REVIEW

Gastrointestinal endoscopy in the pregnant woman

David Friedel, Stavros Stavropoulos, Shahzad Iqbal, Mitchell S Cappell

David Friedel, Stavros Stavropoulos, Shahzad Iqbal, Division of Gastroenterology, Winthrop Medical Center, Mineola, NY 11501, United States
Mitchell S Cappell, Division of Gastroenterology and Hepatology, William Beaumont Hospital, Royal Oak, MI 48073, United States
Mitchell S Cappell, Oakland University Wiliam Beaumont School of Medicine, Royal Oak, MI 48073, United States
Author contributions: Friedel D and Cappell MS contributed equally to this manuscript; all the authors contributed to the writing and approved the final version.
Correspondence to: Mitchell S Cappell, MD, PhD, Division of Gastroenterology and Hepatology, William Beaumont Hospital, 3535 West Thirteen Mile Road, Royal Oak, MI 48073, United States. mscappell@yahoo.com
Telephone: +1-248-5511227   Fax: +1-248-5517581
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Abstract

About 20000 gastrointestinal endoscopies are performed annually in America in pregnant women. Gastrointestinal endoscopy during pregnancy raises the critical issue of fetal safety in addition to patient safety. Endoscopic medications may be potentially abortifacient or teratogenic. Generally, Food and Drug Administration category B or C drugs should be used for endoscopy. Esophagogastroduodenoscopy (EGD) seems to be relatively safe for both mother and fetus based on two retrospective studies of 83 and 60 pregnant patients. The diagnostic yield is about 95% when EGD is performed for gastrointestinal bleeding. EGD indications during pregnancy include acute gastrointestinal bleeding, dysphagia > 1 wk, or endoscopic therapy. Therapeutic EGD is experimental due to scant data, but should be strongly considered for urgent indications such as active bleeding. One study of 48 sigmoidoscopies performed during pregnancy showed relatively favorable fetal outcomes, rare bad fetal outcomes, and bad outcomes linked to very sick mothers. Sigmoidoscopy should be strongly considered for strong indications, including significant acute lower gastrointestinal bleeding, chronic diarrhea, distal colonic stricture, suspected inflammatory bowel disease flare, and potential colonic malignancy. Data on colonoscopy during pregnancy are limited. One study of 20 pregnant patients showed rare poor fetal outcomes. Colonoscopy is generally experimental during pregnancy, but can be considered for strong indications: known colonic mass/stricture, active lower gastrointestinal bleeding, or colonoscopic therapy. Endoscopic retrograde cholangiopancreatography (ERCP) entails fetal risks from fetal radiation exposure. ERCP risks to mother and fetus appear to be acceptable when performed for ERCP therapy, as demonstrated by analysis of nearly 350 cases during pregnancy. Justifiable indications include symptomatic or complicated choledocholithiasis, manifested by jaundice, cholangitis, gallstone pancreatitis, or dilated choledochus. ERCP should be performed by an expert endoscopist, with informed consent about fetal radiation risks, minimizing fetal radiation exposure, and using an attending anesthesiologist. Endoscopy is likely most safe during the second trimester of pregnancy.

Core tip: This article critically analysis the literature on the safety of gastrointestinal endoscopy during pregnancy. Endoscopy is frequently indicated during pregnancy with about 20000 endoscopies performed during pregnancy per annum in America. Although gastrointestinal endoscopy is generally safe in the non-pregnant population the safety of the fetus as well as the patient must be analyzed for endoscopy during pregnancy. This study reviews the literature on the safety of esophagogastroduodenoscopy, endoscopic retrograde cholangiopancreatography, flexible sigmoidoscopy, and colonoscopy during pregnancy and provides guidelines

about the indications, safety precautions, and efficacy of endoscopy during pregnancy.

INTRODUCTION

Gastrointestinal (GI) endoscopy is a mainstay in the evaluation and treatment of GI symptoms and disorders including abdominal pain, reflux esophagitis, biliary disease, and gastrointestinal hemorrhage. It is usually considered a relatively low risk procedure in the general population that is often performed on outpatients with basic cardiopulmonary monitoring. However, there are unique considerations for endoscopy during pregnancy related to physiological alterations during pregnancy and procedural risks to the fetus in utero (Table 1). The safety of gastrointestinal endoscopy during pregnancy is important because of the commonness of GI symptoms and disorders during pregnancy. About 20000 GI endoscopies are performed annually on pregnant women in America, including > 12000 esophagogastroduodenoscopies (EGDs), > 1000 endoscopic retrograde cholangiopancreatographies (ERCPs), and several thousand sigmoidoscopies or colonoscopies[1]. About 0.4% of all endoscopies are performed during pregnancy[1-3]. The risks during pregnancy to the mother and fetus from common procedures, including upper and lower endoscopy, have not been well validated, and decisions regarding procedure performance are usually made on an individual basis based on professional society guidelines[4]. This work comprehensively, critically reviews the current data and literature on endoscopy during pregnancy; proposes recommendations on endoscopy during pregnancy based on the previously published American Society for Gastrointestinal Endoscopy (ASGE) guidelines[4], with modifications based on new data and consideration of previously unaddressed issues; analyzes how to modify procedures to promote maternal and fetal safety; recommends what to advise patients regarding fetal risks from endoscopy; and aims to stimulate new research in this field to resolve current ambiguities and controversies.

This work reviews relatively common endoscopic procedures including EGD, ERCP, flexible sigmoidoscopy, and colonoscopy, but excludes rare procedures, such as percutaneous endoscopic gastrostomy, pancreatic cyst drainage, and endoscopic therapy for achalasia, which have been recently reviewed[5].

