



## The fetal safety and clinical efficacy of gastrointestinal endoscopy during pregnancy

Mitchell S. Cappell, MD, PhD, FACG\*

*Division of Gastroenterology, Department of Medicine, Woodhull Medical Center,  
760 Broadway Avenue, Brooklyn, NY 11206, USA*

*Division of Gastroenterology, Department of Medicine, State University  
of New York Downstate Medical School, 450 Clarkson Avenue, Brooklyn, NY 11203, USA*

Endoscopy has a central role in the diagnosis and an increasingly important role in the therapy of gastrointestinal bleeding and other gastrointestinal disorders. Although safety and efficacy of gastrointestinal endoscopy are generally established [1–4], safety and efficacy in pregnant patients are not well-known. Pregnant patients not infrequently suffer from gastrointestinal conditions, such as gastrointestinal bleeding or complicated cholelithiasis that are strong indications for endoscopy in nonpregnant patients. More than 12,000 pregnant women have a strong indication for esophagogastroduodenoscopy (EGD), more than 6000 pregnant women have a strong indication for sigmoidoscopy or colonoscopy per annum in America, and about 1000 pregnant women have a strong indication for therapeutic endoscopic retrograde cholangiopancreatography (ERCP) [5,6]. Thus, a practicing gastroenterologist encounters a pregnant patient with a strong indication for gastrointestinal endoscopy about once per annum. Diagnostic and therapeutic endoscopy may be particularly valuable during pregnancy because diagnosis by barium radiography is relatively contraindicated because: (1) of radiation teratogenesis [7,8], (2) empirically prescribing gastrointestinal drugs without a definitive endoscopic diagnosis is undesirable owing to medication teratogenesis [9], and (3) the alternative therapy of gastrointestinal surgery for active bleeding or complicated choledocholithiasis is undesirable owing to the risk of fetal wastage [10,11].

Endoscopy during pregnancy raises the unique issue of safety to the fetus because of the risks of induction of premature labor or teratogenesis from

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\* Corresponding author: Department of Medicine, Woodhull Medical Center, 760 Broadway Avenue, Brooklyn, NY 11206.

medication teratogenicity [12–14], placental abruption or fetal trauma during endoscopic intubation, cardiac arrhythmias [15–19], systemic hypotension or hypertension [15], and transient hypoxia. The fetus is particularly sensitive to maternal hypoxia and hypotension [10]. EGD or ERCP can produce respiratory compromise and hypoxia from administered medications [20], vagally mediated bronchospasm, laryngeal impingement during esophageal intubation [17,20–23], and pulmonary aspiration [24–27]. Sigmoidoscopy or colonoscopy can produce hypoxia from intravenous sedation [21,28], and neurohumoral responses to colonic distention [16].

Analysis of endoscopic safety during pregnancy provides multiple benefits. It helps the physician make a judicious decision about recommending endoscopy and the pregnant patient make an informed decision about undergoing endoscopy. It helps the physician reduce the fetal risks from endoscopy: (1) by avoiding potentially teratogenic endoscopic medications; (2) by fetal and maternal assessment before endoscopy; (3) by appropriate fetal and maternal monitoring during endoscopy; and (4) by appropriate therapy before and during endoscopy. Malpractice judgments are sometimes astronomically large in cases of poor fetal outcomes [29]. Documentation of the relative safety of endoscopic procedures during pregnancy, when properly indicated and performed, can prevent unnecessary litigation.

The current knowledge of endoscopic safety during pregnancy is, however, incomplete. The published studies on endoscopy during pregnancy are retrospective. Although a large, case-controlled study of 83 EGDs did not detect any risk from EGD during pregnancy [30], this study had insufficient power to exclude a small, but clinically significant, fetal risk from endoscopy. Endoscopic medications comprise a major component of endoscopic risks during pregnancy, but these risks are currently imprecisely defined, as described below. Despite the current uncertainties, the physician who is referred a patient for gastrointestinal endoscopy during pregnancy can be provided guidance and guidelines. This article analyzes the indications, contraindications, safety, and efficacy of gastrointestinal endoscopy in pregnancy and the fetal safety of endoscopic medications.

### **Safety of endoscopic medications during pregnancy**

Fetal drug safety is a major consideration in the choice and dosage of endoscopic medications during pregnancy. Analysis of fetal risks can help the physician avoid, restrict, or substitute potentially teratogenic endoscopic medications to decrease fetal risks from endoscopy and can help the patient render an informed decision about whether to receive analgesic and sedative endoscopic premedications. For the endoscopist with limited knowledge of the pharmacology of sedatives, attendance of an anesthesiologist at endoscopy in a pregnant patient is prudent, particularly for high-risk endoscopy, such as therapeutic ERCP.

Medication teratogenicity is an inexact science; safety in animal models does not assure safety in humans because of species specificity (a lesson learned, unfortunately, with thalidomide [31,32]), physicians are reluctant to perform and patients are reluctant to enroll in therapeutic clinical trials during pregnancy, there are medicolegal restrictions in performing randomized clinical trials during pregnancy, and confounding variables can potentiate teratogenicity, such as the underlying illness for which a medicine is prescribed. Additionally, neurodevelopmental or cytologic congenital abnormalities may not clinically manifest until late childhood, as occurred with vaginal adenocarcinoma after in utero diethylstilbestrol exposure [33]. Drug studies on human infants, even newborns, are not necessarily relevant to fetal risks. Despite outstanding contributions by Briggs and coauthors [34], and by Heinonen and colleagues [35], clinical studies of drug teratogenicity during the first trimester, when available, are usually small and retrospective. Clinical studies typically fail to stratify drug effects according to trimester of exposure, drug dosage, duration of treatment, and route of drug administration, even though these parameters affect teratogenicity. Historically, teratogenic effects have been appreciated late, unless large or highly unusual. Indeed, thalidomide teratogenicity took years to appreciate despite an extremely large (one in three) and highly unusual (phocomelia) teratogenic effect [34]. Drug studies have to be carefully performed on a large population sample to detect a mild, but highly clinically significant, teratogenic effect.

Nonetheless, the existing data, even though mostly retrospective, nonrandomized, and poorly controlled, provide crude estimates of drug teratogenicity. A large, retrospective study that shows no teratogenicity strongly suggests that the studied drug is not a major teratogen. Several concurring studies strengthen this conclusion. Even a large study that shows a small, but statistically significant, increase in congenital malformations after in utero drug exposure can suggest that the drug is not a major teratogen: the reported association may be caused by confounding variables, such as the underlying illness for which the drug was administered.

General considerations about drug administration during endoscopy in the pregnant patient are summarized in Box 1. The Food and Drug Administration (FDA) classification of drug safety during pregnancy is listed in Box 2.

## **Medications and agents used in all types of gastrointestinal endoscopic procedures**

### *Endoscopic premedications*

#### *Meperidine*

Meperidine, an opiate analgesic, has been commonly administered during gastrointestinal endoscopy for analgesia and sedation. Meperidine is rapidly

**Box 1. General principles and precautions for gastrointestinal endoscopy during pregnancy***Endoscopic drugs during pregnancy*

- Use smallest effective dose
- Involve patients in decisions about potentially fetotoxic drugs
- When alternative drugs are available, use the drug that is safest to the fetus
- Avoid category D drugs
- Do not use category X drugs
- Avoid optional drugs
- Contact pharmacologist or perform literature review as necessary regarding drug teratogenicity
- Consider anesthesiologist referral for administering conscious sedation

*Other procedure recommendations*

- Defer endoscopy to after first trimester when possible
- Defer endoscopy to postpartum period when possible (eg, postpone surveillance colonoscopy)
- Avoid endoscopy for weak indications
- Terminate poorly-tolerated endoscopic procedures
- Consider obstetric consultation
- Fully informed and written consent to include discussion about fetal risks of procedure
- Continuous cardiac monitoring and pulse oximetry, and intermittent sphygmomanometry should be performed during procedure
- Consider fetal monitoring during endoscopy, if available
- Avoid endoscopy during threatened abortion, placental abruption, or other serious obstetric complications
- Postpone endoscopy during active labor until postpartum
- Substitute less invasive procedure if possible: sigmoidoscopy for colonoscopy or possibly MRCP for diagnostic ERCP
- Do procedure expeditiously (eg, avoid examination of distal duodenum at EGD or unnecessary endoscopic biopsies)
- Avoid polypectomy, hot biopsy, or electrocoagulation, if possible
- Performance of endoscopy by experienced attending endoscopist rather than inexperienced fellow-in-training is strongly preferred
- Consider performing ambulatory endoscopy in a hospital endoscopy suite rather than private office
- Avoid fluoroscopy during colonoscopy or EGD, and minimize fluoroscopy during ERCP
- Refer patient with complicated biliary disease during pregnancy to a tertiary medical center

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MRCP- magnetic resonance cholangiopancreatography.

**Box 2. Food and Drug Administration categories of fetal risk from drugs administered during pregnancy**

**Category and fetal risk**

- A Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.
- 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. Drug 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 humans 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.

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*Data from Fed Reg 1980;44:37434–67.*

transferred across the placenta after intramuscular injection [36], or intravenous administration [34]. Peak cord blood concentrations average about 75% of maternal plasma levels [37].

Two large studies revealed no teratogenicity from meperidine administration during the first trimester. In the Collaborative Perinatal Project, meperidine was not teratogenic in a study of 268 mothers with first-trimester exposure, except that six of the infants with in utero exposure had inguinal hernias [35]. In a surveillance study of Michigan Medicaid recipients, 3 of 62 newborns with first trimester in utero exposure had major congenital

defects; the unexposed control group had the same rate of congenital defects [34].

Physicians have extensive experience prescribing meperidine during labor [38–42]. Meperidine is preferred over morphine for obstetric analgesia because it crosses the fetal blood–brain barrier much more slowly [40]. Meperidine administration during delivery depresses neonatal respiration for several hours after maternal administration because normeperidine, its active metabolite, is slowly metabolized [43,44]. Meperidine may impair neonatal neuropsychologic functions, such as attention and social responsiveness, during the first few weeks of life [45–50]; these effects disappear with time [51]. Children whose mothers received meperidine during labor had similar psychological, physical, and intellectual parameters at 5 years of age as compared with children without in utero exposure [52,53]. In utero meperidine exposure during labor does not increase the risk of childhood cancer [54].

Meperidine can cause diminished fetal beat-to-beat cardiac variability that lasts for about 1 hour after maternal intravenous administration [55,56]. Generally, diminished cardiac variability is a sign of fetal distress, such as fetal acidosis or hypoxemia, but the effect produced by a single small-to-medium dose of meperidine is reversible, transient, and not a poor prognostic indicator [38].

Meperidine is rated a category B drug during pregnancy, except for a rating of D when used for prolonged periods and at high doses at term [34]. It is preferred to diazepam or midazolam as an endoscopic premedication during pregnancy. Table 1 summarizes the data on the fetal safety of meperidine and other endoscopic medications. Meperidine dosage should be titrated to produce calmness, relaxation, and mild analgesia without somnolence. Dosage should be restricted to 50 or 75 mg during routine endoscopy.

### *Fentanyl*

Fentanyl, a potent synthetic narcotic agonist, is sometimes used as an alternative to meperidine during endoscopy because of a more rapid onset of action and a shorter recovery time [57]. Fentanyl was not teratogenic, but was embryocidal, in rats who were administered 0.3 times the maximal human equivalent dose for prolonged periods [58,59]. Fentanyl crosses the placenta to the fetus [60,61]. In numerous studies, maternal fentanyl administration during labor produced no neonatal toxicity [62–65]. Fentanyl has, however, been associated in single case reports with respiratory depression [66], respiratory muscle rigidity [67], or opiate withdrawal that lasted for several days after birth in an addicted mother [68]. Fentanyl, like meperidine, can decrease fetal heart rate variability without causing fetal hypoxia [13,40]. Fentanyl is rated a risk category C during pregnancy, except for a rating of D if used for prolonged periods or high doses at term [34,59]. The accumulated data suggest that fentanyl may be used in low dosage for endoscopy during pregnancy.

