American Gastroenterological Association Institute Technical Review on the Use of Gastrointestinal Medications in Pregnancy

This literature review and the recommendations therein were prepared for the American Gastroenterological Association Institute Clinical Practice and Economics Committee. The paper was approved by the Committee on February 22, 2006 and by the AGA Institute Governing Board on April 20, 2006.

Developing guidelines for the use of medications in pregnancy pose unique challenges; there are few controlled trials that include pregnant patients and even fewer that are specifically designed to study this patient population. When an adverse event occurs during pregnancy, the role of a particular medication has to be determined, taking into account the contribution of the underlying disease state and any concomitant medications to which the patient may have been exposed. Causality is best established when the same adverse event (ie, cleft palate, limb deformity) occurs repeatedly with the same drug exposure, a finding that rarely occurs.

Determining the teratogenicity of medications is an inexact science; safety in animal models does not ensure safety in humans because of species specificity and lack of data in controlled human trials. In addition, neurodevelopmental or cytologic congenital abnormalities may not manifest until late childhood, as evidenced by in utero diethylstilbestrol exposure and subsequent vaginal adenocarcinoma.[1] Often, exposure is during parturition rather than during the crucial period of organogenesis in the first trimester. If exposure does occur during organogenesis, not all medications are capable of crossing the placenta or being metabolized by the fetus during that immature stage.

This review examines the safety of medications used by practicing gastroenterologists to treat a myriad of gastrointestinal and hepatic conditions. Although most pregnant patients will take the advice of their obstetrician or primary care physician, in some cases the patient is referred for an acute or chronic illness for which the gastroenterologist has to determine therapy. Each therapy has to be individually assessed as to the potential risks versus therapeutic benefit, and the consequences of no therapy also must be included in the conversation and documented. Close communication with the patient's obstetrician is paramount.

In this review, medications are categorized under the disease state for which they are used and, when available, information regarding breast-feeding is discussed. A literature review was performed using both electronic and manual MEDLINE searches. Search terms included "pregnancy," "congenital abnormality," and "congenital anomaly" crossed with the specific disease and medication in question. The information from those reports was then reviewed and referenced if appropriate. The majority of the evidence presented in this review comes from large retrospective databases and case series. Because the literature regarding medication safety during pregnancy is limited, no pertinent citations were eliminated. Single case reports or small series may have been discarded if larger case-control series or population-based studies were available. The few controlled trials available are noted. The Food and Drug Administration (FDA) classification of drugs offers a guide to the use of medications during pregnancy. The FDA categories are listed in Table 1 and are noted for each drug discussed. Recommendations on breast-feeding come from literature review, the textbook *Drugs in Pregnancy and Lactation*,[2] and the American Academy of Pediatrics (AAP) guidelines, updated on the AAP Web site on June 15, 2005.[3]

Endoscopy

Endoscopy constitutes a large portion of the gastroenterologist's role in patient care. While many pregnant women have appropriate indications for endoscopy, fetal drug safety is a major consideration in the choice and dosage of endoscopic medications. For particularly high-risk endoscopy such as therapeutic endoscopic retrograde cholangiopancreatography (ERCP), an anesthesiologist may be helpful in titration of medications and patient monitoring. In patients who present with signif-

Abbreviations used in this paper: AAP, American Academy of Pediatrics; CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; FDA, Food and Drug Administration; GERD, gastroesophageal reflux disease; H2RA, H_2-receptor antagonist; IBS, irritable bowel syndrome; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor.

0016-5085/06/$32.00
doi:10.1053/j.gastro.2006.04.049

Table 1. FDA Categories for the Use of Medications in Pregnancy[231]

FDA pregnancy category	Interpretation
A	Controlled studies in animals and women have shown no risk in the first trimester, and possible fetal harm is remote
B	Either animal studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester
C	No controlled studies in humans have been performed, and animal studies have shown adverse events, or studies in humans and animals are not available; give if potential benefit outweighs the risk
D	Positive evidence of fetal risk is available, but the benefits may outweigh the risk if life-threatening or serious disease
X	Studies in animals or humans show fetal abnormalities; drug contraindicated

icant gastrointestinal bleeding, where diagnosis and therapeutic intervention are necessary, therapeutic endoscopes should be utilized. Table 2 summarizes the use of medications for endoscopy.

