies showed significant fetal mortality from laparotomy during pregnancy, recent studies show a much more favorable fetal prognosis. Laparotomy, however, still results in a high risk of preterm delivery and low birth weight, factors associated with neonatal complications and neurodevelopmental deficits. Laparotomy during pregnancy is considered in detail in the articles on abdominal surgery during pregnancy and on colon cancer during pregnancy.

Special types of ulcers

Ulcers associated with Helicobacter pylori

In the nonpregnant population *H pylori* is a major cause of ulcers, particularly duodenal ulcers. Although duodenal ulcers occur less frequently in women than in men, *H pylori* occurs equally frequently in women and men [219]. The seroprevalence of *H pylori* in Belgium, an industrialized Western country, is about 31% in pregnant women between 36 and 40 years old and about 20% in pregnant women between 26 and 30 years old, rates that are similar to those of age-matched men in industrialized countries [220]. One study reported increased susceptibility to *H pylori* infection during pregnancy, attributed to immunologic tolerance during pregnancy [221]. In this study, 61 of 229 pregnant women had recent *H pylori* infection, as evidenced by the presence of IgM antibodies to *H pylori* in the serum. Further studies are needed on the natural history of *H pylori* infection during pregnancy.

Anti-*Helicobacter* antibodies are passively transferred by the placenta to the fetus in infected mothers. The antibodies are present at birth but then

rapidly disappear in the neonate [222,223]. Maternal *H pylori* infection does not seem to be transmitted in utero or during parturition [13,44,224]. For example, only 1 of 67 infants born to actively infected mothers had antibodies to *H pylori* and a positive 13C-urea breath test, indicative of active infection, at 1 year of age [222]. This finding is important because a neonatal *H pylori* infection would place a person at high risk for eventually contracting PUD and at significantly increased risk of gastric cancer.

Ulcers induced by nonsteroidal anti-inflammatory drugs

Many rheumatic diseases, such as systemic lupus erythematosus, are more common in women, particularly in women of childbearing age [225,226]. Although arthritis from several rheumatologic diseases, such as rheumatoid arthritis, improves during pregnancy [227,228], the arthritis from other rheumatic diseases, such as systemic lupus erythematosus or ankylosing spondylitis, does not remit during pregnancy [229]. Nonsteroidal anti-inflammatory drugs are a critical therapy for arthritis in the general population. Studies suggest that many NSAIDs are not teratogenic and are safe during pregnancy [226]. Nonsteroidal anti-inflammatory drugs are, however, not recommended in late pregnancy because NSAIDs inhibit prostaglandin; and prostaglandin promotes the normal physiologic fetal pulmonary maturation and vascular dilation during the third trimester, the normal constriction of the ductus arteriosus at term, and the normal contraction of the uterus during labor [228]. Nonsteroidal anti-inflammatory drugs are ulcerogenic in the general population, with an estimated risk of ulcers of 2% to 4% per year from long-term NSAID therapy [230,231]. Selective cyclooxygenase-2 (COX-2) inhibitors seem to have a significantly lower risk of inducing ulcers than nonselective NSAIDs. Misoprostol is recommended for the treatment and prophylaxis of NSAID-induced ulcers in the general population [232]. Use of NSAIDs during pregnancy raises concern about maternal risk of NSAID-induced ulcers and about fetal risk from drugs used to prevent or treat NSAID-induced ulcers.

Ulcers induced by NSAIDs are rare during pregnancy, with only two reported cases revealed by a literature review [233]. Use of NSAIDs led to a clinically severe ulcer in one reported case [234]. In the second case, a 29-year-old pregnant patient administered 75 mg of aspirin daily developed a possible NSAID-induced ulcer [235]. Prophylaxis against NSAID-induced ulcers is currently not recommended during pregnancy, because of the unsuitability of misoprostol during pregnancy because of its abortifacient effect [191], the potential fetal toxicity of other therapies, and the apparent rarity of NSAID-induced ulcers during pregnancy.

Stress ulcers

Stress ulcers are uncommon during pregnancy. A review of the English-language literature revealed no reported cases [233]. A review of the Ger-

man-language literature revealed three cases of stress ulcers during the puerperium and one occurring near term in association with eclampsia [236–238]. No data exist to support the use of prophylactic acid suppression to prevent stress ulcers during pregnancy. Esophagogastroduodenoscopy should be performed when stress ulcers cause significant bleeding during pregnancy.

Upper gastrointestinal ulcers in immunocompromised patients

About 0.17% of childbearing women in the United States have human immunodeficiency virus (HIV) infection [239]. The differential diagnosis of an upper gastrointestinal ulcer in an immunocompromised HIV-seropositive pregnant patient includes opportunistic infections by cytomegalovirus, *Herpes simplex*, *Histoplasma capsulatum*, *Mycobacterium tuberculosis*, and other opportunistic pathogens as well as idiopathic retroviral ulcers, gastric lymphoma, and PUD. In an immunocompromised patient, ulcer biopsy specimens should be analyzed by special histologic stains and inoculated in viral, mycologic, and mycobacterial cultures to exclude opportunistic pathogens. Human immunodeficiency virus infection during pregnancy is reviewed in another article in this issue.

Zollinger-Ellison syndrome

The Zollinger-Ellison syndrome accounts for about 1 of 1000 duodenal ulcers in the general population [240]. It is less common in women than in men. This syndrome has been rarely reported during pregnancy, but the incidence during pregnancy is increasing because earlier diagnosis and improved therapy are enabling patients to live longer and healthier lives. The Zollinger-Ellison syndrome is suggested by ulcer multiplicity, ulcer refractoriness to intense medical therapy, atypical ulcer location in the descending duodenum or distal esophagus, and the presence of an acidic diarrhea. Serum gastrin levels are not significantly increased during pregnancy, and serum gastrin level determination is useful in pregnant patients, as in the general population, as a screening test for this syndrome [42].