### *Propofol*

Anesthesiologists often administer propofol, a short-acting parenteral anesthetic, during endoscopy, but gastroenterologists have usually avoided propofol because of a narrow therapeutic index and potential respiratory depression [57]. Administration of the maximal recommended human equivalent dose in pregnant rats or rabbits revealed no teratogenicity [59]. Propofol rapidly transfers across the placenta near term [69,70]. In one study, 20 infants who were exposed to propofol during parturition had depressed Apgar scores and transient neurologic depression at birth compared with unexposed controls, but the neurologic depression rapidly reversed postpartum [71]. In contrast, numerous other studies that involved hundreds of patients reported no neonatal toxicity from propofol administered during parturition [34,72–75]. Propofol is rated a risk factor B and is considered relatively safe during pregnancy, but the safety of first trimester exposure has been inadequately studied [59,76].

### *Diazepam*

Benzodiazepines, including diazepam and midazolam, are commonly administered before gastrointestinal endoscopy to reduce anxiety, induce brief amnesia, and produce muscle relaxation. Diazepam rapidly crosses the placenta and accumulates in the fetal circulation at levels equal to, or higher than, maternal serum levels [77–79].

Diazepam administration to pregnant mice was associated with cleft palates in their offspring [80]. Several studies suggested an association between diazepam use during pregnancy and neonatal cleft lips or palates in humans [81–84]. For example, a retrospective study of 278 mothers by Safra and Oakley [85] reported in 1975 that mothers of children with a cleft lip or palate had a fourfold increased rate of diazepam use during the first trimester as compared with mothers of children with other congenital defects. These same investigators, however, concluded from a review of the literature in 1976 that diazepam had not been proven to cause oral clefts, and even if this relationship existed, the risk of neonatal oral clefts from in utero exposure was only about 0.4% [86].

More recent studies demonstrated no association between diazepam and oral clefts [14,87–89]. Notably, no association was detected in a study that compared 611 infants with oral clefts to 2498 infants with other congenital defects [14], and in a study that compared 355 infants with oral clefts to 11,073 healthy infants [90]. No oral clefts occurred in the offspring of 80 mothers with frequent, high-dose diazepam use during pregnancy [91]. The current consensus is that diazepam does not cause oral clefts [92,93].

Other studies raised a possible association between diazepam exposure and other congenital abnormalities, including an association with congenital inguinal hernia in two studies [94,95], cardiac defects and pyloric stenosis in a study that compared the rate of diazepam exposure among 1427 malformed newborns versus 3001 healthy controls [95], and Mobius syndrome

Table 1  
Fetal safety of drugs and other therapies commonly used in gastrointestinal endoscopy: Food and Drug Administration categorization and summary of a literature review of fetal safety in humans

Drug	Category	Recommendations during pregnancy	Summary of literature review of safety to human fetus
<b>Endoscopic premedications</b>			
Meperidine	B	Use in low dose for endoscopy.	Apparently not teratogenic. Causes transient neonatal respiratory depression and decreased alertness when administered during labor. Can cause diminished fetal beat-to-beat cardiac variability that lasts for about 1 hour after maternal administration.
Diazepam	D	Probably midazolam preferred for endoscopy.	Association with oral clefts raised in literature but not demonstrated in large controlled studies. Associated with floppy infant syndrome, which produces transient neonatal effects. High maternal doses can lead to a fetal withdrawal syndrome. Association with neurologic defects or mental retardation raised in literature but unproven.
Midazolam	D <sup>a</sup>	Use cautiously and in low dose for endoscopy.	Administration during labor may transiently depress respiration and may transiently depress neurobehavioral responsiveness of newborns. Pharmacologic effects resemble that of diazepam, but no reports published of an association with oral clefts. Drug is less well-studied than diazepam during pregnancy.
Propofol	B	Administration by an anesthesiologist.	Considered relatively safe during pregnancy. Can cause respiratory depression.
Fentanyl	C	Use in low dose for endoscopy.	Generally safe to fetus when administered during labor. Rare case reports of transient neonatal toxicity.
<b>Medications during endoscopy</b>			
Simethicone	C <sup>a</sup>	Avoid during endoscopy.	Two studies showed no or minimal (statistically insignificant) increase in the rate of congenital defects after maternal administration during pregnancy
Glucagon	B	Avoid during endoscopy except for ERCP	Two small studies of glucagon administration to a combined total of 34 pregnant women showed no fetal toxicity.

Ampicillin	B	Use when antibiotic prophylaxis strongly indicated.	<p>Extensive clinical experience of ampicillin administration during pregnancy. One old, small retrospective study showed an association with congenital cardiac anomalies, but this finding has not been confirmed. Three large controlled studies demonstrated no teratogenicity. Apparently relatively safe to the fetus, provided the mother is not penicillin allergic.</p> <p>Similar to other aminoglycosides, maternal administration might rarely produce fetal ototoxicity. One report of administration in 11 women in labor without neonatal toxicity. No significant toxicity in one large case-controlled study.</p>
Gentamicin	C	Use when antibiotic prophylaxis strongly indicated	<p>Similar to other aminoglycosides, maternal administration might rarely produce fetal ototoxicity. One report of administration in 11 women in labor without neonatal toxicity. No significant toxicity in one large case-controlled study.</p>
Medications after endoscopy			
Naloxone	B	Avoid. Use only for narcotic overdose.	<p>Naloxone administration after meperidine administration to mothers in labor produced no untoward neonatal effects in two small studies. Administration in subjects dependent on opiates can precipitate opiate withdrawal and is dangerous.</p> <p>Two cases reported of drug administration during pregnancy. In both cases healthy infants were subsequently delivered.</p>
Flumazenil	C	Avoid. Use only for benzodiazepine overdose.	<p>Two cases reported of drug administration during pregnancy. In both cases healthy infants were subsequently delivered.</p>
Agents used in selected procedures			
Polyethylene glycol electrolyte	C	Insufficient data.	<p>One large study reported safety in treating constipation in the puerperium. No studies located on safety during pregnancy.</p>
Sodium phosphate solution	C	Insufficient data.	<p>One case reported of neonatal bone demineralization after chronic maternal use during pregnancy. Single use for colonoscopy should not cause this complication.</p>
Diatrizoate	D <sup>a</sup>	Use minimal dose for therapeutic ERCP.	<p>Iodine contained in drug could theoretically impair fetal thyroid function. Two studies suggest that maternal administration of the drug solubilized in water does not produce fetal thyroid toxicity because of an apparent lack of drug transfer into fetal circulation. One study of 69 patients showed slightly increased risk of congenital malformations, that was not statistically significant, after maternal administration. Used in 14 pregnant patients for intraoperative cholangiography without fetal complications.</p>

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Table 1 (continued)

Drug	Category	Recommendations during pregnancy	Summary of literature review of safety to human fetus
Epinephrine	C	Avoid unless necessary.	In one large study in utero epinephrine exposure associated with increased rate of congenital anomalies possibly caused by underlying disease. No congenital malformations in another study of 35 patients.
Methylene blue	C	Insufficient data.	See text.
Lidocaine	B	Patient to gargle and spit out and not to swallow.	Intravenous administration was generally safe in one large study.
Electricity		Use electrocautery for therapeutic sphinterotomy, defer for polypectomy during pregnancy.	Relatively good pregnancy outcome after performing sphinterotomy during pregnancy in small clinical series and multiple case reports.

<sup>a</sup> *Data from* Briggs GG, Freeman RK, Yaffe SJ. *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. 6th edition. Philadelphia: Lippincott Williams & Wilkins; 2002.

(sixth and seventh nerve palsies) after in utero diazepam exposure in one case report [96]. These associations are unconfirmed. In a study from the Israeli Teratogen Service, 11 (3.1%) of 355 infants with in utero first trimester exposure to a benzodiazepine, including diazepam in 25% of cases, had major congenital malformations compared with 10 (2.6%) of 382 unexposed control infants [97]. A meta-analysis of nine cohort studies revealed no association with major malformations, whereas a meta-analysis of nine case-controlled studies showed an association with major malformations (OR 3.01, 95% CI 1.32–6.84) [98].

Several reports raised a possible association between frequent, high-dose diazepam administration during pregnancy and neonatal mental retardation or neurologic defects. For example, in one study seven mothers who had ingested high doses of diazepam during pregnancy had mentally retarded infants [99,100]. Several investigators reported the floppy infant (overdose) syndrome characterized by hypotonia, lethargy, and sucking difficulties [101–103], and a neonatal withdrawal syndrome characterized by intra-uterine growth retardation, tremors, irritability, hypertonicity, diarrhea, vomiting, and vigorous sucking [104,105] after administration of high doses of diazepam during labor. The risk of either syndrome is increased by a high dosage or prolonged period of use. Generally, infants gradually recover from the floppy infant syndrome as diazepam is metabolized and disappears from the neonatal circulation.

Diazepam is categorized as a class D drug during pregnancy, and its use should be carefully restricted during endoscopy, particularly during the first trimester [34].

### *Midazolam*

Many endoscopists prefer midazolam over diazepam for endoscopic premedication because of faster onset and recovery time, more intense transient antegrade amnesia, and lower risk of thrombophlebitis [106]. Administration of 10 and five times the maximal recommended human equivalent dose in pregnant rats and rabbits, respectively, revealed no teratogenicity [59]. Midazolam crosses the human placenta, but fetal serum levels rise to only about one third to two thirds of maternal serum levels after oral, intramuscular, or intravenous maternal administration [107,108].

Several studies suggested that maternal midazolam administration during parturition transiently depressed neonatal respiration [109–112] and neurobehavioral responsiveness [111]. Three of 19 infants whose mothers had received midazolam during cesarean section had transient neurobehavioral abnormalities in body temperature, body tone, and arm recoil [111]. In a controlled study of 52 infants, the infants who were exposed to midazolam during cesarean section had lower Apgar scores at 1 minute after birth compared with unexposed controls [109]. Another study confirmed these results [113]. These sedative effects are attributable to direct neonatal effects of midazolam and should disappear after drug elimination.

Aside from endoscopic studies described subsequently [30,114], no published reports analyzed the effects of first or second trimester fetal exposure [34]. Midazolam was, however, successfully used for patient sedation during intrafallopian gamete transfer with subsequently normal pregnancies in a small clinical series [115]. This benzodiazepine has not been associated with oral clefts.

This drug is classified a risk factor D during pregnancy [59], but seems to be preferable to diazepam during pregnancy because of the potential, albeit unlikely, association between diazepam and oral clefts and neonatal neurobehavioral abnormalities. Because of a similar mechanism of action as diazepam, midazolam should be used cautiously and in low doses during pregnancy, particularly during the first trimester. Dosage should be titrated to an end point of relaxation and calmness without somnolence.

### *Medications during endoscopy*

#### *Simethicone*

Simethicone is a silicon product that defoams and disperses gas bubbles. Small bubbles coated by secretions and mucus usually form near the ampulla of Vater in the descending duodenum and duodenal bulb as a result of the foaming action of bile. Simethicone is sometimes injected through an endoscopic port at EGD or ERCP to clear an endoscopic field that is obscured by bubbles and bilious secretions.

Among 248 newborns who were exposed to simethicone during the first trimester, 14 major birth defects were observed, as compared with 11 expected [34]. This small observed increase was statistically insignificant and was most likely the result of 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 [116].

Simethicone is classified as a category C drug during pregnancy [34]. Simethicone is best avoided at endoscopy during pregnancy. Water perfusion followed by endoscopic aspiration may reduce the volume of bubbles at endoscopy. When necessary, simethicone is best administered in low concentration and small volume during endoscopy in a pregnant patient.

#### *Glucagon*

Glucagon, an antispasmodic, is often used to decrease duodenal motility during choledochal intubation at ERCP [117], and is occasionally used to relax a spastic colon at colonoscopy [118]. Glucagon does not relax uterine smooth muscle [119]. Reproduction studies in rats at doses up to 40 times the recommended maximal human equivalent dose revealed no teratogenicity [59].

Glucagon was administered to reverse severe hypoglycemia in 12 instances in seven pregnant women [120]. In 11 instances, glucagon produced immediate reversal of maternal unconsciousness; in one instance,

glucose infusion was also required for complete recovery. Glucagon produced no short- or long-term toxicity. Twenty-seven pregnant women underwent an intravenous beta-cell stimulation test, using 1 mg of glucagon, without complications [121]. One neonate rapidly improved after receiving glucagon for an overdose of labetalol, a beta-adrenergic receptor antagonist, without any toxicity [122].