PRE-PROCEDURE EVALUATION AND STABILIZATION

A medical history focused on the GI history, obstetric status, comorbidities, and anesthesiology risks is obtained before scheduling endoscopy during pregnancy. Endoscopy should be scheduled in consultation with an obstetrician. Patients should be medically stabilized before endoscopy, with an endpoint of relatively stable vital signs and relatively normal levels of key serum electrolytes and blood counts. In particular, patients with GI bleeding should receive volume resuscitation, including transfusion of crystalloid or packed erythrocytes as necessary, and should have severe coagulopathy corrected by transfusion of fresh frozen plasma or platelets as necessary. Relative normalization of coagulation parameters is important for successful endoscopic hemostasis.

Patients with active upper GI hemorrhage may undergo nasogastric tube lavage or administration of prokinetic agents, such as parenteral erythromycin, to clear the endoscopic field, potentially shorten procedure time, and decrease intraprocedural aspiration risks[6]. Even though no studies have focused on nasogastric tube insertion during pregnancy for GI bleeding, numerous studies have shown tolerability and safety of nasogastric tube intubation for feeding during pregnancy. These studies demonstrate that nasogastric tube intubation and feeding is generally well tolerated by the mother, with rare and mild maternal complications and with mostly favorable fetal outcomes[7]. Erythromycin is rated by the Food and Drug Administration (FDA) as a category B drug during pregnancy. No evidence of erythromycin teratogenicity was found in a study of 230 child-mother pairs exposed to erythromycin during pregnancy[8]. A large survey of Medicaid recipients in Michigan exposed to erythromycin during pregnancy found minimally or no increased rate of major congenital malformations compared to unexposed controls[9].

Patients are maintained nothing per os (npo) for several hours before EGD or ERCP to avoid intraprocedural aspiration of gastric contents. Patients with ascending cholangitis should receive antibiotic therapy to control sepsis and intravenous fluids as required for hypovolemia before ERCP. Fluid resuscitation is even more important in pregnant patients than in the general population to ensure adequate uterine/fetal perfusion during endoscopy. The patient should be positioned on the left side during endoscopy, if possible, to optimize uterine/fetal perfusion. The patient is administered supplemental oxygen by nasal cannula to optimize uterine/fetal oxygenation. Semi-elective GI endoscopy or GI surgery is optimally scheduled during the second trimester to avoid the highest risk of teratogenesis which occurs during organogenesis during the first trimester and to avoid the highest risk of inducing premature delivery which occurs during the third trimester[4]. Fetal cardiac monitoring should be considered when fetal cardiac sounds become detectable, but few cases of fetal cardiac monitoring have been reported during endoscopy and this monitoring is not considered standard of care[4].

Fetal risks from exposure to endoscopic medications, particularly anesthetics, are an important concern. Nearly 2% of pregnant women receive anesthesia without a sta-

Table 1 Unique features of endoscopy during pregnancy
1 Two or more patients at risk
2 Medications and anesthesia usually used may be contraindicated due to fetal risks
3 Patient position an issue in terms of placental blood flow
4 Greater concerns for blood pressure fluctuations due to concerns about placental perfusion
5 Greater concern for aspiration in later pregnancy
6 Disease states that may be exacerbated by pregnancy (GERD) or specific to pregnancy (hyperemesis gravidarum, gestational diabetes, third trimester liver syndromes-HELLP syndrome, *etc.*)
7 Deferral of procedure to more optimal times (*e.g.*, defer procedure from second trimester to postpartum, with possible expedited delivery)
8 Duration of procedure prime concern
9 Obstetric input and monitoring usually necessary
10 Screening for malignancy and Barrett's esophagus less of a concern
11 Avoidance of radiation-based and interventional ancillary procedures (computed tomography imaging, angiography)
12 Monopolar electrocautery (*e.g.*, with sphincterotomy) may harm fetus

GERD: Gastroesophageal reflux disease.

Table 2 Fetal risks of endoscopic or peri-endoscopic medications used during pregnancy[1]		
Medication class	FDA category of safety in pregnancy	Medications
Proton pump inhibitors	B	Lansoprazole, Pantoprazole, Dexlansoprazole, Esmeprazole, Rebeprazole
	C	Omperazole
Histamine-2 antagonists	B	Cimetidine, Famotidine, Nizatidine, Ranitidine
Antiemetics	B	Odansetron, Metoclopramide, Diphenhydramine, Trimethobenzamide, Prochloropromazine, Doxyamine Succinate and Pyridoxine
	C	Promethazine
Prokinetic agents	B	Metoclopramide, Erythromycin
Anesthesia	B	Propofol, Ketamine
Narcotics	B	Meperidine
	B	Morphine, Fentanyl
Benzodiazepines	D	Diazepam, Midazolam
Reversal agents	B	Nalozone
	C	Flumazenil
Colonic preparations	C	Polyethylene glycol, Phosphate preparations[2]
Antispasmodic	B	Glucagon

[1]FDA categorizations of drug safety during pregnancy accepted as guidelines in the current report and by the American Society for Gastrointestinal Endoscopy (ASGE[4]); [2]This review does not recommend use of phosphate preparations during pregnancy. The ASGE recommends its use "with caution"[4]. FDA: United States Food and Drug Administration.

tistically significant correlation of worse outcomes, other than a trend towards lower neonatal birth weight[10]. The FDA classifies drugs according to fetal safety, including teratogenic and abortifacient potential as follows: Category B drugs are considered relatively safe; category C drugs are likely safe or negligibly harmful; category D drugs are potentially dangerous; and category X drugs are contraindicated during pregnancy (Table 2)[4,9,11]. Generally, category B or C drugs are selected at endoscopy during pregnancy, and category D drugs are avoided unless deemed essential and no safer alternative exists. Medications are more likely to be teratogenic when administered during the first trimester during organogenesis. Attendance of an anesthesiologist is recommended at endoscopy performed during pregnancy to optimize fetal safety of anesthetic drugs. Drugs should be administered at the lowest dosage consistent with good anesthetic practice.