The main problem during pregnancy is control of hyperchlorhydria. When possible, this syndrome is best controlled by curative surgery or primary tumor resection with parietal cell vagotomy before conception to obviate or reduce the need for acid suppressive therapy during pregnancy [241]. When gastrinomas are diagnosed during pregnancy, surgery is usually postponed until postpartum because gastrinomas grow slowly. Antacids generally control the gastric hyperchlorhydria poorly in this syndrome [241]. Proton-pump inhibitors are the therapy of choice to control the hyperchlorhydria in nonpregnant patients, although H₂ receptor antagonists are also useful [242,243]. In pregnant patients, ranitidine has been traditionally used for acid suppression, with PPIs reserved for refractory cases because of the more established fetal safety of ranitidine. The hyperchlorhydria was

effectively controlled during pregnancy, however, by high-dose omeprazole therapy, without fetal toxicity, as documented by satisfactory Apgar scores in infants, in several case reports [158,160]. Omeprazole therapy was started in the first trimester and continued throughout pregnancy in one case and was used in combination with H₂ receptor antagonists in the other cases.

Malignant gastric ulcers

In the general population, about 5% of gastric ulcers are malignant. Adenocarcinoma is the most common cause of gastric malignancy and malignant gastric ulcers. Risk factors for gastric adenocarcinoma include advanced age, atrophic gastritis, pernicious anemia, genetic factors, gastric adenomas, *H pylori* infection, and residence in Japan. Ulcer malignancy is suggested by clinical findings of involuntary weight loss or cachexia; by endoscopic findings of location outside the antrum or prepylorus, an associated gastric mass, large ulcer diameter, induration or a ridge at the ulcer margin and absence of gastric folds radiating to the ulcer base; and by nonhealing of the ulcer with acid-suppressive therapy. At EGD, gastric ulcers are biopsied to exclude malignancy. Malignant gastric ulcers are reliably differentiated from benign ulcers by endoscopy and pathologic analysis of multiple endoscopic biopsy specimens. In the general population, gastric ulcers are generally followed until healing by sequential EGD, usually at 6-week intervals, to exclude malignancy. When the clinical and endoscopic findings and the pathologic examination of an endoscopic biopsy suggest benignity, repeat follow-up EGD for a gastric ulcer should be deferred until postpartum because of the small, but nonzero, fetal risk of EGD during pregnancy [26] and the rarity of gastric malignancy during pregnancy in the United States [49,244,245].

Gastric adenocarcinoma is rare during pregnancy with an incidence of about 2 in 100,000 pregnancies in one 20-year study [246]. Common symptoms include nausea, vomiting, epigastric pain, anorexia, weight loss, and malaise. These symptoms may be mistakenly attributed to normal pregnancy or nausea and vomiting of pregnancy [247]. Gastric cancer during pregnancy is characterized by a high incidence of poorly differentiated histology, a scirrhous growth pattern, widespread dissemination, and a high incidence of linitis plastica [247]. Gastric cancer, like colon cancer, may frequently metastasize to the ovaries (Krukenberg's tumors) during pregnancy [248,249].

The treatment of gastric adenocarcinoma in the pregnant patient, as in the general population, is partial or subtotal gastrectomy, when metastatic disease is absent. During the first 20 weeks of gestation, gastric cancer surgery is generally not delayed until term because of the risk of cancer spread during a delay [247]. After 24 weeks of gestation, the surgery may be reasonably briefly delayed to improve fetal viability.

The prognosis for gastric cancer during pregnancy is poor. In a review of 61 pregnant Japanese women with gastric cancer, the 3-year survival rate

was 21% [250]. Another large review reported an even worse prognosis during pregnancy [251]. The poor prognosis has been attributed to more aggressive cancer in young people, cancer growth acceleration during pregnancy [252], and delayed diagnosis during pregnancy [244]. About 20% of gastric cancers have estrogen receptors [253]. Some authorities have speculated that gestational hyperestrogenemia may stimulate these estrogen receptors and accelerate cancer growth [254]. Early diagnosis improves survival [246]. Other rare forms of gastric cancer can occur during pregnancy [255,256].

Summary

The frequency, symptoms, and complication rate of PUD seem to decrease during pregnancy. Yet clinicians often have to treat dyspepsia or pyrosis of undetermined origin during pregnancy because the frequency of pyrosis significantly increases during pregnancy, and clinicians reluctantly perform EGD during pregnancy for pyrosis to differentiate reliably between GERD and PUD. Dyspepsia or pyrosis during pregnancy is initially treated with dietary and lifestyle modifications. If the symptoms do not remit with these modifications, sucralfate or antacids, preferably magnesium-containing or aluminum-containing antacids, should be administered. Histamine₂ receptor antagonists are recommended when symptoms are refractory to antacid or sucralfate therapy. Ranitidine seems to be a relatively safe H₂ receptor antagonist. If symptoms continue despite H₂ receptor antagonist therapy, the patient should be evaluated for possible EGD or PPI therapy. Pregnant women with hemodynamically significant upper gastrointestinal bleeding or other worrisome clinical findings should undergo EGD. Indications for surgery include ulcer perforation, ongoing active bleeding from an ulcer requiring transfusion of six or more units of packed erythrocytes, gastric outlet obstruction refractory to intense medical therapy, and a malignant gastric ulcer without evident metastases.

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