Glucagon is classified as a category B drug during pregnancy [59]. Glucagon is rarely needed for colonoscopy in nonpregnant patients. When glucagon is necessary for colonoscopy because of colonic spasm in pregnant patients, the endoscopist should strongly consider procedure termination rather than persist at a difficult, high-risk colonoscopy. Although fetal risk is incompletely characterized, glucagon administration is justifiable to help cannulate the choledochus during therapeutic ERCP for choledocholithiasis to help prevent life-threatening maternal cholangitis. Prompt choledochal cannulation by an expert endoscopist, without repeated unsuccessful attempts, excessive papillary manipulation and trauma, can prevent duodenal hypermotility and preclude the need for glucagon.

### *Antibiotics*

#### *Ampicillin*

The American Heart Association recommends ampicillin for intravenous antibiotic prophylaxis for patients at medium or high risk of endocarditis who undergo endoscopic sclerotherapy for esophageal varices, endoscopic dilation of an esophageal stricture, and ERCP in the presence of biliary obstruction [123]. Ampicillin prophylaxis is considered optional in high-risk patients who undergo colonoscopy and EGD [123]. The indications for antibiotic prophylaxis are controversial, however, because of insufficient data [124–126].

Ampicillin, a penicillin antibiotic, rapidly crosses the placenta, and fetal serum levels equilibrate with maternal values within 3 hours of maternal administration [127]. Administration of 10 times the maximal equivalent human dose to pregnant mice, rats, and rabbits revealed no fetal toxicity [59]. Physicians have extensive experience prescribing ampicillin during pregnancy [128,129]. One retrospective study found a statistically significant association between first trimester use and congenital cardiac anomalies [95], but this study was subject to a recall bias because drug histories were obtained up to 1 year after drug exposure [34]. This study, moreover, did not control for the antibiotic indication; the increased rate of cardiac malformations may have been caused by the underlying infection that required antibiotic therapy [130].

Three large studies did not demonstrate ampicillin teratogenicity. The Collaborative Perinatal Project found ampicillin use during the first trimester among 3546 expectant mothers was unassociated with congenital malformations [35]. A surveillance study of 10,011 newborns with first trimester in utero

exposure revealed no association between ampicillin and teratogenicity; 441 major birth defects were observed compared with 426 expected [34]. In the Hungarian Case-Control Surveillance of Congenital Abnormalities Study the rate of ampicillin use was the same among 22,865 pregnant women whose offspring had congenital abnormalities as compared with 38,151 pregnant women whose offspring were healthy [131]. No increased risk was found for any specific abnormality, except for an increased incidence of cleft palate, which the researchers attributed to chance alone.

Ampicillin is rated a category B drug during pregnancy [59]. Extensive clinical experience does not support an association between ampicillin and congenital defects, if the mother is not allergic to penicillin [131]. One infant was born with neurologic deficits after the mother developed an anaphylactic reaction to ampicillin that was administered during labor [132]. Ampicillin prophylaxis is reasonable in pregnant patients who must undergo endoscopy and who have a high-risk cardiac lesion.

### *Gentamicin*

The American Heart Association recommends administration of gentamicin, an aminoglycoside antibiotic, as part of a prophylactic antibiotic regimen for patients at medium or high risk of endocarditis who undergo ERCP in the presence of biliary obstruction [123]. Gentamicin administration is considered optional in high-risk patients who undergo colonoscopy and EGD [123]. The indications are controversial and the physician should carefully weigh the benefits versus risks of gentamicin administration [124,133].

Gentamicin is not teratogenic in rats, except for nephrotoxicity and hypertension in offspring who are exposed to extremely high drug levels in utero [134,135]. Gentamicin rapidly crosses the placenta, and fetal serum levels peak at about one half of maternal levels after maternal administration [136]. No harmful effects were detected in 11 newborns after intra-amniotic installation of gentamicin for preterm rupture of membranes [137]. In the Hungarian Case-Control Surveillance of Congenital Abnormalities Study, 19 (0.08%) of 22,865 newborns with congenital abnormalities had in utero exposure to gentamicin, whereas 19 (0.05%) of 38,151 healthy newborns had in utero exposure to gentamicin [138]. The investigators concluded that gentamicin was not teratogenic. Fetal outcomes were similar in 52 pregnant females who were treated with gentamicin and ampicillin, compared with 117 pregnant females who were treated with a cephalosporin for acute pyelonephritis [139]. One infant whose mother had an allergic reaction to gentamicin during the first trimester had short stature, renal insufficiency, and renal cystic dysplasia [140].

Gentamicin, like other aminoglycosides, is ototoxic [141]. Other aminoglycoside antibiotics rarely cause neonatal eighth cranial nerve damage after in utero exposure [34,142–144]. In one small study, four infants who were

exposed to gentamicin and vancomycin in utero had normal auditory function as demonstrated by comprehensive auditory testing at 1 year of age [145]. Although a literature review revealed no cases of gentamicin-associated fetal ototoxicity, high-dose maternal gentamicin administration might cause fetal ototoxicity [34], but a single moderate dose of gentamicin, administered for endocarditis prophylaxis, would be unlikely to be ototoxic [146].

The FDA rates the drug a risk factor C during pregnancy [34]. Because of insufficient data, the physician should use caution in administering gentamicin prophylaxis for endoscopy during pregnancy, particularly during the first trimester. The drug should be administered, however, if it is required to treat known sepsis, such as biliary sepsis.

### *Medications after endoscopy*

#### *Naloxone*

Naloxone, a rapidly acting opiate antagonist, is sometimes administered after endoscopy to reverse the effects of narcotics that were administered during endoscopy. It does not produce narcotic effects at clinically used dosages [147]. It rapidly crosses the placenta, and appears in fetal plasma within 2 minutes of intravenous maternal injection [34,148]. Fetal serum levels peak at about one half of maternal levels after maternal intravenous injection [148]. Naloxone administered at up to 50 times the maximal equivalent human dose in pregnant mice and rats was not fetotoxic, but rat pups who were exposed to naloxone during lactation developed long-lasting hyperalgesia [59,149].

Naloxone administration was analyzed during the third trimester. Intravenous infusion of 0.4 mg of naloxone in 27 healthy pregnant women at 37 to 39 weeks of gestation led to an increase in fetal gross movements, respiratory movements, and heart rate acceleration, without subsequent neonatal toxicity [150]. Infant neurobehavioral scores were similar after their mothers had received meperidine alone or meperidine plus naloxone during labor [47,151]. Naloxone was safely administered to newborns immediately postpartum to reverse narcotic depression, including depressed respiration or somnolence, following maternal narcotic administration during labor [152,153].

In one study, eight otherwise normal fetuses who had decreased heart beat variability intrapartum were administered naloxone to increase the heart beat variability based on the theory that elevated fetal endorphin levels depress the normal fetal heart rate and beat variability. One of the infants developed fatal respiratory failure and convulsions soon after drug administration [154].

Naloxone administration is contraindicated in pregnant patients who are dependent on opiates because opiates cross the placenta. Naloxone can precipitate a neonatal syndrome that resembles opiate withdrawal. Symptoms include restlessness, anxiety, insomnia, irritability, hyperalgesia,

nausea, and muscle cramps [155,156]. One newborn, whose mother was opioid-dependent, suffered convulsions that were precipitated by naloxone administration [157].

Naloxone is rated a category B drug during pregnancy [59]. Naloxone is not recommended for routine use after endoscopy during pregnancy because of one reported fatality associated with neonatal administration. Patients should be monitored in a recovery unit with intravenous access and electrocardiographic monitoring until they recover from narcotic-induced drowsiness. Naloxone administration should be restricted to pregnant patients who suffer signs of potential narcotic toxicity, such as respiratory depression, systemic hypotension, or unresponsiveness, and should be administered, in these cases, in small graded doses that are titrated to the desired effect.

### *Flumazenil*

Flumazenil rapidly reverses the central effects of benzodiazepines [158]. It is used after endoscopy to reverse the effects of oversedation with benzodiazepines that were administered during endoscopy [159]. The administration of flumazenil to pregnant rats and rabbits at several hundred times the maximal recommended human dose revealed no teratogenicity [59]. Flumazenil was not embryocidal when administered at 60 times the recommended human dose in pregnant rabbits, but was embryocidal at 200 times the recommended human dose [59]. Prolonged, high-dose administration to pregnant rats in late gestation may result in subtle neuro-behavioral changes in their male offspring [160].

Little is known about flumazenil safety during pregnancy or in neonates. One somnolent pregnant patient at 36 weeks of gestation developed fetal cardiocographic abnormalities of a decreased basal fetal heart rate, decreased beat-to-beat cardiac variability, and absent cardiac accelerations after a diazepam overdose. The patient rapidly awoke and the fetal cardiocographic abnormalities rapidly reversed after intravenous flumazenil administration [161]. The mother delivered a healthy infant 2 weeks later. In another case report, a healthy infant was born after in utero exposure to flumazenil just before cesarean section [162]. Flumazenil was successfully used to reverse recurrent apnea in two newborn infants whose mothers had taken high doses of diazepam during late pregnancy [163,164]. Intravenous flumazenil was also successfully used to reverse unresponsiveness and hypotonicity in a 4-month-old infant after intravenous midazolam sedation [165]. The infant subsequently did well.

Flumazenil is rated a category C drug during pregnancy [59]. Flumazenil should be used only to reverse benzodiazepine overdose during pregnancy because the fetal risks are unknown [59]. Overdose can be prevented by careful and slow titration and the administration of the minimal dosage of benzodiazepines that is required for endoscopic examination [166].

## Medications and agents used in selected endoscopic procedures

### *Colonic preparations*

#### *Polyethylene glycol electrolyte solution*

Polyethylene glycol electrolyte (GoLYTELY, NuLYTELY, or Colyte) solution is an isotonic cathartic solution that is used to clean the bowel before colonoscopy. Animal reproduction studies have not been conducted with this solution [59]. It is also unstudied and unknown whether this solution can cause fetal harm when administered during pregnancy [59]. A literature review revealed one study of 225 patients that demonstrated the safety of this solution when used to treat constipation in the puerperium [167]. This solution is classified as a grade C risk during pregnancy [59].

#### *Sodium phosphate solution*

Sodium phosphate solution (Fleet Phospho-Soda, C. B. Fleet Co., Lynchburg, VA) is a poorly absorbed salt that produces intestinal fluid retention because of the osmotic load and causes thorough bowel fluid evacuation (lavage) at the high doses that are used for colonic preparation for colonoscopy [168]. Patients should drink several glasses of water after taking this preparation for colonoscopy. Patients often prefer sodium phosphate solution to polyethylene glycol electrolyte solution because of the need to drink much less fluid.

One newborn experienced bone demineralization and bone growth failure because of maternal phosphate overload; the anorectic mother had repeatedly taken phosphate enemas during pregnancy [169]. One-time use in preparation for colonoscopy during pregnancy should not cause this complication. Visicol (Inkine Pharmaceutical Co., Blue Bell, PA), a drug that contains primarily sodium phosphate, is rated a category C drug during pregnancy [59]. Gentle tap water enemas until clear is an alternative colonic preparation for flexible sigmoidoscopy during pregnancy.

#### *Epinephrine*

Epinephrine, a potent peripheral vasoconstrictor, is injected during endoscopy at or around bleeding gastrointestinal lesions to achieve hemostasis. High-dose epinephrine could theoretically compromise placental perfusion because of alpha-adrenergic effects [170]. Epinephrine was teratogenic in some animal models at 25 times the recommended human equivalent dose, but was not teratogenic at high dose in others [59,80]. One infant had a fatal intracranial hemorrhage at birth after massive in utero epinephrine exposure [171]. In the Collaborative Perinatal Project, the 189 infants with first trimester in utero exposure had a significantly higher rate of major congenital malformations, in general, and of congenital inguinal hernias, in particular, than unexposed controls [35]. These reported associations might be the result of the confounding variable of severe maternal

disease for which the epinephrine was prescribed [34]. In contrast, in a study of Michigan Medicaid recipients no congenital malformations occurred among 35 neonates with first trimester in utero exposure [34]. Epinephrine has been used during parturition without fetal toxicity [172,173].