Meperidine (Demerol) is generally felt to be relatively safe during pregnancy (FDA category B), but is increasingly being replaced by short acting narcotics, such as fentanyl, because of faster recovery time. Fentanyl is rated FDA category C during pregnancy. Midazolam is generally preferred over diazepam for endoscopy because it produces transient amnesia in addition to sedation. All benzodiazepines are FDA category D, but midazolam is preferred over diazepam during pregnancy because diazepam was associated with teratogenicity, especially cleft palate malformations, in several, early, small studies[12]. Recent large studies, however, have not shown this association[13,14]. Midazolam has not been associated with cleft palate abnormalities, but might have some potential for fetal injury during the first trimester[15]. Propofol is generally safe during pregnancy (FDA category B). It is generally the anesthetic agent of choice during pregnancy, provided an anesthesiologist is available for administration[4,9-11].

A woman in late pregnancy is best served by endotracheal intubation to prevent aspiration during upper endoscopy. Endotracheal intubation is often advisable during all trimesters of pregnancy for prolonged or invasive procedures, such as therapeutic ERCP, and for patients with active upper GI bleeding, particularly from esophageal varices. A consideration unique to ERCP is teratogenicity from fetal exposure in utero to intraprocedural radiation. This concern restricts ERCP to particularly strong indications, as described below. High risk endoscopies, such as therapeutic ERCP, or low risk endoscopies in high risk patients due to comorbidities or life-threatening indications for endoscopy, should ideally be performed in tertiary medical centers by expert endoscopists where an experienced team of anesthesiologists and obstetricians is available.

When obtaining consent the endoscopist should inform the patient about the potential for fetal complications even though these risks are not believed to be particularly large. The patient should be specifically apprised of fetal risks from radiation exposure if ERCP is contemplated.

UPPER ENDOSCOPY

EGD is the most commonly performed endoscopic procedure during pregnancy. Diagnostic EGD is useful for diagnosing gastroesophageal reflux disease (GERD), gastritis, *Helicobacter pylori* (*H. pylori*) infection, peptic ulcer disease, esophageal varices, and malignancy; whereas

Table 3 Indications for esophagogastroduodenoscopy during pregnancy

Strong indications[1]

Dysphagia > 1-2 wk, especially with diminished intake or weight loss

Odynophagia > 1-2 wk

Gross gastrointestinal hemorrhage with hematemesis and/or melena, especially if patient becomes hypotensive, requires blood products, or has a significant acute hemoglobin decline

GI hemorrhage with strong clinical suspicion of varices

Suggestion of malignancy on radiologic imaging studies (*e.g.,* MRI)

Possible gastric outlet obstruction (*e.g.,* from peptic ulcer disease)

Endoscopic therapy for continued UGI bleeding

Balloon dilatation of symptomatic UGI stricture (*e.g.,* endoscopic therapy for reflux stricture)

Moderate indications

 Recurrent nausea and emesis (including possible hyperemesis gravidarum) if patient > 16-18 wk pregnant and concern exists for peptic ulcer disease with inadequate patient response to > 2 wk of conservative therapy, including PPI

Strong need for endoscopic placement of enteric tube (*e.g.,* for hyperemesis or severe, prolonged, acute pancreatitis)

Nausea and emesis after UGI surgery (including bariatric surgery) with concern for postsurgical stricture

Weak indications

Hyperemesis gravidarum during first trimester

Self-limited nausea, emesis or abdominal pain

GERD symptoms, excluding dysphagia not responsive to empiric PPI therapy

Routine endoscopic surveillance for higher risk patients (*e.g.,* EGD for personal history of familial polyposis coli)-can be deferred until postpartum

Iron deficiency anemia-should generally be deferred until postpartum

[1]These recommendations incorporate the American Society for Gastrointestinal Endoscopy (ASGE) guidelines[4] as recommendations 1-4, and 7, but the current report adds recommendations 5, 6 and 8 that were not addressed in the ASGE guidelines. MRI: Magnetic resonance imaging; UGI: Upper gastrointestinal; GERD: Gastroesophageal reflux disease; EGD: Esophagogastroduodenoscopy; PPI: Proton pump inhibitor.

therapeutic EGD is useful for hemostasis of variceal or non-variceal bleeding, dilatation of strictures, and ablation of Barrett's esophagus. Patient position, administered medications, and length of procedure are modest considerations for EGD in the general population, but become critical issues during pregnancy.

EGD appears to be relatively safe for the expectant mother and fetus, though follow-up data is limited. In a case series of 83 pregnant women undergoing EGD, 95% delivered normal infants, and the bad outcomes were uncommon and not clearly related to the EGD but were generally related to high risk pregnancies antecedent to performance of the EGD[16]. Only one maternal complication occurred after EGD: transient pyrexia 12 h after EGD with rapid defervescence without requiring antibiotic therapy and without any source of fever identified by a thorough fever work-up. In an Israeli study, only one fetus died among 60 pregnant females undergoing EGD, and no congenital abnormalities were observed in the 56 live-borne infants, excluding three voluntary abortions[17]. A mailed survey of 3300 gastroenterologists regarding 73 pregnant patients undergoing EGD yielded similarly

favorable, pregnancy outcomes[18].

In the study of 83 EGDs during pregnancy, the endoscopic indications were GI hemorrhage in 45%, abdominal pain in 34%, and other in 21%. EGD was diagnostic in 95% of cases performed for acute GI bleeding during pregnancy, similar to the diagnostic yield of EGD in the general population for the same indication[16]. EGD was diagnostic in only about 60% of cases for other indications. The most common diagnosis was reflux esophagitis which occurred in 62%; this high prevalence is explained by increased acid reflux during pregnancy from increased intraabdominal pressure from the enlarged, gravid uterus and decreased LES pressure mediated by gestational hormones[19]. Mallory-Weiss tears occurred in 14%; this relatively high prevalence compared to that in nonpregnant patients is explained by the ubiquity of nausea and emesis during pregnancy. Peptic ulcer was diagnosed in only 14% of cases; this relatively low prevalence compared to that in the general population may be explained by decreased gastric acid secretion during pregnancy mediated by gestational hormones[20]. A low rate of peptic ulcer disease during pregnancy was similarly found in the Israeli study[17].