Meperidine

Meperidine, a pregnancy category B drug, is commonly used in gastrointestinal endoscopy for analgesia and sedation. Meperidine is rapidly transferred across the placenta. Peak cord blood concentrations average about 75% of maternal plasma levels. Physicians have extensive experience prescribing meperidine during pregnancy, particularly during labor. Two large studies revealed no teratogenicity from meperidine administration during the first trimester. The Collaborative Perinatal Project, a national study with the primary aim of documenting the teratogenicity of drugs taken during the first 4 months of pregnancy, followed up more than 50,000 women in 12 US centers between 1959 and 1965. They reported no teratogenicity from use of meperidine in 268 mothers with first-trimester exposure.[4] In a surveillance study of Michigan Medicaid recipients, 229,101 pregnancies were followed from 1985 to 1992. Three of 62 newborns with first-trimester in utero exposure to meperidine had major congenital defects, similar to the rate in the unexposed control group.[5] Meperidine is preferred over morphine for obstetric pain because it is slower to cross the fetal blood-brain barrier.[6] In a placebo-controlled randomized trial, there was no difference in fetal outcomes when pethidine (the European name for meperidine) was used for pain control during parturition.[7] Meperidine can cause diminished fetal beat-to-beat cardiac variability that lasts for approximately 1 hour after maternal intravenous administration[8] and is a common cause of decreased fetal cardiac variability during endoscopy. 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.

The FDA-approved labeling for meperidine carries the following warning: "Meperidine should not be used in pregnant women prior to the labor period, unless in the judgment of the physician the potential benefits out-

Table 2. Medications Used for Endoscopy

Drug	FDA pregnancy category	Recommendations for pregnancy	Recommendations for breast-feeding[2]
Ampicillin	B	Low risk to use when prophylaxis required	Compatible
Diatrizoate	D	Minimal use for therapeutic ERCP	Limited human data: probably compatible
Diazepam	D	Midazolam preferred benzodiazepine	Limited human data: potential toxicity
Electricity	—	Use for therapeutic ERCP	No human data
Epinephrine	C	Avoid unless for hemostasis	No human data: potential toxicity
Fentanyl	C	Use in low doses	Compatible
Flumazenil	C	Only for significant benzodiazepine overdose	No human data: probably compatible
Gentamicin	C	Short courses low risk, check serum levels if used for >48 hours	Compatible
Glucagon	B	Avoid except for ERCP	No human data
Lidocaine	B	Gargle and spit	Limited human data: probably compatible
Meperidine	B	Use in low doses	Compatible
Midazolam	D	Use in low doses	Limited human data: potential toxicity
Naloxone	B	Only for severe narcotic overdoses	No human data: probably compatible
PEG electrolyte	C	No human studies available	Probably low risk
Propofol	B	Avoid in first trimester	Limited human data: probably compatible
Simethicone	C	Can be avoided but low risk	No human data: probably compatible
Sodium glycol electrolyte	C	Low risk one-time use	No human data

weigh the possible hazards, because safe use in pregnancy prior to labor has not been established relative to possible effects on fetal development." Meperidine is preferred over diazepam or midazolam as an endoscopic premedication during pregnancy. Dosage of meperidine should be titrated to produce calmness, restfulness, and mild analgesia without somnolence. Approved by the AAP for use in breast-feeding mothers, a single dose is appropriate, but the possibility of accumulation should be considered if meperidine is given repeatedly. In 9 women given a single dose of 50 mg, peak breast milk levels after 24 hours still produced an average milk/plasma ratio >1.[9] In another study of 2 women who received 75 or 150 mg of meperidine, breast milk levels were significantly high even after 56 hours, reflecting the slow clearance of the metabolite.[10]