Epinephrine is rated a risk factor C during pregnancy [59]. Because of the theoretical and actual reported risks, high-dose epinephrine is relatively contraindicated during pregnancy, but low-dose exposure seems to be relatively safe [174]. At endoscopy, epinephrine should be injected around, but not directly into, bleeding vessels to minimize systemic toxicity while achieving hemostasis. Normal saline is a safer alternative hemostatic agent for endoscopic injection during pregnancy.

### *Methylene blue*

Methylene blue is occasionally injected at colonoscopy to tattoo colonic lesions for future identification at surgery or repeat endoscopy. Fetal safety has not been studied in laboratory animals [59]. In the Collaborative Perinatal Project oral administration of methylene blue in nine pregnant mothers did not result in congenital abnormalities in their offspring [35]. In one case report, intravenous methylene blue was successfully used to treat toxicity from an ingested herbicide during pregnancy, with the subsequent birth of a healthy neonate [175]. In contrast, intra-amniotic injection is fetotoxic; it can cause neonatal hemolytic anemia, jaundice, methemoglobinemia [176], and jejunoileal atresia or stenosis [177].

In utero exposure from systemic maternal administration was associated with hemolysis in neonates with glucose-6-phosphate dehydrogenase (G6PD) deficiency [178], and cutaneous phototoxicity in neonates who received phototherapy for jaundice [179,180]. An infant with G6PD deficiency can develop both side effects as the result of phototherapy for hemolytic jaundice. Methylene blue is rated a risk factor C when orally ingested, a risk factor D when injected intra-amniotically, and should be considered a risk factor X in a fetus with suspected G6PD deficiency [59]. Although intracolonic injection during pregnancy may be safe, colonoscopic injection should be avoided because of the known, significant risks of intra-amniotic injection and the dearth of data on the fetal safety of intracolonic maternal injection.

India ink is also used to tattoo colonic lesions. A literature review failed to reveal any clinical studies on the fetal safety of India ink during pregnancy.

### *Iodinated contrast for endoscopic retrograde cholangiopancreatography: diatrizoate*

Diatrizoate, a contrast agent, is injected into the biliary tree and pancreatic duct during ERCP. It was used in diagnostic and therapeutic amniography without fetal harm [181–187], except for possible fetal thyroid toxicity. For example, 7 of 69 infants who were exposed to radiopaque media in utero had congenital malformations. The standardized relative risk

for drug administration was 1.34; the slightly increased risk in this study was not statistically significant [35]. Similarly, 14 pregnant patients received iodinated contrast material during intraoperative cholangiography without fetal complications [188].

When administered intra-amniotically and solubilized in oil, diatrizoate can transiently impair fetal thyroid function. For example, seven pregnant women received diatrizoate that was solubilized in oil within 2 weeks of term. Five days postpartum, six of their infants had markedly elevated thyroid-stimulating hormone levels, including three who had clinically evident hypothyroidism [189]. This toxicity did not occur when diatrizoate was solubilized in water because inorganic iodine dissolved in water does not cross the placenta [190,191]. For example, 28 infants whose mothers had received intra-amniotic injections of 50 ml of diatrizoate that was solubilized in water during pregnancy had normal cord blood parameters of thyroid function at birth [192].

Diatrizoate is classified as a class D drug during pregnancy [34]. The risks of diatrizoate should be less from cholangiography than amniography because of less fetal absorption. The theoretical risk of transient fetal hypothyroidism from diatrizoate injection is less than the real threat of maternal cholangitis from choledocholithiasis; diatrizoate injection is, therefore, acceptable for therapeutic ERCP during pregnancy. Risks are minimized by use of a low concentration, of a water soluble form, few intraductal injections, low-pressure injection, and avoidance of unnecessary pancreatography.

### *Lidocaine*

Lidocaine, an aminoethylamide local anesthetic, is often applied topically to the oropharynx before EGD and ERCP to decrease the gag reflex and alleviate oropharyngeal discomfort during endoscopic intubation. No fetal harm occurred after pregnant rats received 6.6 times the maximal recommended equivalent human dose [59]. Lidocaine rapidly crosses the placenta in humans [193]. Epidural lidocaine administration during parturition resulted in mild transient neurologic depression of the newborn in some studies [194], but not others [195]. The current consensus is that lidocaine block during parturition is safe to the fetus [196,197]. In the Collaborative Perinatal Project, lidocaine was generally not associated with fetal malformations among 293 infants with first trimester in utero exposure [35]. Lidocaine is classified as a risk factor B during pregnancy [59]. Although the teratogenic potential of oral lidocaine is small, topical application is often unnecessary for endoscopy during pregnancy. The pregnant patient who is administered topical lidocaine should be instructed to gargle and spit out, rather than swallow, the preparation to minimize systemic absorption.

### *Electricity*

During pregnancy, electric current crossing the uterus traverses the fetus because amniotic fluid is an excellent conductor of electricity [198]. The fetal

risk from electricity depends upon the voltage and current amplitude, duration, frequency, type (monopolar versus bipolar current), and path through the body. Fetal mortality is 25% to 75% from electric shock with household current [199,200], about 50% from lightning strikes [201], and extremely rare from electroconvulsive therapy [202], or direct current cardioversion during pregnancy [203].

Electricity is used for endoscopic hemostasis, hot biopsy, polypectomy, and papillotomy. Endoscopic current is delivered at a very high frequency, but the voltage and pulse duration varies with the endoscopic technique. The theoretical risks from controlled electrocautery during endoscopy are much less than that from hand-to-foot electric shock in household accidents. Monopolar current should not be used during endoscopy during pregnancy to minimize stray current conduction through the uterus. During bipolar endoscopic electrocautery, the grounding pad should be positioned so that the uterus is not directly between the electrical catheter and grounding pad to minimize fetal exposure [34]. Although probably safe, polypectomy or electrocautery are currently considered experimental during pregnancy because of insufficient data. Colonoscopic polypectomy during pregnancy is reasonably deferred to postpartum. Papillotomy is indicated during pregnancy for choledocholithiasis discovered at ERCP, as described below.

### **Special considerations in endoscopy for gastrointestinal bleeding during pregnancy**

EGD and sigmoidoscopy are most commonly performed during pregnancy for gastrointestinal bleeding; physicians usually avoid endoscopy for weaker indications during pregnancy [5,204]. Hematocrit is not a reliable indicator of bleeding severity in the general population because of the lag between blood loss and hematocrit decline. The hematocrit is an even less reliable indicator during pregnancy because of the conflicting effects of intravascular fluid accumulation and increased total erythrocyte mass during normal pregnancy [205]. Maternal blood pressure is not a reliable indicator of fetal well being [206]. The central venous pressure is usually lower in the pregnant woman. Fluid, including transfusions of packed erythrocytes when indicated, should be aggressively administered in pregnant patients because of the extraordinary fetal sensitivity to hypoperfusion, the difficulty in assessing volume status during pregnancy, and the usually satisfactory cardiac function of pregnant patients. Hemodynamic compromise from bleeding during pregnancy leads to maternal catecholamine release, which produces uterine vasoconstriction, placental hypoperfusion and potential fetal injury [207,208]. The pregnant patient should receive supplemental oxygenation during endoscopy because of the extraordinary fetal sensitivity to maternal hypoxemia.

Pregnant patients with significant gastrointestinal bleeding should have obstetric consultation. Tocolytics may be necessary if premature uterine

contractions occur [209,210]. An abdominal roentgenogram is not routinely ordered in pregnant patients with gastrointestinal bleeding because of radiation teratogenicity.

Nasogastric aspiration in patients with active upper gastrointestinal bleeding before EGD helps prevent aspiration during endoscopy and helps clear the endoscopic field. This maneuver is even more important during pregnancy because the pregnant state promotes nausea and vomiting, particularly during the first trimester, as a result of the effects of gestational sex hormones and gastric compression by the gravid uterus [211]. The risk of pulmonary aspiration in the actively bleeding patient is also reduced by placing the patient in the left lateral decubitus position and by pharyngeal aspiration by the nurse assistant, when necessary, during EGD.

## **Endoscopy during pregnancy: clinical studies and recommendations**

### *Esophagogastroduodenoscopy*

#### *Clinical studies*

In a case-controlled study of 83 EGDs during pregnancy, EGD indications included gastrointestinal bleeding in 37, abdominal pain in 28, vomiting in 14, and other in 4 [30]. The mean gestation was 20 weeks. EGD was diagnostic in 65 patients (79%). The diagnostic yield was 95% for acute gastrointestinal bleeding, and ranged from 50% to 82% for the other indications. Esophagitis was identified in 62% of patients with a diagnostic EGD. Similarly, in a mailed survey of 3300 gastroenterologists who provided information about 73 EGDs during pregnancy, endoscopic diagnoses included esophagitis in 34%, gastritis in 25%, ulcers in 11%, Mallory-Weiss tear in 10%, other in 13%, and none in 7% [212]. Pregnant patients have an increased risk of reflux esophagitis because of esophageal dysmotility that is induced by gestational hormones and gastric compression by the gravid uterus [213–215].

In the case-controlled study, endoscopic medications included meperidine in 47 patients (mean dose in these patients,  $57.9 \pm 21.0$  mg), midazolam in 21 (mean dose,  $2.8 \pm 1.4$  mg), diazepam in 18 (mean dose,  $7.1 \pm 4.3$  mg), and other in four patients. Five patients received 0.4 mg of naloxone after EGD. No maternal complications occurred in this study. EGD did not induce labor. Excluding six voluntary abortions and three unknown pregnancy outcomes, 70 (95%) of 74 patients delivered healthy infants. Nine infants were born prematurely, one of whom died of severe prematurity. In this study, the four bad pregnancy outcomes, including three stillbirths and one 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 mean Apgar scores of live-born infants at 1 and 5 minutes were not significantly different from the

mean American scores [216,217]. EGD did not induce abnormal fetal heart rates in three cases with fetal cardiac monitoring [30].

Although the rate of 95% healthy infants in the study patients was not significantly different from the national American average of 98.4% for all pregnancies [216,217], it might be argued that the 3.4% lower rate in study patients represents a trend that could reach statistical significance in a larger study. Comparison of study patients with the national average is, however, unsatisfactory because study patients had a condition that required EGD that increased their obstetric risks, and had a different age, racial, and geographic distribution than the American population of pregnant women. The pregnant patients who underwent EGD, therefore, were compared with 48 pregnant controls matched for age, race, hospital, and EGD indication who did not undergo EGD because of the pregnancy. The pregnancy outcome in study patients, including the mean infant Apgar scores at 1 and 5 minutes and the frequency of male sex, multiparity, low birth weight, infant mortality, congenital defects, and delivery by cesarean section, was not statistically significantly different from the mean scores or rates for these controls. For example, 95% of pregnant patients who underwent EGD delivered healthy infants compared with 94% of controls. Study patients who underwent EGD had as good a pregnancy outcome as the controls despite the fact that the study patients were generally sicker and had a stronger indication for EGD [30]. 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 and efficacy of EGD performed for gastrointestinal bleeding. Excluding two unknown pregnancy outcomes and four voluntary abortions, the fetal outcomes in the 31 other patients who underwent EGD for acute bleeding included 30 (97%) healthy infants and one stillbirth. This pregnancy outcome was at least as good as that for the pregnant study controls who did not undergo EGD for acute bleeding.

In the mailed survey, 71 of 73 patients (97%) who underwent EGD during pregnancy delivered healthy infants; two miscarriages occurred at 1 and 5 months after EGD for reasons unrelated to EGD [212]. A mailed survey is, however, subject to selection bias because of its reliance on voluntary reporting of complications. The rate of EGD during pregnancy per physician reported in the mailed survey was only about 1% of the rate that was reported in the case controlled study (73 EGDs by 3300 physicians versus 83 EGDs by 53 physicians).

No direct complications from EGD were reported in case reports of 28 other pregnancies [218–237]. The pregnancies resulted in 21 healthy infants, one voluntary abortion, three stillbirths for reasons unrelated to EGD, and one extremely premature birth for reasons unrelated to EGD. One delivery was described as normal but the infant's health was not stated [234]. One mother died from metastatic gastric cancer before delivery [219].