Nausea and emesis are extremely common during pregnancy. A survey reported 63% of women had nausea and emesis early in pregnancy, and 45% of women had these symptoms late in pregnancy[21]. Extreme cases, associated with paradoxical weight loss despite the pregnancy or electrolyte derangements, are called hyperemesis gravidarum. Two case series reported that endoscopic abnormalities commonly occur in pregnant patients with nausea and emesis, but diagnosis of these endoscopic abnormalities rarely altered patient management beyond instituting proton pump inhibitor therapy[16,17]. This therapy is believed to be relatively safe during pregnancy (all proton pump inhibitors but omeprazole are FDA category B, Table 2), and might reasonably be instituted empirically based on symptomatology without subjecting the patient and fetus to the risks of endoscopy. Although possibly associated with hyperemesis gravidarum, *H. pylori* infection can be reliably diagnosed noninvasively by serum antibodies or stool antigen tests[22]. EGD can therefore be typically deferred for symptoms of hyperemesis gravidarum with administration of empirical therapy comprising antiemetics and proton-pump inhibitors; EGD can be performed in the second trimester or postpartum if symptoms persist. This strategy usually obviates the need for EGD during pregnancy because symptoms of hyperemesis gravidarum typically remit after the twentieth week of pregnancy. Contrariwise, acute gross gastrointestinal hemorrhage manifested by melena, hematemesis, or hypotension, constitutes a strong indication for EGD. Patients with this indication generally have significant endoscopic findings and often require endoscopic therapy[23]. Endoscopy should also be strongly considered when upper GI malignancy is suspected, for dysphagia of recent onset persisting for ≥ 7 d, or when endoscopic therapy is anticipated (Table 3)[5,14,24].

Variceal hemorrhage is rare during pregnancy be-

cause advanced liver disease decreases fertility, but can occasionally occur in patients with underlying cirrhosis (*e.g.*, mother contracted hepatitis B in utero by vertical transmission) or from development of one of several liver failure syndromes occurring during late pregnancy, such as acute fatty liver of pregnancy. Variceal hemorrhage can, moreover, occur in noncirrhotic patients with hepatic fibrosis or portal vein obstruction because these disorders generally do not impair fertility. Pregnancy exacerbates portal hypertension mostly from gestational increases in plasma volume[25]. Almost one-third of pregnant patients with portal hypertension developed de novo varices during pregnancy, whereas about two-thirds of patients with antecedent varices experience variceal bleeding during pregnancy[26]. Patients administered beta-adrenergic receptor antagonists, such as propranolol, to prophylax against variceal bleeding should be maintained on these drugs during pregnancy. Endoscopic band ligation (EVL) is the preferred initial therapy for esophageal variceal bleeding in the general population[27], but scant published data exists concerning EVL during pregnancy, with only one published case series and about one dozen case reports[28,29]. These limited data show relatively favorable maternal and fetal outcomes of esophageal banding, compared with the poor prognosis in untreated patients[5]. Despite limited current data, endoscopic banding is considered justifiable during pregnancy. Sclerotherapy has been available for decades but is now considered a second-line therapy for variceal bleeding in the general population. The literature on sclerotherapy during pregnancy comprises < 50 patients[5,30]. The main conclusion from the limited literature is that outcomes are best for both the mother and fetus if variceal bleeding is successfully stopped by endoscopy or other interventions[31].

Data on therapeutic EGD for nonvariceal upper GI hemorrhage consist of only 4 patients, including one each of sclerotherapy for bleeding Mallory-Weiss tear, epinephrine injection for esophageal ulcer, thermocoagulation for peptic ulcer with high risk stigmata of recent hemorrhage, and electrocoagulation for duodenal ulcer with high risk stigmata of recent hemorrhage[5]. The bleeding ceased or did not recur in three patients, while the fourth patient experienced continued bleeding after endoscopic therapy that required gastric surgery. All four pregnant patients and their fetuses had favorable outcomes. This extremely limited data on therapeutic endoscopy for hemorrhage from peptic ulcers or Mallory-Weiss tears may suggest good maternal and fetal outcomes provided hemostasis is achieved[5,16]. Although considered experimental during pregnancy due to scant data, endoscopic therapy is justifiable for strong indications, including active bleeding, oozing, and nonbleeding visible vessel. This recommendation is based on expert opinion derived primarily from data on efficacy in nonpregnant patients. The current data are insufficient to recommend specific endoscopic therapies during pregnancy, among the options of banding, hemoclips, sclerotherapy, thermocoagulation, argon plasma coagulation (APC), or electrocoagulation.

Endoscopic electrocoagulation raises special concerns during pregnancy. Amniotic fluid can conduct electricity to the fetus[32]. The grounding pad should, therefore, be positioned to avoid current transmission through the uterus and fetus from the cautery device. Epinephrine is frequently injected during endoscopy to control active GI bleeding in the general population, but may decrease uterine/fetal perfusion and is rated FDA category C drug, with a weak association with teratogenesis during pregnancy[33]. This association may reflect the underlying medical condition for which the epinephrine was administered rather than intrinsic fetal toxicity[9]. Mechanical therapies, such as endoclips or bands, have a theoretical advantage for hemostasis in pregnancy because these therapies avoid fetal exposure to electricity or chemical agents.

Capsule endoscopy is generally considered contraindicated during pregnancy, as reported by the manufacturer, due to no clinical trials performed in pregnant patients[34]. Theoretically, capsule progress through bowel might be retarded in pregnant patients from bowel compression by the enlarged, gravid uterus or from anti-kinetic properties of progestin, a gestational hormone. Only a few cases of capsule endoscopy have been reported during pregnancy, including one case of bleeding from jejunal carcinoid diagnosed by capsule endoscopy and then treated surgically, with ultimate delivery of a healthy infant[35]. Although the reported cases resulted in favorable maternal and fetal outcomes, the current data are insufficient to promulgate clinical guidelines. Capsule endoscopy is currently experimental during pregnancy, but may be considered when extremely strongly indicated, especially when the alternative is gastrointestinal surgery. In providing informed consent, the physician should consider mentioning that pregnancy may theoretically increase the risk of capsule retention.