Fentanyl

Fentanyl is a pregnancy category C drug, and accumulated anecdotal experience suggests that it may be used in low doses for endoscopy during pregnancy. Fentanyl is sometimes used as an alternative to meperidine during endoscopy because of a more rapid onset of action. While not teratogenic, fentanyl was found to be embryocidal in rats administered 23 times the maximal human equivalent for prolonged periods.[11] However, in a number of human studies, maternal fentanyl administration during labor produced no neonatal toxicity.[12–15] It has been associated in single case reports with respiratory depression,[16] muscle rigidity,[17] and opioid withdrawal.[18]

Fentanyl is excreted in breast milk, but its bioavailability to the breast-feeding infant is low, so it is considered acceptable to breast-feed following its use.[2]

Propofol

Propofol is a pregnancy category B drug and is now a preferred agent for sedation in some endoscopy centers. However, it has not been extensively studied in women in the first and second trimesters and therefore is not recommended for use during this time based on the dearth of studies in the obstetric literature. It rapidly transfers across the placenta near term. In one study, 20 infants exposed to propofol during parturition had depressed Apgar scores at birth compared with unexposed controls, but the neurodepression quickly reversed.[19] Numerous other studies have failed to demonstrate any neonatal toxicity when administered during parturition, but again, the safety of first-trimester exposure has been inadequately studied.[20–22] Experience with propofol and breast-feeding is limited, but it is believed to be compatible. Small amounts are excreted into breast milk and colostrum, but the concentration is considered negligible when compared with amounts the infant receives before birth from placental transfer.[23]

Naloxone

Naloxone is a pregnancy category B drug. In subjects who are opiate dependent, small doses of naloxone precipitate a syndrome resembling that produced by opiate withdrawal. Symptoms include restlessness, anxiety, insomnia, irritability, hyperalgesia, nausea, and muscle cramps. Because opiates cross the placenta, naloxone administration is dangerous and contraindicated in the pregnant patient who is specifically opiate dependent.[24] For example, one newborn, born to a mother with opiate dependency, experienced convulsions precipitated by naloxone administration.[25] The FDA-approved labeling for naloxone has the following precaution about use during pregnancy: "Naloxone should be used in pregnancy only if clearly needed." There is one reported fatality associated with neonatal administration, and naloxone is not recommended for routine use in endoscopy during pregnancy. Administration of naloxone is appropriate, however, for pregnant patients with serious signs of potential meperidine toxicity, such as respiratory depression, systemic hypotension, or unresponsiveness. There are no human data regarding naloxone concentrations in breast milk.

Benzodiazepines

Diazepam and midazolam, pregnancy category D drugs, should have restricted use during endoscopy in pregnant patients, particularly during the first trimester. Benzodiazepines, including diazepam and midazolam, are commonly administered before gastrointestinal endoscopy to reduce anxiety, induce brief amnesia, and produce muscle relaxation. Diazepam freely and rapidly crosses the placenta and accumulates in the fetal circulation at levels equal to or higher than maternal serum levels. The FDA-approved labeling for diazepam carries the following warning about use in pregnancy: "An increased risk of congenital malformations associated with the use of minor tranquilizers during the first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided." Early studies suggested an increased risk for cleft palate.[26] However, more recent studies have not found this association.[27] There is a possible association with other congenital abnormalities, including congenital inguinal hernias, cardiac defects, pyloric stenosis, and Möbius' syndrome, after in utero exposure.[28,29] In a study of 355 infants with in utero first-trimester exposure, including diazepam in 25% of cases, there was a

congenital malformation rate of 3.1% compared with 2.6% in unexposed controls.[30] A meta-analysis of 9 cohort studies did not show any association with congenital malformations, whereas a meta-analysis of 9 case-control studies did (odds ratio [OR], 3.01; 95% confidence interval [CI], 1.32–6.84).[31] Diazepam is not recommended by the AAP because it, along with its metabolite *N*-demethyldiazepam, can accumulate in breast-fed infants.[32]

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. Midazolam crosses the human placenta, but fetal serum levels increase to only about one third to two thirds of maternal serum levels after oral, intramuscular, or intravenous maternal administration.