Two historical studies further support the safety of EGD during pregnancy. In 1961, McCall and colleagues [238] published a pioneering study on flexible esophagoscopy and gastroscopy in 15 pregnant patients, performed at 5 to 9 months of gestation. Eleven patients had pyrosis or epigastric pain. Patients with these symptoms generally had edema, erythema, or erosions in the distal esophagus or gastric cardia identified at EGD. Patients received 100 mg of meperidine and 0.4 mg of atropine hypodermically before endoscopy. Fourteen patients (93%) delivered at term. There were nine spontaneous vaginal deliveries, five low forceps deliveries, and one cesarean section. Although fetal outcomes were not specifically addressed, apparently two neonates had distress at birth; one had a mother with chronic hypertension and one had a mother with hyperemesis gravidarum and hematemesis during pregnancy. Neither neonatal complication seemed to be temporally or etiologically related to the endoscopy.

In 1967, Castro [239] reported on esophagoscopy and esophagoscopic biopsy performed from the third to the ninth month of gestation in 43 females with pyrosis. He noted a high rate of endoscopic and pathologic findings of reflux esophagitis in these patients. The study did not analyze or report the safety of esophagoscopy during pregnancy. Table 2 summarizes the clinical data on fetal safety of EGD and other endoscopic procedures during pregnancy.

#### *Clinical recommendations*

These clinical studies suggested that the benefits of EGD, when performed for overt gastrointestinal bleeding, exceeded the risks; EGD has a high diagnostic sensitivity, provides an immediate diagnosis, and can be used to apply hemostasis. Nausea and vomiting are common during the first trimester [240]. EGD is rarely helpful and rarely indicated for nausea and vomiting, or even hyperemesis gravidarum, during pregnancy (Table 3). These conditions are almost always caused by physiologic changes during pregnancy, including gestational female sex hormones and gastric compression by the enlarged gravid uterus, and rarely arise from pathologic mucosal or mural gastrointestinal lesions. EGD is reserved for atypical situations, such as severe and refractory nausea and vomiting accompanied by significant abdominal pain (but not pyrosis), hematemesis, or signs of gastroduodenal obstruction.

Pyrosis from gastroesophageal reflux is also extremely common during pregnancy and is attributed to gestational hormones and gastric compression by the enlarged gravid uterus [241]. EGD is neither necessary nor indicated to evaluate typical symptoms of gastroesophageal reflux during pregnancy. EGD should be reserved for cases when the presentation is atypical and severe, when the condition is refractory to intense pharmacologic therapy, when esophageal surgery is contemplated, and when complications, such as gastrointestinal bleeding or dysphagia, occur. Surgical

Table 2

Review of the literature on the safety of gastrointestinal endoscopy during pregnancy

Type of study	Reference	Number of patients	Fetal outcome
<b>Esophagogastroduodenoscopy</b>			
Case controlled	Cappell et al, 1996 [30]	83	95% healthy infants vs. 94% in study controls.
Mailed survey	Cited in Frank 1994 [212]	73	97% healthy infants.*
Clinical series	Castro 1967 [239]	43	Pregnancy outcomes unstated.
Clinical series	McCall et al, 1961 [238]	15	Apparently 93% healthy infants (two poor outcomes mentioned).
Case reports	See text	28	22 healthy infants, three stillbirths unrelated to EGD, one very prematurely born infant, one voluntary abortion, & one maternal death from metastatic cancer.
<b>Therapeutic esophagogastroduodenoscopy-variceal sclerotherapy</b>			
Clinical series	Kochhar et al, 1999 [247]	10	All 10 infants had normal vaginal delivery at term.
Clinical series	Aggarwal et al, 2001 [252]	17	Eight healthy infants, three stillbirths, one neonatal death, & five voluntary abortions.
Case reports	Dhiman et al, 2000 [248]	2	Two uncomplicated deliveries.
Case reports	See text	7	Seven healthy infants.
<b>Therapeutic esophagogastroduodenoscopy-nonvariceal bleeding lesions</b>			
Case report	Cappell et al, 1996 [30]	1	One healthy infant.
Case report	Macedo et al, 1995 [253]	1	One uncomplicated pregnancy.
Case report	Brunner et al, 1998 [221]	1	One healthy infant.
<b>Therapeutic endoscopic retrograde cholangiopancreatography (ERCP)</b>			
Clinical series	Jamidar et al, 1995 [263]	23	89% healthy infants. One neonatal fatality related to post-ERCP pancreatitis.
Clinical series	Farca et al, 1997 [265]	10	10 healthy infants after ERCP with biliary stenting.
Clinical series	Vandervoort et al, 1996 [266]	6	All delivered healthy infants with Apgar scores higher than eight or continuing uneventful pregnancy as of publication date.
Clinical series	Sungler et al, 2000 [264]	5	Five healthy full-term infants.
Case reports	See text	32	Eighteen healthy infants, eight other “uneventful” pregnancies, one healthy premature infant, five unknown outcomes.
<b>Diagnostic endoscopic retrograde cholangiopancreatography</b>			
Clinical series	Vandervoort et al, 1996 [266]	8	All deliveries resulted in healthy infants; continuing pregnancy in others uneventful so far.

Table 2 (continued)

Type of study	Reference	Number of patients	Fetal outcome
Case reports	See text	4	Four healthy infants (including one pair of twins), one spontaneous abortion unrelated to ERCP.
Percutaneous endoscopic gastrostomy (PEG)			
Case reports	Godil and Chen, 1998 [304]	2	Two healthy infants.
	Shaheen et al, 1997 [233]	1	One infant with same genetic syndrome as mother.
	Koh and Lipkin, 1993 [303]	1	One healthy infant.
Percutaneous endoscopic gastrojejunostomy			
Case reports	Serrano et al, 1998 [305]	2	Two healthy infants.
	Pereira et al, 1998 [306]		
Endosonographic cystogastrostomy			
Case report	Gyokeres et al, 2001 [254]	1	One healthy infant born after pseudocyst drainage by endosonographic cystogastrostomy.
Case report	Ryan 1992 [255]	1	Temporarily successful cystogastrostomy but patient required surgery 2 months later because of drain migration. Subsequently delivered healthy baby.
Flexible sigmoidoscopy			
Case controlled	Cappell et al, 1996 [114]	46	38 (93%) of 41 infants born healthy, one unknown fetal outcome, & four voluntary abortions. Similar rate in controls.
Mailed survey	Cited in Frank 1994 [212]	13	All infants healthy*
Case reports	See text	10	Six healthy infants, two miscarriages unrelated to sigmoidoscopy, two voluntary abortions.
Therapeutic partial colonoscopy – colonoscopic release of impacted gravid uterus			
Clinical series	Seubert et al, 1999 [317]	5	All five procedures successful. No pregnancy losses due to procedure, but pregnancy outcome not reported.
Colonoscopy			
Clinical series	Cappell et al, 1996 [114]	8	Six healthy infants, one miscarriage unrelated to procedure, & one voluntary abortion.
Mailed survey	Cited in Frank 1994 [212]	13	No complications*.
Case reports	See text	7	Four healthy infants, two stillbirths, & one unknown fetal outcome.

\* See text for discussion about limitations in the reliability of a mailed survey.

Table 3  
 Indications for esophagogastroduodenoscopy during pregnancy<sup>a</sup>

Accepted indication in general population	Recommendations for EGD in pregnancy
Gross acute bleeding <sup>b</sup>	Generally recommended for acute bleeding causing hemodynamic instability or requiring packed erythrocyte transfusions.
Nausea and vomiting	Generally unnecessary, Nausea and vomiting usually caused by physiologic effects of pregnancy and not mucosal or mural gastrointestinal disease. Consider EGD for atypical situations such as when condition is severe, refractory to therapy, and associated with significant abdominal pain (but not pyrosis).
Pyrosis	Generally unnecessary. Consider EGD when presentation atypical, severe, and refractory to intense medical therapy. Generally recommended when complications such as dysphagia or gastrointestinal bleeding occur or when esophageal surgery is contemplated.
Abdominal pain	Generally unnecessary. Consider when pain severe or refractory to medical therapy. Generally recommended when complications such as gastrointestinal bleeding occur.
Dysphagia	May be necessary when cause unknown. Strongly consider when associated with involuntary weight loss.
Follow-up of gastric ulcer	Use judgment and discretion. Strongly consider delay of follow-up EGD for a gastric ulcer that appeared benign by endoscopy and by histopathologic analysis of endoscopic biopsies.
Guaiac-positive stool	Consider endoscopy when associated with iron deficiency anemia if colonic lesion excluded.
Biopsy of gastrointestinal mass/suspected cancer	Generally recommended.

<sup>a</sup> This is a general outline of one physician's suggestions for patient care. Each physician should use his or her own clinical judgment in each clinical situation. Special precautions when performing endoscopy during pregnancy are discussed in text. Endoscopy is contraindicated during pregnancy when the patient has placental abruption, ruptured membranes, imminent delivery, or uncontrolled eclampsia.

<sup>b</sup> Hematemesis or melena.

intervention is rarely necessary for gastroesophageal reflux during pregnancy, and the symptoms of gastroesophageal reflux typically improve or resolve postpartum.

EGD should be performed in relatively stable patients with electrocardiographic monitoring after obstetric consultation and after normalization of vital signs, which may require transfusion of packed erythrocytes and supplemental oxygenation. Pulse oximetry renders endoscopy safer by avoiding endoscopy in hypoxic patients, by identifying patients who require

supplemental oxygen administration or endotracheal intubation before endoscopy, and by alerting physicians to respiratory decompensation during endoscopy [242,243]. Fetal monitoring should be performed, if available, when fetal heart sounds are detectable. Informed consent is particularly important during pregnancy. The patient should be informed of the benefits and apparent safety of endoscopy, but the patient should be cautioned that the potential fetal risks are incompletely characterized.

*Therapeutic esophagogastroduodenoscopy: clinical studies and recommendations*

Pregnancy may increase the risk of variceal bleeding from portal hypertension because of the gestational increase in plasma volume [244,245]. Endoscopic variceal sclerotherapy or banding are particularly attractive therapies during pregnancy because intravenous vasopressin seems to be ineffective during pregnancy because of a circulating gestational vasopressinase and variceal surgery can cause fetal wastage [246]. In one clinical series, 10 patients underwent a mean of three (range one to six) esophageal variceal sclerotherapy sessions with absolute alcohol during pregnancy for active variceal bleeding in five and for prophylaxis in five [247]. Hemostasis was achieved in all five actively bleeding patients. One patient suffered a complication from sclerotherapy of an esophageal stricture, successfully treated using Savary-Gilliard dilators (Wilson-Cook Medical, Winston-Salem, NC). All patients had a normal vaginal delivery at term [247]. In another study, two pregnant patients successfully underwent three or seven sessions of endoscopic sclerotherapy with either sodium tetradecyl sulfate or N-butyl-2 cyanoacrylate for active or recent maternal bleeding [248]. Both patients had uncomplicated deliveries, although the health of the neonates was not specified. Seven other patients successfully underwent endoscopic sclerotherapy, using sodium tetradecyl sulfate in two, polidocanol in four, and polidocanol plus epinephrine in one, for actively or recently bleeding esophageal varices, with delivery of healthy infants in all cases [30,218,249–251]. The available data should justify endoscopic sclerotherapy during pregnancy for actively bleeding esophageal varices after informed consent.

One study reported less favorable pregnancy outcomes after sclerotherapy, attributable to the underlying maternal disease. Seventeen patients with noncirrhotic portal hypertension, caused by extrahepatic portal vein obstruction or portal fibrosis, underwent endoscopic sclerotherapy for variceal bleeding without complications during pregnancy [252]. Pregnancy outcomes included six healthy full-term infants, two preterm deliveries, three stillbirths, one neonatal death, and five voluntary abortions.