Deep enteroscopy, including single or double balloon enteroscopy, has not been reported during pregnancy. Pregnancy may theoretically render deep enteroscopy more technically challenging because of compression of bowel lumen and displacement of bowel by the enlarged, gravid uterus. Data are needed to promulgate clinical guidelines regarding safety, efficacy, and indications of deep enteroscopy during pregnancy.

LOWER ENDOSCOPY

Flexible sigmoidoscopy, a relatively simple, quick procedure, usually requires only enema preparation and minimal or no sedation and analgesia. Tap water enemas usually suffice for sigmoidoscopy[4]. Colonoscopy, however, requires more thorough colonic preparation, longer procedure times, and significant sedation and analgesia. Polyethylene glycol preparation has been reported as a preparation for colonoscopy during pregnancy but is inadequately studied in this population. Among 40 women receiving polyethylene glycol for constipation during

pregnancy, 37 had favorable fetal outcomes, and three had poor outcomes: one spontaneous abortion and two very early preterm deliveries[36]. Sodium phosphate preparations have not been studied and should not be used during pregnancy. These current recommendations are stricter than the prior ASGE recommendations to use sodium phosphate "with caution"[4], because of occasional reports of electrolyte abnormalities and even renal failure associated with administration of these preparations to dehydrated nonpregnant patients[37,38].

Despite > 6000 women having indications warranting sigmoidoscopy or colonoscopy per annum during pregnancy[39], only about sixty cases of sigmoidoscopy and only about 40 cases of colonoscopy have been reported during pregnancy[5,40]. Most procedures were performed during the second trimester. The literature likely captures a small fraction of performed procedures. In a study of 46 patients undergoing 48 sigmoidoscopies, after excluding one unknown pregnancy outcome and four voluntary abortions, 38 of the remaining 41 patients delivered healthy infants[40]. Poor pregnancy outcomes included death from prematurity of one live-borne infant, one stillbirth, and one infant with a congenital malformation. All poor outcomes occurred in high risk pregnancies and were not attributed to sigmoidoscopy. Control patients, who were matched for sigmoidoscopy indications but who did not undergo sigmoidoscopy because of the pregnancy, had similar fetal outcomes. Sigmoidoscopy during pregnancy was associated with a high diagnostic yield. Sigmoidoscopy was diagnostic in 59% of the 46 patients. It was significantly more frequently diagnostic when performed for hematochezia than for other indications [22 of 29 (76%) *vs* 5 of 17 (29%), $P < 0.03$ χ^2 test]. Sigmoidoscopic diagnoses among 29 patients with hematochezia included: de novo diagnosis or flares of IBD in 15, acute proctosigmoiditis in 3, bleeding internal hemorrhoids in 2, pseudomembranous colitis in 1, and sigmoid adenoma in 1. Among 17 patients undergoing sigmoidoscopy for other indications diagnoses included: ulcerative colitis in 2, nonspecific colitis/proctitis in 2, and postsurgical anastomotic ulcer in 1. Publication bias of reporting only dramatic cases and treatment bias of performing sigmoidoscopy only for very strong indications may have contributed to the high reported diagnostic yield. The consensus is that sigmoidoscopy is well tolerated during pregnancy with good fetal outcomes in relatively medically stable patients. Sigmoidoscopy should be strongly considered in patients with relatively strong procedure indications, including clinically significant acute lower GI bleeding, refractory chronic diarrhea of unknown etiology, distal colonic stricture, suspected IBD flare, and potential colonic malignancy.

In a study of 20 pregnant patients undergoing colonoscopy, one therapeutic colonoscopy was successfully used to decompress a colon dilated from colonic pseudoobstruction, and colonoscopy was diagnostic in 53% of the 19 remaining colonoscopies[41]. Diagnosed disorders included ulcerative colitis in 5, Crohn's colitis in 2, ischemic colitis in 2, and lymphocytic colitis in 1.

Only two mothers developed clinical sequelae temporally associated with colonoscopy; they experienced hypotension which was mild and transient without further clinical sequelae. Fetal outcomes were relatively favorable: 18 healthy infants, one involuntary abortion, and 1 infant born with septum secundum congenital cardiac defect. Study patients undergoing colonoscopy, moreover, had similar or better fetal outcomes than control pregnant patients with the same indications for colonoscopy but who did not undergo colonoscopy because of the pregnancy. In another study of 8 pregnant patients undergoing colonoscopy, pregnancy outcomes included six healthy infants, one voluntary abortion, and one miscarriage four months after colonoscopy[40]. The miscarriage occurred in a mother who experienced a severe flare of ulcerative colitis after self-discontinuing her chronic immunosuppressive therapy. Similar data have been reported in about one dozen individual case reports of colonoscopy during pregnancy: a relatively high diagnostic yield of colonoscopy and a relatively low rate of poor outcomes attributable to colonoscopy[5]. As for sigmoidoscopy, the high diagnostic yield of colonoscopy may reflect publication bias and treatment bias.

Colonoscopy should generally be avoided during pregnancy and be performed only when strongly indicated. Colonoscopy should be considered for the following strong indications: evaluation of a known colonic mass or stricture detected by radiologic examination; active, clinically significant lower GI bleeding; colonoscopic decompression of colonic pseudoobstruction; or other situations to avoid colonic surgery by colonoscopic therapy. These recommendations concur with the published ASGE guidelines[4], except for adding the last two new recommendations. Colonoscopy is not all-or-none and the colonoscopist encountering technical difficulty reaching the cecum or intraprocedural patient intolerance may reasonably abort the colonoscopy without reaching the cecum. Even though the enlarged gravid uterus can compress the colonic lumen and distort normal colonic anatomy, cecal intubation is often achievable at colonoscopy during pregnancy. Reported untoward outcomes in the pregnant mother or fetus are generally related to underlying pathology, such as IBD or colon cancer, rather than the colonoscopy. When necessary, colonoscopy is preferentially performed during the second trimester[4,5,39,40]. Colonoscopy may theoretically be more teratogenic during the first trimester when organogenesis occurs and may theoretically cause more fetal injury in the third trimester by mechanical compression of the enlarged preterm uterus or by neonatal respiratory depression from colonoscopic medications administered just before labor.