Midazolam appears to be preferable to diazepam for endoscopy during pregnancy because of the potential association between diazepam and oral clefts and neonatal neurobehavioral abnormalities. In a controlled study of 52 infants, exposure to midazolam during cesarean section resulted in lower Apgar scores at 1 minute after birth compared with unexposed controls.[33] Another study found similar results.[34] Two small, uncontrolled observational studies following endoscopy with sedation have not shown any adverse effects with exposure in the first or second trimesters.[35,36] Because the mechanism of action is similar to that of diazepam, midazolam should be used cautiously and in low doses during pregnancy, particularly during the first trimester. Dosages should be carefully titrated to an end point of relaxation and calmness but not somnolence.

Midazolam and its metabolite are excreted into milk, and one study has estimated that the exposure of the infant would be nil in early breast milk if breast-feeding was held for 4 hours after administration of a 15-mg dose.[37]

Flumazenil

Flumazenil, a pregnancy category C drug, is a benzodiazepine antagonist that rapidly reverses the central effects of benzodiazepines. It is sometimes used to reverse the effects of benzodiazepines administered during endoscopy. Little is known about the safety of flumazenil during pregnancy or in infants. In a case report, fetal cardiac rhythm abnormalities were reversed after a maternal diazepam overdose, and the infant was born healthy 2 weeks later.[38] Flumazenil should be used during pregnancy only if the potential benefit clearly outweighs the risks. The need for flumazenil can be prevented by careful and slow titration of benzodiazepine dosage and by use of the minimal benzodiazepine dosage required for endoscopic examination. There are no human data regarding the use of flumazenil during breast-feeding.

Simethicone

Simethicone, a pregnancy category C drug, is used to reduce gastric foam during upper endoscopy. The Michigan Medicaid Study failed to show a statistically significant difference between exposed and nonexposed pregnancies, and there is a low risk for use during endoscopy because it is not systemically absorbed.[5] There are no human data regarding use of simethicone during breast-feeding, but its risk to the breast-feeding infant is most likely negligible because it is not absorbed.

Glucagon

Glucagon is a pregnancy category B drug. Reproduction studies have been performed in rats at dosages up to 2 mg/kg twice daily (up to 120 times the human dosage) and have revealed no evidence of harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women, and thus this drug should be used during pregnancy only if clearly needed. It has not been shown to relax uterine muscle,[39] and it has been used to reverse severe hypoglycemia in 12 pregnant patients without harm.[40] Although fetal risk is incompletely characterized, administration of glucagon appears to be justified to decrease motility to help reduce procedure time and aid in cannulation of the bile duct and sphincterotomy during therapeutic ERCP because of the high risk of untreated maternal cholangitis.

Antibiotics

Ampicillin. Ampicillin, a pregnancy category B drug, is recommended by the American Heart Association as intravenous antibiotic prophylaxis for patients at high and medium risk for endocarditis (ie, artificial heart valves, certain congenital heart defects) undergoing endoscopic sclerotherapy for esophageal varices, endoscopic dilation of an esophageal stricture, and ERCP in the presence of biliary obstruction. Ampicillin, a penicillin antibiotic, rapidly crosses the placenta, and fetal serum levels equilibrate with maternal values within 3 hours of maternal administration. Physicians have extensive experience prescribing ampicillin and related penicillins during pregnancy.[4] First-trimester use in 3546 expectant mothers was not associated with any congenital malformations. Another surveillance study of 10,011 newborns with first-trimester in utero exposure noted 441 major birth defects observed compared with 426 expected.[5] In the Hungarian Case Control Surveillance of Congenital

Abnormalities Study, the rate of congenital anomalies seen after ampicillin use in 22,865 exposed women was the same as the rate of congenital anomalies seen in 38,151 controls.[41] Penicillin has been approved by the AAP as compatible with use during breast-feeding.[42]

Gentamicin. Gentamicin, a pregnancy category C drug, is recommended by the American Heart Association as part of a prophylactic antibiotic regimen for patients at high and medium risk for endocarditis undergoing ERCP in the presence of biliary obstruction. Gentamicin, an aminoglycoside antibiotic, rapidly crosses the placenta, and fetal serum levels peak at about one half of maternal levels after administration. Even though a literature review revealed no cases of gentamicin-associated congenital defects, maternal gentamicin administration may potentially cause fetal ototoxicity.[43] Nineteen of 22,865 babies (0.08%) born after exposure had a congenital abnormality versus 19 of 38,151 controls (0.05%). Given the incomplete data concerning the safety of gentamicin, caution in administering gentamicin prophylaxis for endoscopy during pregnancy, particularly during the first trimester, has been advised. The drug should be administered, however, if required to treat known biliary sepsis. Gentamicin is compatible with use during breast-feeding because small amounts get into milk and are poorly absorbed by the infant.[44]