Three patients underwent endoscopic hemostasis for nonvariceal causes of bleeding during pregnancy. One patient underwent endoscopic sclerotherapy for bleeding from a Mallory-Weiss tear and had an uncomplicated

pregnancy, although the infant's health was not specifically stated [253]. Another patient underwent endoscopic thermocoagulation of a bleeding duodenal ulcer and delivered a healthy infant [30]. Another patient underwent endoscopic epinephrine injection for bleeding esophageal ulcers and subsequently delivered a healthy infant [221]. Therapeutic EGD for nonvariceal bleeding is currently considered experimental during pregnancy because of scant data. If contemplating therapeutic endoscopy, the pregnant patient should be informed of potential risks versus benefits, and apprised that the fetal risk is poorly characterized.

#### *Therapeutic endoscopic ultrasound*

Therapeutic endoscopic ultrasound is rarely indicated during pregnancy. A large pancreatic pseudocyst might rupture during pregnancy because of increasing intra-abdominal pressure from the growing gravid uterus. A large pancreatic pseudocyst can be safely drained by an expert endoscopist by transgastric puncture using endoscopic ultrasonography, if the pseudocyst is near the gastric wall. Gyokeres et al [254] punctured a large, chronic nonresolving pseudocyst by a needle knife and inserted a catheter over a guidewire under endoscopic ultrasound guidance in a pregnant patient at 21 weeks of gestation. The patient experienced transient mild pyrexia and abdominal pain, but these symptoms resolved after the insertion of a 10 French stent and pseudocyst collapse. Follow-up abdominal ultrasound revealed no residual pseudocyst and the mother delivered a healthy baby at 36 weeks of gestation. In another case, endoscopic cystogastrostomy during pregnancy was temporarily successful, but a different therapy was subsequently performed because of drain migration [255]. The mother subsequently delivered a healthy baby. Endoscopic cystogastrostomy is currently experimental during pregnancy.

#### *Endoscopic retrograde cholangiopancreatography*

##### *Clinical studies*

Approximately 8% of women have cholelithiasis during pregnancy [256, 257]. Cholecystectomy or ERCP can usually be delayed until postpartum for uncomplicated cholelithiasis [258,259], but choledocholithiasis usually requires urgent therapy because of potentially life-threatening cholangitis or gallstone pancreatitis.

Cholecystectomy is the second most common nonobstetric surgical procedure that is performed during pregnancy [10]. Symptomatic choledocholithiasis is best managed by therapeutic ERCP in the nonpregnant patient to avoid complex biliary surgery during cholecystectomy. Therapeutic ERCP for choledocholithiasis is theoretically a more attractive alternative to biliary surgery during pregnancy because surgery entails a risk of fetal wastage [260,261]. In experienced hands, therapeutic ERCP in the

general population has acceptable morbidity of about 5% to 10% and low mortality of about 0.5% to 1.0% [262]. Diagnostic ERCP during pregnancy poses greater theoretical fetal risks than EGD because of longer procedure time, prolonged duodenal intubation, higher risk of maternal complications, increased administered medications, and roentgenographic exposure. Therapeutic ERCP adds further risks.

Jamidar and colleagues [263] analyzed 29 ERCPs that were performed on 23 pregnant patients at six medical centers. The patients' average age was 25.3 years. Fifteen ERCPs were performed in the first trimester, eight in the second trimester, and six in the third trimester. All patients had abdominal pain. Twenty-one patients had elevations of serum biochemical parameters of liver function, and one had an elevated serum amylase. Eighteen had abnormal gallbladder or choledochal findings that were detected by abdominal ultrasonography. Indications for ERCP included suspected choledocholithiasis in 19, severe cholestasis without viral hepatitis in two, and severe, recurrent idiopathic pancreatitis in two. ERCP findings included choledocholithiasis in 15, bile leaks after open or laparoscopic cholecystectomy in three, primary sclerosing cholangitis in two, cholelithiasis and a dilated choledochus in one, pancreas divisum in one, and pancreatic stricture after previous surgical sphincteroplasty in one. Therapy at ERCP included sphincterotomy with stone extraction for choledocholithiasis in 14, biliary stent placement for primary sclerosing cholangitis in two, endoscopic sphincterotomy for possible choledocholithiasis in one, biliary stent for choledochal dilation and cholecystolithiasis in one, minor papilla endoscopic sphincterotomy and pancreatic stent placement for pancreas divisum-associated pancreatitis in one, and a biliary stent for a bile leak in one.

Excluding two unknown pregnancy outcomes and two elective abortions, 17 of the 19 pregnancies (89%) resulted in healthy infants, including 16 born at term. One pregnant patient spontaneously aborted 3 months after ERCP, but the abortion did not seem to be temporally or etiologically related to the procedure. One pregnant patient, who experienced pancreatitis after each of three ERCPs for pancreatic stent placement to treat a pancreatic stricture, delivered an infant at term who appeared to be healthy at birth but who died 26 hours later from pulmonary hypertension and sepsis. This was the only maternal or fetal procedure-related complication.

In a prospective study, five pregnant patients successfully underwent therapeutic ERCP for biliary pancreatitis or jaundice [264]. Two of the patients then underwent laparoscopic cholecystectomy during pregnancy. All patients delivered healthy babies at term.

In a Mexican study, 10 pregnant patients underwent biliary stenting without sphincterotomy for indications of choledocholithiasis in six, biliary pancreatitis in two, and retained choledochal stones after cholecystectomy in two [265]. Three patients were in the first trimester, five were in the second trimester, and two were in the third trimester. Cannulation was performed with a guidewire without sphincterotomy. Fluoroscopy was briefly used to

confirm correct cannula insertion. Nine patients had rapid symptomatic relief. The remaining patient developed recurrent pain one day after ERCP that was caused by a stone impacted in the left intrahepatic duct. This symptom was relieved by performing a sphincterotomy and placing a stent in this duct. All mothers subsequently remained asymptomatic during the pregnancy and delivered healthy infants.

A Boston study reported in an abstract about six ERCPs and sphincterotomies that were performed for choledocholithiasis during pregnancy [266]. All therapies were successful, with only one mild maternal complication of mild transient pancreatitis and no procedure-induced premature labor. All infants born to the date of the publication had Apgar scores greater than eight at birth, and the other continuing pregnancies were described as uneventful.

Therapeutic ERCP was reported in 32 additional pregnant patients [133,250,267–282]. The patients were 20 to 29 years old, except for four younger and eight older patients. Symptoms included abdominal pain in 29, nausea and vomiting in 19, jaundice in 17, and pyrexia in nine. Two patients had recently undergone cholecystectomy without common bile duct exploration and two patients had previously undergone laparoscopic cholecystectomy. At the time of ERCP, nine patients were in the first trimester, 11 patients were in the second trimester, 11 patients were in the third trimester, and one was not reported. Serum biochemical parameters of liver function were elevated in 22, including hyperbilirubinemia in 21, and elevated serum alkaline phosphatase levels in 16. Fourteen had hyperamylasemia. Abdominal ultrasonography, which was reported in 28 patients, demonstrated a dilated choledochus and choledocholithiasis in 10, dilated choledochus and cholecystolithiasis in 10, and other biliary abnormalities in eight. ERCP indications included a dilated choledochus and choledocholithiasis in 10, dilated choledochus and cholecystolithiasis in nine, suspected gallstone pancreatitis in 11, and persistently elevated serum bilirubin and alkaline phosphatase levels in two. ERCP revealed a dilated choledochus and choledocholithiasis in 15, choledocholithiasis in eight, edematous papilla and cholecystolithiasis in two, cholecystolithiasis in two, dilated choledochus and cholecystolithiasis in one, impacted choledochal stone in one, stones in the right intrahepatic ducts in one, and other in two. Therapeutic ERCP included sphincterotomy and stone extraction in 22, sphincterotomy for cholecystolithiasis in five, sphincterotomy with unsuccessful stone extraction and biliary stent placement in two, and sphincterotomy with unsuccessful stone extraction in one. Three patients had a transpapillary stent advanced into the gallbladder after sphincterotomy because of residual cholecystolithiasis. Excluding the four patients who had previously undergone cholecystectomy, 26 of 28 patients had cholecystectomy successfully deferred until postpartum after ERCP. The 27 reported pregnancy outcomes included 18 healthy infants delivered at term, one healthy premature baby, and eight “uneventful” pregnancies. One patient presented with preterm uterine

contractions that were associated with ascending cholangitis, but tocolysis was achieved and maintained during ERCP with magnesium sulfate [250]. Another patient developed preterm uterine contractions during ERCP, but tocolysis was achieved with terbutaline, and the pregnancy was carried to term [272]. Another patient suffered transient exacerbation of pancreatitis after ERCP which was managed conservatively without clinical sequelae [269].

Diagnostic ERCPs have been reported during pregnancy. In these cases, ERCP revealed findings that were generally managed surgically. For example, one patient presented clinically with gallstone pancreatitis during the third trimester. Abdominal ultrasound revealed cholecystolithiasis with a nondilated choledochus [283]. ERCP performed after pancreatitis resolution revealed a gallstone that was impacted in the cystic duct and no choledocholithiasis. The patient underwent laparoscopic cholecystectomy for acute cholecystitis and subsequently delivered a healthy infant at term. Two pregnant patients underwent diagnostic ERCP for symptomatic cholelithiasis that revealed no choledocholithiasis and then underwent laparoscopic cholecystectomy [284,285]. They both delivered healthy infants. One pregnant patient underwent ERCP during the second trimester for cholestasis and choledochal dilatation on abdominal ultrasound [286]. ERCP revealed high-grade choledochal obstruction and a suggestion of a mass in the head of the pancreas. Healthy twins were delivered by cesarean section 8 weeks later. At this surgery, unresectable metastatic pancreatic cancer was diagnosed. The patient died 3 months postpartum. Another patient underwent diagnostic ERCP during pregnancy with the finding of a type I choledochal cyst [287]. This patient was initially managed non-operatively because of the pregnancy, but suffered an acute abdomen with biliary peritonitis from choledochal cyst rupture at 18 weeks of gestation. She underwent successful emergency laparotomy but spontaneously aborted postoperatively. In another study, reported as an abstract, eight diagnostic ERCPs during pregnancy resulted in either delivery of healthy infants with Apgar scores greater than eight at birth, or the pregnancy was described as continuing but uneventful at the date of publication [266]. One patient underwent diagnostic ERCP to define the anatomy of a pancreatic pseudocyst, and subsequently underwent cystogastrostomy using endoscopic ultrasound [255].

One patient underwent percutaneous transhepatic cholangiography as an alternative to diagnostic ERCP during pregnancy to delineate the anatomy of a choledochal cyst that had been identified by abdominal ultrasonography [288]. The patient underwent laparotomy and cyst removal during the second trimester and then delivered a healthy infant by cesarean section at term. ERCP is generally preferred over percutaneous transhepatic cholangiography, however, because of greater therapeutic capability and the higher success rate in patients without ductular dilation. Moreover, percutaneous transhepatic cholangiography, like ERCP, exposes the fetus to radiation.

*Clinical recommendations*

Women with biliary colic are strongly advised to undergo laparoscopic cholecystectomy before contemplating pregnancy [289]. Pregnant patients with right upper quadrant pain, abnormal serum biochemical parameters of liver function, unexplained pancreatitis, or possible biliary sepsis should undergo abdominal ultrasonography. Abdominal ultrasound is safe during pregnancy [290,291]. When the ultrasound demonstrates cholecystolithiasis with neither choledocholithiasis nor choledochal dilation, surgeons generally defer cholecystectomy until postpartum, provided that the acute attack resolves quickly, the serum biochemical parameters of liver function rapidly normalize, and gallstone pancreatitis is not suspected [258].

ERCP should be strongly considered during pregnancy, when highly trained personnel are available, for cholelithiasis complicated by persistent cholestasis, suspected choledocholithiasis, pancreatitis, or cholangitis. ERCP should be performed, after obstetric consultation, in the hospital to be able to rapidly detect and treat complications. Maternal monitoring by continuous electrocardiography, continuous pulse oximetry, and periodic sphygmomanometry is recommended during ERCP. Fetal monitoring is recommended during intra-abdominal surgery in the third trimester [292,293]. The value of fetal monitoring during ERCP is unstudied and unknown, but this monitoring may help detect fetal distress or premature uterine contractions that require tocolytic therapy [292]. The patient may be reasonably hospitalized for 24 hours after ERCP because complications, such as pancreatitis, may be delayed [133]. To minimize fluoroscopy time, ERCP should be performed by a well-trained, thoroughly experienced endoscopist; fellows in-training should not attempt choledochal cannulation. Fetal radiation is limited by lead shielding, minimizing fluoroscopy time, and avoiding spot radiographs, which deliver more radioactive energy than fluoroscopy [133,294,295]. Photography of fluoroscopic videotapes is an alternative to spot radiography [268]. Radiation dosimetry badges that are placed on the mother's abdomen over the fetus can measure radiation exposure [133,268].