Hemorrhoidal bleeding is common during advanced pregnancy because of venous pooling from increased intravascular volume and because of prolonged defecation and increased rectal pressure from increased constipation during pregnancy. Lower endoscopy may often be reasonably deferred during pregnancy for bright red blood per rectum because of this high incidence of hemorrhoidal bleeding during pregnancy and the low incidence

Table 4 Concerns about performance of endoscopic retrograde cholangiopancreatography during pregnancy

1 The procedure is technically challenging

2 The patient is normally placed in prone position for ERCP with consequently decreased placental perfusion for the significant duration of the procedure

3 The patient requires considerable anesthetic medications during ERCP due to discomfort during this particularly prolonged procedure

4 Patients often have preexisting pain and significant acute disease, such as gallstone pancreatitis or cholangitis

5 Fluoroscopy is usually required during ERCP with consequent fetal radiation exposure

6 Complications are more common in ERCP than in other endoscopic procedures and can potentially be severe (*e.g.*, pancreatitis, cholangitis, hemorrhage)

7 Sphincterotomy entails monopolar electrocautery with current possibly traversing the fetus

8 Endoscopic sphincterotomy entails risks of postsphincterotomy bleeding or perforation

9 Repeat procedures may be required, such as ERCP for retained biliary stones or stent malfunction and cholecystectomy for gallstones

ERCP: Endoscopic retrograde cholangiopancreatography.

of colon cancer in this generally relatively young female population. Colon cancer and colonic polyps, however, become a concern in older (> 40 years old) pregnant patients with chronic lower gastrointestinal bleeding[42,43]. Sigmoidoscopy can often reasonably replace colonoscopy to evaluate suspected IBD flares during pregnancy. Polypectomy can usually be deferred until after parturition for small polyps to avoid electricity traversing the fetus because such polyps are unlikely to grow much or become malignant during the interim[4]. However, medium-to-large (> 6 mm in diameter) polyps, polyps displaying high risk features such as multinodularity or central ulceration, or polyps causing lower GI bleeding should likely be removed at an index colonoscopy without deferral until postpartum. Lower endoscopy has been used several times to release an incarcerated, gravid uterus[44]. Sigmoidoscopy should be sufficient to reach this area and relieve the incarceration. Iron deficiency anemia is common during pregnancy due to physiologically increased erythropoiesis. Although colonoscopy is typically indicated to evaluate iron deficiency in the elderly, colonoscopy may generally be reasonably deferred during pregnancy until after delivery for this indication.

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY AND ENDOSCOPIC ULTRASOUND

Gastroenterologists are concerned about ERCP during pregnancy (Table 4). The most common indication for ERCP during pregnancy is symptomatic choledocholithiasis, often presenting with jaundice, cholangitis, or gallstone pancreatitis. Pregnancy promotes lithogenesis due to gestational hormones. Estrogen promotes cholesterol synthesis which tends to increase cholesterol saturation of bile, and progesterone decreases gallbladder motility which tends to increase bile stasis[45]. Although cholelithiasis is estimated to have a prevalence of 3%-12% during pregnancy, only 1 per 1000 pregnancies or less are complicated by choledocholithiasis[46]. ERCP is generally the preferred therapy for choledocholithiasis to avoid complex biliary surgery for choledocholithiasis during cholecystectomy[47]. Less common ERCP indications include post-cholecystectomy bile leak, biliary strictures, or pancreatic stents for pancreatic-fluid collections. Menstruating females should be screened by urine or blood tests before ERCP to prevent accidental performance of ERCP during pregnancy with fetal exposure to ionizing radiation. For example, 3 of the 29 patients in one study undergoing ERCP during pregnancy were not known to be pregnant at the time of ERCP and were exposed to ionizing radiation without anticipation or patient discussion about potential fetal consequences[48].

The medical literature includes about 350 cases of ERCP during pregnancy. The individual studies are generally flawed due to small study size, retrospective design, failure to capture all outcomes, and limited follow-up after delivery[5,48-50]. Three retrospective series incorporating > 100 pregnant women, with almost all requiring therapeutic intervention (mostly for choledocholithiasis), imply relatively good outcomes in maternal health status, maintenance of pregnancy, and fetal outcome. These three combined studies were notable for maternal pancreatitis in 5%-16%, one spontaneous abortion 3 mo after ERCP, one fetal demise 26 h after delivery, and prematurity rate of 8%[48-50]. A retrospective study of 65 pregnant patients undergoing ERCP with sphincterotomy similarly reported favorable results[49]. There were 11 maternal complications of pancreatitis, all of which were managed medically without requiring surgery. There were no fetal deaths, perinatal deaths, or congenital malformations among the 59 known fetal outcomes[49]. In the largest prospective study, ten patients underwent biliary stenting for choledocholithiasis, biliary pancreatitis, or retained choledochal stones after cholecystectomy[51]. Cannulation was performed without sphincterotomy by using a guidewire to avoid electrocautery during pregnancy. Nine of ten patients had successful therapy, and the tenth patient underwent repeat ERCP with sphincterotomy and stent placement which was successful. All expectant mothers subsequently did well with births of healthy infants in all cases. One study of 18 patients noted no congenital abnormalities and no developmental defects detected in 11 children followed up until 11 years old[52].

A comprehensive analysis in 2011 of 296 ERCP's during pregnancy with 254 accountable pregnancy outcomes revealed (after excluding 1 voluntary abortion) healthy infants at birth in 237; premature, low-birth weight infants in 11; and bad outcomes of spontaneous abortion or infant death after live birth in 5[5]. The mother experienced post-ERCP pancreatitis in 5%-6%, and post-sphincterotomy hemorrhage in 1%, rates similar to that after ERCP with sphincterotomy in the general popula-

Table 5 Recommendations for endoscopic retrograde cholangiopancreatography during pregnancy[1]
1 Weigh conservative management and/or deferral. Radiation early in gestation is a particular concern. Second trimester may be optimal time
2 Consult with obstetrician
3 Consult with radiation physicist if feasible to calculate appropriate dosimetry
4 Obtain MRCP if useful and available
5 Employ experienced ERCP physician
6 Endoscopic ultrasound may obviate ERCP (if CBD gallstones are not extremely likely)
7 Shield fetus/Employ unit with highly collimated beam/Avoid continuous radiation
8 Employ tactics to minimize/obviate radiation: Aspirate bile/intraductal ultrasound/biliary balloon sweeps w/o fluoroscopy/cholangioscopy/biliary stent placement
9 Avoid taking hard copy radiographs of findings because these use greater amounts of radiation than fluoroscopy
10 Minimize monopolar cautery during sphincterotomy. Employ grounding pad so that electric current does not traverse uterus/fetus

[1]These current recommendations incorporate the American Society for Gastrointestinal Endoscopy (ASGE) guidelines[4] as recommendations 1,2,5, and 7-10, but the current report adds recommendations 3 and 4 that were not addressed in the ASGE guidelines. ERCP: Endoscopic retrograde cholangiopancreatography; MRCP: Magnetic resonance cholangiopancreatography; CBD: Common bile duct.

tion[5,53]. ERCP was deemed beneficial for both mother and fetus for cases of symptomatic or complicated choledocholithiasis, manifested by jaundice, cholangitis, or pancreatitis. Caveats included that ERCP should be performed only if therapy is likely necessary and that the endoscopist should be an expert endoscopist, as technical failures resulted in relatively worse outcomes. A novice endoscopist-in-training should, therefore, not perform ERCP on a pregnant patient, even under supervision by an experienced endoscopist.

Fetal radiation exposure is a major concern for ERCP during pregnancy. Fetal risks are highest during the first trimester during organogenesis when they are considered significant at five rads of exposure[54]. Thresholds are higher and risks are lower during the second and third trimesters. Fetal radiation exposure should be estimated by fetal dosimetry, in which a detection device is placed on the abdomen over the uterus, if the anticipated dose may exceed 10 rads (100 milliGrays)[55]. Radiation exposure is usually considerably less than this amount during ERCP[56]. ERCP without fluoroscopy utilizes aspiration of bile to verify biliary cannulation, but the accuracy of this maneuver is not well validated; only a few, small, clinical series have analyzed this technique[50,57]. Other stratagems can minimize radiation exposure (Table 5), but some fluoroscopy is usually necessary. The endoscopist should minimize fluoroscopy dosage, irradiated area (small field and anterior-posterior projection), and duration by avoiding hard-copy radiographic images in favor of only fluoroscopy, utilizing a medical physicist, using a modern highly-collimated radiation unit, and employing pelvic shielding whenever possible[58].

Endoscopic spyscope (cholangioscopy) enables direct endoscopic visualization of the choledochal and pancreatic ducts. This is useful to confirm complete clearance of stones after balloon sweep or to directly examine or sample focal ductal lesions, including growths or strictures, in the general population. The safety of Spyscope technology is inadequately studied during pregnancy, with only 6 reported cases[50,59]. Although these 6 cases reported favorable maternal outcome, the ultimate fetal outcome was not reported. Direct visualization of bile ducts via cholangioscopy is appealing to confirm ductal clearance, but this maneuver may be time consuming and necessitate copious duct lavage[59]. More studies investigating fetal outcomes are needed to determine fetal safety.

Although the reported studies generally suffer from retrospective study design with only one small prospective study, relatively small numbers of study patients, lack of long term follow-up after birth, and substantial number of unknown fetal outcomes, these studies generally suggest that ERCP should be performed when strongly indicated. Strong indications for ERCP include choledocholithiasis complicated by jaundice, ascending cholangitis, or gallstone pancreatitis; and presentation with abnormal (cholestatic) liver function tests in a patient with gallstones and choledochal dilatation detected by abdominal ultrasound. These recommendations correspond with the published ASGE guidelines[4]. ERCP should not be performed for weak indications, *e.g.*, when therapy is unlikely at ERCP. In such cases MRCP is generally preferred over ERCP because of greater safety in the general population. Clinical studies of ERCP appear to show acceptable small risks to the mother that is comparable to that in the nonpregnant patient, as aforementioned for pancreatitis or post-sphincterotomy hemorrhage, and acceptable fetal risks. The benefits of stone clearance from therapeutic ERCP seem to exceed the fetal risks from performing ERCP during pregnancy. Therapeutic ERCP failed to clear choledocholithiasis in about 10% of reviewed cases. Options after therapeutic ERCP failure include repeat ERCP or surgery.