Endoscopic sphincterotomy and stone extraction should be performed if ERCP demonstrates choledocholithiasis. Endoscopic biliary stenting should be considered for severe biliary strictures and bile leaks. Siegel and Cohen [296] recommended considering endoscopic transpapillary stenting of the gallbladder after sphincterotomy for cholecystolithiasis if cholecystectomy is to be delayed until postpartum. Direct sphincterotome cannulation for diagnostic ERCP avoids another cannulation for sphincterotomy and decreases fluoroscopy time [263]. Several pregnant patients underwent successful and uncomplicated endoscopic sphincterotomy using ultrasonography to confirm sphincterotome intubation of the choledochus [32,281]. Also, one patient with a bulging papilla underwent successful and uncomplicated sphincterotomy using only visual endoscopic guidance and aspiration of bile through the sphincterotome to confirm choledochal

intubation [282]. Table 4 summarizes recommended and experimental methods to limit fetal radiation and risk during ERCP.

Severe or recurrent cholecystitis may require laparoscopic cholecystectomy during pregnancy. Approximately 100 laparoscopic cholecystectomies have been reported during pregnancy. The procedure is effective and safe, with few maternal complications and rare fetal losses [188,272,274,285,289,297]. In a literature review, all 30 pregnant patients who underwent laparoscopic cholecystectomy delivered healthy infants, including 29 who delivered at full term and one infant who was delivered 3 weeks premature [188]. Several patients developed mild uterine contractions after laparoscopy, which were successfully controlled with a single dose of terbutaline [188,297]. Laparoscopy is safest during the second trimester [298]. During the third trimester, the risk of uterine puncture during laparoscopy is greatest because the gravid uterus is so large [299]. The open laparoscopic technique decreases the risk of this complication [299]. During the first trimester, the risk of teratogenicity is greatest.

During laparoscopy on pregnant patients, intraperitoneal pressure should be maintained at 15 mm Hg or lower to ensure uterine perfusion while maintaining adequate intraperitoneal visualization [297]. Other technique modifications during pregnancy include use of carbon dioxide for pneumoperitoneum, placement of the patient in the reverse Trendelenberg in the left-side down position, and fetal intraoperative monitoring [188,272,274,285,297,300]. When cholangitis from gallstone disease presents at term, an obstetrician should deliver the infant, and a gastrointestinal surgeon should then perform gallbladder surgery at the same laparotomy, to reduce the fetal risks from maternal cholangitis [301]. Choledocholithiasis has been successfully removed by laparoscopic choledocholithotomy during pregnancy [302].

#### *Percutaneous endoscopic gastrostomy: clinical studies and clinical recommendations*

Percutaneous endoscopic gastrostomy (PEG) has advantages over other techniques of long-term intensive nutritional support during pregnancy. PEG does not require roentgenographic confirmation of tube position, as required for a nasogastric tube or central venous line, and does not require general anesthesia, as required for surgical gastrostomy. PEG is subject to the theoretical risk of uterine puncture during transabdominal needle insertion because of gastric compression by the enlarged gravid uterus. This risk is greatest during late pregnancy. Shaheen and colleagues [233] recommended marking the uppermost border of the gravid uterus using ultrasonography before PEG, so as to insert the PEG needle at least 5 cm more rostrally.

One PEG was successfully placed in a comatose patient at 13 weeks of pregnancy for intensive nutritional support to carry the pregnancy to term

Table 4

Methods of minimizing fetal radiation exposure and risk from endoscopic retrograde cholangiopancreatography during pregnancy

Reference	Measures
	Recommended measures
Current report	Formation of a team consisting of a gastroenterologist, obstetrician, radiation physicist, anesthesiologist, and surgeon to manage complicated biliary disease during pregnancy at tertiary medical centers.
Current report	Referral of patients with complicated biliary disease during pregnancy to tertiary medical centers for management by a team of experts.
Current report	Consult with a radiation physicist about reducing radiation exposure.
Current report	Informed, written, and witnessed consent to include fetal risks from radiation and ERCP.
Cappell 1998 [324]	Perform ERCP after obstetric consultation.
Cappell 1998 [324]	Anesthesiologist in attendance during ERCP to minimize medication dosage and risks.
Baillie et al, 1990 [133]	Lead shielding of the mother's abdomen except for region of proximal pancreas and biliary tree. <sup>a</sup>
Cappell 1998 [324]	Use modern fluoroscopy machine to minimize radiation leakage.
Cappell 1996 [6]	ERCP by a physician well-trained and experienced in therapeutic ERCP.
Cappell 1996 [6]	Avoid choledochal cannulation and sphincterotomy by fellows-in-training.
Baillie et al, 1990 [133]	Minimize fluoroscopy time for cannulation and confirmation of position.
Baillie et al, 1990 [133]	Avoid spot radiographs for documentation because they require considerable radiation energy.
Axelrad et al, 1994 [268]	For documentation use fluoroscopic videotaping if available.
Baillie et al, 1990 [133]	Monitor fetal irradiation by placing radiation dosimetry badges on the maternal abdomen, over the uterine fundus.
Cappell 1998 [324]	If possible, defer ERCP during the first trimester to the second trimester to reduce teratogenic potential of irradiation.
Nesbitt et al, 1996 [250]	Maintain patient in left lateral recumbent position during ERCP to promote uterine perfusion.
	Possibly helpful (optional) measures
Rahmin et al, 1994 [280]	After sphincterotomy consider biliary stenting without sweeping the choledochus with a balloon to reduce procedure time and fluoroscopy exposure.
Siegel and Cohen, 1994 [296]	In the presence of retained (gallbladder) stones after sphincterotomy and sweeping the choledochus with a balloon-tipped catheter consider biliary stenting if cholecystectomy will be delayed until postpartum.
Jamidar et al, 1995 [263]	Direct sphincterotome cannulation for diagnostic and therapeutic ERCP to decrease fluoroscopy time by avoiding the need for a second cannulation after cholangiography.
Nesbitt et al, 1996 [250]	Magnesium administration for tocolysis may also decrease biliary tract spasm during ERCP.

Table 4 (continued)

Reference	Measures
	Experimental (unproven) measures
Parada et al, 1991 [279]	Use ultrasonography, instead of fluoroscopy, to confirm sphincterotome intubation of the choledochus to avoid radiation exposure.
Zagoni and Tulassay, 1995 [282]	When papilla bulges into the duodenal lumen perform sphincterotomy using endoscopic visual guidance without fluoroscopy.
Rahmin et al, 1994 [280]	Use aspiration of bilious fluid, instead of fluoroscopy, to confirm sphincterotome intubation of the choledochus.

<sup>a</sup> The lead apron should be placed underneath the patient when using fluoroscopy with a C-arm because the radiation source lies underneath the patient.

[303]. A normal infant was delivered at 37 weeks of gestation. Three other PEGs were successfully placed during pregnancy for hyperemesis gravidarum, anorexia nervosa, or severe esophagitis, without maternal complications and with favorable fetal outcomes [233,304]. After undergoing an uncomplicated PEG during pregnancy, one mother delivered an infant who suffered from the same genetic syndrome that the mother had [233]. In addition, two percutaneous endoscopic gastrojejunostomies were successfully performed during pregnancy for severe hyperemesis gravidarum without maternal complications and with favorable fetal outcomes [305,306]. PEG is considered experimental during pregnancy because of inadequate data on fetal safety, but may be considered for life-threatening conditions. In all reported cases, PEG seemed to improve fetal outcome by ensuring maternal nutritional well-being and weight gain.

### *Sigmoidoscopy*

#### *Clinical studies*

Endovaginal ultrasound is often used for high-risk obstetric conditions and is very safe for the mother and her fetus [291,307,308]. The safety of this test indirectly argues for the safety of a limited sigmoidoscopy during pregnancy, although in sigmoidoscopy an instrument is intubated further into a hollow viscus.

No woman suffered endoscopic complications in a study of 46 patients who underwent sigmoidoscopy during pregnancy [6,114,204]. Procedure indications included hematochezia in 29, diarrhea in 10, abdominal pain in four, and other in three. The sigmoidoscope was inserted to a mean of  $38.1 \pm 14.9$  cm (range 15 to 70 cm) from the anal verge. Endoscopic medications included midazolam in four patients (range 0.8 to 2.0 mg) and meperidine in three (range 25 to 50 mg). Twenty-seven (59%) of the 46 patients, including 22 of 29 patients with rectal bleeding, had a lesion that was diagnosed by sigmoidoscopy. Excluding one unknown pregnancy outcome and four voluntary abortions, 38 (93%) of 41 pregnant women

delivered healthy infants, including 27 at term. Their mean Apgar scores were not significantly different than the mean national Apgar scores [216]. The poor pregnancy outcomes included one stillbirth, one live-born infant who died of prematurity, and one infant with a cleft palate. The incidence of congenital defects was not different from that expected in the general population [114]. Poor pregnancy outcomes occurred in high-risk pregnancies and were unrelated to sigmoidoscopy.

Pregnancy outcome in study subjects was compared to the outcome in a study control group of pregnant patients who were matched for sigmoidoscopy indications but who did not undergo sigmoidoscopy because of the pregnancy. Study patients did not have a worse pregnancy outcome than the controls despite undergoing sigmoidoscopy, as measured by mean infant Apgar scores at birth and by rates of miscarriage, neonatal demise, premature delivery, low birth weight, and delivery by cesarean section.

In case reports, ten pregnant patients who underwent sigmoidoscopy had six healthy infants, two miscarriages from causes that were unrelated to sigmoidoscopy, and two voluntary abortions [220,309–316]. No endoscopic complications were reported in 13 patients who underwent flexible sigmoidoscopy during pregnancy as gathered by a mailed survey of 3300 gastroenterologists [212]. All pregnancies resulted in delivery of healthy infants at term. This mailed survey is subject to selection bias, however, because of reliance on voluntary reporting of complications.

Five pregnant females presented at approximately 12 weeks of gestation with a gravid uterus that was incarcerated by the inferior margin of the sacral promontory [317]. Abdominal ultrasound demonstrated a retroverted uterus that was compressing the anterior rectal wall [317]. Rectosigmoid compression by the uterus in this syndrome promotes colonoscopic looping during colonic intubation. Partial colonoscopy was successfully used to release the incarceration: the torque exerted by this colonoscopic loop was used to push the uterine fundus away from the inferior margin of the sacral promontory. Release of the incarceration was signaled by abrupt patient pain relief and simultaneous decreased resistance to colonoscopic advancement. No pregnancy losses occurred from the procedure, but the pregnancy outcomes were not reported [317].

### *Clinical recommendations*

These studies suggested that sigmoidoscopy during pregnancy does not induce labor or cause congenital malformations, is not contraindicated, and should be considered in medically stable patients with important indications. Current guidelines for sigmoidoscopy during pregnancy are listed in Table 5. Sigmoidoscopy should be performed with maternal monitoring by electrocardiography and pulse oximetry, after obstetric consultation and after medical stabilization. Medical stabilization may require blood transfusions and supplemental oxygenation.

Table 5  
 Guide to indications for sigmoidoscopy and colonoscopy during pregnancy<sup>a</sup>

Accepted indication in general population	Recommendations for endoscopy in pregnancy
<b>Sigmoidoscopy</b>	
Lower gastrointestinal bleeding	Generally recommended. Consider deferral in consultation with patient when patient has long history of typical hemorrhoidal bleeding and when rectal examination confirms existence of hemorrhoids.
Sigmoid or rectal mass	Generally recommended.
Sigmoid or rectal structure/ obstruction	Generally recommended.
Severe diarrhea	Generally recommended for diagnosis when the diarrhea is prolonged or atypically severe.
Lower abdominal pain	Generally defer until after pregnancy.
Change in bowel habits	Generally defer until after pregnancy.
<b>Colonoscopy</b>	
See next column	Considered experimental because of inadequate data on safety. Would, however, strongly consider colonoscopy for suspected colonic cancer, to evaluate colonic mass of unknown cause, for uncontrolled severe colonic hemorrhage, and when necessary before urgent colonic surgery. Would generally defer surveillance colonoscopy for prior history of colon cancer or colonic polyps until after delivery.