Conventional trans-abdominal ultrasound is relatively insensitive for choledocholithiasis but MRI/MRCP (magnetic resonance cholangiopancreatography) and endoscopic ultrasound (EUS) are highly accurate, radiation-free modalities to detect choledocholithiasis[60]. MRCP has a very important diagnostic role in directing management of biliary disorders in the general population, but only a couple of studies examined MRCP during pregnancy, with inadequate analysis of fetal safety. One study noted sensitivity was greatest when biliary dilation was detected on prior abdominal ultrasound[61]. In another study, MRCP was used to guide ERCP without radiation[62]. There are scant data on EUS during pregnancy, with about one dozen reported cases[50,63]. There were no maternal complications related to EUS. However, several fetal deaths were reported, which were not temporally related to the EUS and were attributed to the poor medical status of the mother at the time of undergoing EUS,
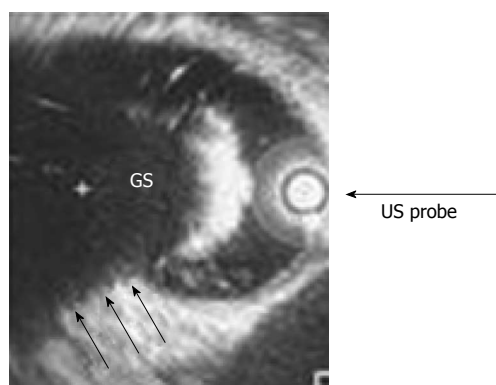
Figure 1 Intraductal ultrasound reveals a gallstone (labeled gallstone) in the common bile duct exhibiting acoustic shadowing (3 parallel arrows) in a middle-aged female patient presenting acutely with right upper quadrant pain, hyperbilirubinemia, and elevated aspartate and alanine aminotransferase levels. During pregnancy, endoscopic ultrasound provides a method to diagnose common bile duct stones without exposing the fetus to the risks of ionizing radiation from endoscopic retrograde cholangiography. US probe: Ultrasound probe; GS: Gallstone.

including recurrent cholangitis or the HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome. EUS can help gauge choledochal size and number and size of choledochal stones, but there is concern about the utility of a negative exam, especially when cholelithiasis is present. Intraductal ultrasound may be useful to verify biliary cannulation and duct clearance (Figure 1). The safety of EUS has not been validated during pregnancy, especially regarding fetal outcomes[5].

Tenets of ERCP in pregnancy include: (1) schedule ERCP expeditiously to improve patient and pregnancy outcome (*e.g.*, do not postpone indicated ERCP to second trimester of pregnancy); (2) minimize or eliminate radiation time to reduce fetal exposure; (3) achieve ductal clearance of stones or at least ensure adequate biliary drainage; and (4) facilitate cholecystectomy if necessary. Conservative management of choledocholithiasis is usually unjustified unless, perhaps, very early in pregnancy during organogenesis[64]. Various endoscopic approaches to choledocholithiasis and its complications are reported during pregnancy. Insertion of biliary stents after ductal clearance without sphincterotomy may obviate fetal risks from monopolar cautery, but the stent may become clogged and promote subsequent cholangitis[51]. Performance of both sphincterotomy and biliary stenting still mandates another ERCP that is optimally postponed until postpartum[65]. One group employed nasobiliary drainage, without fluoroscopy, in patients with severe biliary pancreatitis followed by ERCP when the patient stabilized[66].

FUTURE DIRECTIONS

In the future, the burgeoning volume of endoscopies during pregnancy may strengthen the data underlying current guidelines or help formulate modifications. Large studies, preferably prospective, with follow-up of fetal outcome are needed to determine fetal safety of endos-

Table 6 Basic principles of endoscopy during pregnancy
1 Weigh benefits of endoscopy versus conservative management
2 Defer endoscopy to second trimester or post-delivery when appropriate
3 Evaluate all proposed medications in terms of teratogenicity and abortifacient potential
4 Obtain consultation from obstetrics and preferably employ anesthesiologist
5 Position patient on left side. Avoid perturbations of blood pressure
6 Minimize drug administration and procedure time
7 For ERCP, minimize or obviate radiation (Table 5). Utilize radiation physicist and calculate dosimetry
8 Utilize bipolar electrocautery. Minimize monopolar use

ERCP: Endoscopic retrograde cholangiopancreatography.

copy. Further data are especially needed on fetal outcome for sigmoidoscopy or colonoscopy performed during pregnancy. The scant data on therapeutic endoscopy must be augmented to determine fetal safety of various techniques of hemostasis including thermocoagulation, electrocoagulation, and APC therapy. "Best practice" recommendations may reduce controversies, such as the optimal approach to symptomatic choledocholithiasis during pregnancy. Combined cholecystectomy and ERCP has not been reported during pregnancy but might become an option[67].

Technology will be emphasized with likely sanctioned use of modalities that have been employed in pregnancy but not recommended due to insufficient data, including MRI, EUS, or capsule endoscopy. Procedures used in the general population, such as unsedated, nasal endoscopy, may be extrapolated to pregnancy. Innovations in capsule endoscopy, such as active propulsion or steering, may prevent capsule retention and thereby render it safer during pregnancy[68]. In particular, colonoscopy with sedation may be replaced by capsule endoscopy without sedation if smaller, steerable capsules are developed. Molecular genetic tests of stool or serum may obviate the need for colonoscopy to evaluate patients for rectal bleeding or colon cancer during pregnancy[69]. New colonoscopic techniques to assess polyp histology before polypectomy, such as narrow band imaging or chromoendoscopy, might help to defer polypectomy of polyps encountered at colonoscopy during pregnancy[70]. Most importantly, new technology may facilitate diagnosis and treatment in pregnancy, such as ultrasound-contrast agents for GI hemorrhage[71], mini-endoscopes, endoscopic glues for hemostasis, and novel mechanical hemostatic devices, such as endoscopic suturing[72]. The new contrast agents for MRCP should be tested in the future regarding safety during pregnancy.

CONCLUSION

Conservatism in performing endoscopy during pregnancy is rational. Endoscopy is usually performed when there is a strong likelihood of significant diagnostic findings and/or endoscopy therapy (*e.g.*, GI hemorrhage, IBD, compli-

cated choledocholithiasis). Patient preparation and physician adherence to general guidelines (Table 6) should help optimize outcomes. There is often multidisciplinary input from obstetricians, perinatologists, and anesthesiologists. Most pregnant women do not sustain untoward effects from endoscopy and the same seems to be the case for the fetus, although long-term follow-up data on subsequently born infants are minimal. More evidence-based guidelines and technological innovations will lessen the ambiguities and challenges in performing endoscopy during pregnancy.

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