<sup>a</sup> This is a general outline of one physician's suggestions for patient care. Each physician should use his or her own clinical judgment in each clinical situation. Special precautions when performing endoscopy during pregnancy are discussed in text. Endoscopy is contraindicated during pregnancy when the patient has placental abruption, ruptured membranes, imminent delivery, or uncontrolled eclampsia.

Sigmoidoscopy is not recommended during pregnancy for indications of a change in bowel habits, abdominal pain, a family history of colon cancer, and routine screening or surveillance. In these cases, sigmoidoscopy is best deferred until at least 6 weeks postpartum. In particular, sigmoidoscopy may be painful soon after cesarean section.

#### *Colonoscopy: clinical studies and clinical recommendations*

Guidelines for colonoscopy during pregnancy are not available because of insufficient data. Fifteen pregnant women underwent colonoscopy for colon cancer or other important indications [114,204,314,318–322]. In the largest published study, four colonoscopies were performed in the first trimester and four were performed in the second trimester [114]. Four of the patients received endoscopic medications, including meperidine in four (range 50 to 75 mg), midazolam in two (6 or 8 mg), and diazepam in one (10 mg). Pregnancy outcomes included six healthy infants, one voluntary

abortion, and one miscarriage 4 months after colonoscopy; this patient developed severe hematochezia and a severe flare of ulcerative colitis after discontinuing therapy on her own.

Excluding one case report in which the fetal outcome was not reported [320], colonoscopy was performed in the second trimester in three case reports and in the third trimester in three others [314,318,319,321,322]. Fetal outcomes included three healthy preterm infants, one healthy full-term infant, and two stillborn infants. The fetal deaths were attributed to massive colonic hemorrhage and colonic surgery in one and metastatic colon cancer in the other case. In neither case was the stillbirth temporally or etiologically related to the colonoscopy. No endoscopic complications were reported in 13 colonoscopies that were performed during pregnancy as gathered by a mailed survey of 3300 gastroenterologists [212]. This study, however, is subject to recall bias because of the retrospective nature of the questionnaire and selection bias because of the dependence on voluntary physician reporting of endoscopic complications.

Colonoscopy may be considered, after obstetric consultation, for severe, life-threatening colonic conditions or when the only alternative is colonic surgery (see Table 5). During the colonoscopy, the pregnant patient should be monitored by pulse oximetry, electrocardiography, and sphygmomanometry. Colonoscopy is not recommended during pregnancy for indications of a change in bowel habits, abdominal pain, a family history of colon cancer, and routine screening or surveillance. In these cases, colonoscopy is best deferred for several months postpartum.

Patients often are placed in the supine position during colonoscopy. The physician should avoid placing the pregnant patient with gastrointestinal bleeding in the supine position during colonoscopy because, in this position, the enlarged gravid uterus compresses the inferior vena cava, decreases venous return, and decreases uterine perfusion [323]. Maneuvers such as placing the patient in the left lateral or right lateral decubitus positions minimize vena caval compression by the gravid uterus during colonoscopy. During a difficult colonoscopy, endoscopists occasionally place the patient in the prone position to aid in colonic intubation. This colonoscopic maneuver should not be done during pregnancy; if the colonoscopy is so difficult that it necessitates this maneuver, then the colonoscopy should be aborted. External abdominal compression during colonoscopy should be applied gently and away from the uterus in patients with advanced pregnancy to avoid uterine trauma.

#### *Alternatives to gastrointestinal endoscopy*

Other tests are useful alternatives to gastrointestinal endoscopy in the general population. Test selection depends upon the gastrointestinal condition and the patient's medical status. Safety of these alternative tests during pregnancy is briefly summarized in Table 6.

Table 6

Fetal safety of diagnostic gastrointestinal examinations during pregnancy: alternatives to endoscopy

Procedure	Fetal risks	Recommendations during pregnancy
Abdominal ultrasound	Safe on basis of extensive clinical experience	First line test
Magnetic resonance imaging (MRI)	No fetal toxicity reported so far with limited experience during pregnancy	Use only if approved by a radiologist for strong indications when other tests with established fetal safety were nondiagnostic
Angiography	Radiation teratogenicity	Avoid
Bleeding scan	Risks of ionizing radiation	Avoid
Barium enema	Radiation teratogenicity	Contraindicated
Upper gastrointestinal series	Radiation teratogenicity	Contraindicated
Computerized tomogram of abdomen	Radiation teratogenicity	Avoid. Try to substitute safer alternatives of abdominal ultrasound or MRI
Abdominal roentgenogram	Small fetal radiation exposure from one or two abdominal radiographs	Use when imperative (eg, suspected gastrointestinal perforation)
Virtual colonoscopy	Radiation teratogenicity	Avoid

### Future trends

Since the publication of a review five years ago [324], endoscopy has become more widespread during pregnancy because of greater appreciation of patient benefits, better recognition of fetal safety, and technological endoscopic improvements. This trend should continue. Ultranarrow upper GI endoscopes may permit gastrointestinal intubation with minimal anesthesia and with reduced mechanical pressure on the uterus [325]. These benefits are especially attractive during pregnancy to minimize exposure to potentially teratogenic anesthetic medications and to avoid endoscopic trauma to the uterus.

Automated electroencephalogram monitors that use the bispectral (BIS) index (Aspect Medical Systems, Natick, MA) or Narcotrend (NT; Monitor Technik, Germany), are being tested to quantitatively define the level of anesthesia [326–328]. This technology might reduce anesthesia requirements for endoscopy during pregnancy and thereby decrease fetotoxicity. The fetus is routinely monitored during surgery in the third trimester to rapidly detect fetal distress. Fetal monitoring may, likewise, improve fetal safety during endoscopy, particularly for therapeutic ERCP [30].

The endoscopic management of complicated gastrointestinal disease during pregnancy, particularly symptomatic cholelithiasis, is improved by the formation of a team that includes a gastroenterologist, obstetrician, anesthesiologist, surgeon, and radiation physicist. Such a team is ideally formed at tertiary medical centers where the requisite experience and

expertise is available. Pregnant patients who present to community hospitals with complicated gastrointestinal disease could be referred to these tertiary hospitals.

Videocapsule endoscopy is currently used to examine the small bowel beyond the ligament of Treitz because this area is relatively inaccessible to conventional tube endoscopy [329]. Videocapsule endoscopy has theoretical advantages during pregnancy; the examination does not require sedation and does not cause mechanical pressure on the uterus. Videocapsule endoscopy of the upper gastrointestinal tract or colon is, however, currently impractical because EGD and colonoscopy are superior because of greater image resolution, ability to wash and clear the endoscopic field, ability to steer, and ability to perform biopsies or apply therapy. The safety of videocapsule endoscopy during pregnancy is currently unstudied and unknown. Intestinal compression by the enlarged gravid uterus might theoretically retard videocapsule progression, but this is unlikely to constitute a significant practical problem. Technical innovations could render videocapsule endoscopy a viable alternative to EGD or colonoscopy during pregnancy.

Fecal or serologic molecular markers are being experimentally used to detect early colon cancer. In a preliminary study, a multitarget molecular assay for mutations in p53, APC, microsatellite instability, and other molecular markers had a sensitivity of 91% and specificity of 100% for colon cancer [330]. Such a test could be used to screen for suspected colon cancer to limit colonoscopy during pregnancy.

Virtual colonoscopy using computerized tomography is touted as an alternative to colonoscopy in the general population [331], but has no foreseeable role in pregnancy because of radiation teratogenicity. Virtual colonoscopy using magnetic resonance imaging (MRI), rather than radiation, would theoretically be attractive during pregnancy because MRI is apparently much safer than radiation during pregnancy.

Transabdominal and transvaginal ultrasound are safe during pregnancy [9,290,291,307,308]. Transabdominal ultrasound is a relatively insensitive test [332,333], and endoscopic ultrasound is a very sensitive test [332,334] for choledocholithiasis. Current disadvantages of endoscopic ultrasound are the high procedure cost, limited instrument availability, and need for highly trained personnel [335]. During the next several years instrument costs should decline and trained personnel should become more widely available.

Endoscopic ultrasound is a theoretically attractive test to diagnose choledocholithiasis during pregnancy, as an alternative to diagnostic ERCP, because of the better documented fetal safety of ultrasound than radiation. Application of endoscopic ultrasound during pregnancy may remain limited because of the need for endoscopic intubation and inability to perform endoscopic sphincterotomy. Endoscopic ultrasound may have a future role to evaluate a submucosal gastric mass during pregnancy, but this procedure should be deferred until postpartum unless malignancy is suspected or surgical resection is contemplated.

Magnetic resonance cholangiopancreatography (MRCP) is increasingly supplanting diagnostic ERCP in the general population [336–339]. In MRI, multifrequency pulses are applied in the presence of a magnetic field gradient to excite hydrogen ions. MRI without contrast has no known harmful effects in nonpregnant humans, except in patients with metallic foreign bodies or with implanted electronic devices, such as cardiac pacemakers [340,341].

MRCP is a particularly attractive alternative to diagnostic ERCP during pregnancy because it avoids radiation teratogenicity [342]. MRI is being used increasingly to evaluate the abdomen and retroperitoneum during pregnancy [341]. Short-term exposure to electromagnetic radiation from MRI does not produce harmful fetal effects [294,341,343–345]. A recent study showed that MRI during pregnancy does not significantly affect fetal heart rate variability [346].

Gadolinium, a contrast agent for MRI, is very safe in nonpregnant patients, with an incidence of severe toxicity of about 1 per 400,000 cases, a rate that is much lower than that for iodinated contrast [347]. Gadolinium crosses the placenta in rabbits and humans [348]. Gadolinium administered as gadobenate dimeglumine, at 20 times the usual MRI dose, was safe without maternal toxicity, fetal teratogenicity, or mutagenicity in laboratory animals [349]. Gadolinium has been administered as MR contrast during pregnancy without maternal or fetal toxicity in multiple, small, clinical studies [350–352].

The American College of Radiology currently recommends that MRI examination during pregnancy be approved by a radiologist. MRI should be performed during the first trimester only if clearly indicated, if an abdominal ultrasound was or would be unhelpful for this indication, and if postponing the examination until after delivery is imprudent [340,353]. The criteria for MRI approval during the second and third trimester, after the period of fetal organogenesis, are less strict.

## **Summary**

More than 12,000 pregnant patients in the United States per annum have conditions that are normally evaluated by EGD. More than 6000 pregnant patients in the United States per annum have conditions that are normally evaluated by sigmoidoscopy or colonoscopy. About one thousand more have symptomatic choledocholithiasis during pregnancy, which is a strong indication for endoscopic sphincterotomy in nonpregnant patients. Endoscopy during pregnancy raises the unique issue of fetal safety. Endoscopic medications comprise a significant component of fetal endoscopic risks. Safety of EGD during pregnancy has been examined in a case-controlled study of 83 patients, a mailed survey of 73 patients, and 28 case reports. Safety of sigmoidoscopy during pregnancy has been examined in a case-controlled study of 46 patients, a mailed survey of 13 patients, and 10 case

reports. Safety of therapeutic ERCP during pregnancy has been analyzed in studies of 23, 10, 6, and 5 patients, and in 32 case reports. These studies suggested that EGD, sigmoidoscopy, and ERCP should be performed when strongly indicated: EGD for significant upper gastrointestinal bleeding, sigmoidoscopy for nonhemorrhoidal rectal bleeding, and ERCP for symptomatic choledocholithiasis when sphincterotomy is contemplated. PEG and colonoscopy are currently considered experimental during pregnancy because of insufficient data on fetal safety. Several cases of PEG and colonoscopy were successfully performed during pregnancy. Performance of endoscopy during pregnancy should increase with further technical refinements, and greater awareness of procedure safety.

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