Colonic Lavage Preparations

Polyethylene glycol (PEG) electrolyte solution has not been extensively studied in pregnancy, and it is unknown whether it can cause fetal harm. One study of 225 patients demonstrated safety of the agent when used to treat constipation.[45] Sodium phosphate solution is also used at high doses for colonic preparation. One newborn experienced bone demineralization and bone growth failure because of maternal phosphate use; however, the mother had repeatedly taken phosphate enemas during pregnancy.[46] Because full colonoscopy is rarely indicated during pregnancy, tap water enemas are recommended as bowel preparation for lower endoscopy.

Lidocaine

Lidocaine, a pregnancy category B drug, is often applied topically to the oropharynx before upper endoscopy and ERCP. No fetal harm was noted during parturition in the Collaborative Perinatal Project, where 293 infants were exposed in the first trimester.[4] The pregnant patient who is administered topical lidocaine should be instructed to gargle and spit it out, rather than swallow the preparation, to minimize systemic absorption.

Therapeutic Agents for Hemostasis

Injection of epinephrine is used during endoscopy to achieve hemostasis of actively bleeding lesions. In the Collaborative Perinatal Project, 189 infants with first-trimester in utero exposure to epinephrine had a significantly higher rate of major congenital malformations, and in particular congenital inguinal hernias, than unexposed controls.[4] This finding was not seen in the Michigan Medicaid study.[5] Epinephrine has been used during parturition without fetal toxicity. During therapeutic endoscopy, its use is to stop active bleeding, and in this clinical scenario the benefit outweighs the potential risk of its use.

Electricity is readily transferred across the uterus because amniotic fluid is an excellent conductor. Fetal risk depends on the voltage and current amplitude, duration and frequency time, and location on the body. Fetal mortality is rare from electroconvulsive therapy or direct current cardioversion during pregnancy. During endoscopy, bicap electrocautery should be used, because no grounding pad is necessary. For therapeutic ERCP with sphincterotomy, the grounding pad should be positioned so that the uterus is not directly between the electrical catheter and grounding pad.

Contrast Dye

Diatrizoate, a contrast agent injected into the biliary tree, has been used in diagnostic and therapeutic amniography without fetal harm.[47] Although it has been documented to impair fetal thyroid function and is classified as pregnancy category D, the risk of its use for cholangiography is less than for amniography because of the doses used. The risk of maternal cholangitis will likely outweigh the theoretical risk of transient fetal hypothyroidism in the appropriate clinical setting.

Nausea and Vomiting

Nausea and vomiting are extremely common symptoms during pregnancy and have multiple etiologies. Most women can be supported through their episodes without the use of antiemetics. However, for those with a protracted course or underlying conditions that may predispose to these symptoms, medical therapy is warranted to prevent complications from volume depletion. Table 3 summarizes the use of antiemetic medications during pregnancy.

Metoclopramide

As discussed in the following section on gastroesophageal reflux disease (GERD), metoclopramide is a pregnancy category B drug. Its use as an antiemetic is

Table 3. Medications Used in the Treatment of Nausea and Vomiting

Drug	FDA pregnancy category	Recommendations for pregnancy	Recommendations for breast-feeding[2]
Dolasetron	B	No human studies	No human data: probably compatible
Domperidone	C	Safety unknown	Limited human data: probably compatible
Granisetron	B	No human studies	No human data: probably compatible
Metoclopramide	B	No teratogenicity, low risk: population-based study	Limited human data: potential toxicity
Ondansetron	B	No teratogenicity, low risk: controlled trial	No human data: probably compatible
Prochlorperazine	C	No teratogenicity, low risk: large database study	No human data: potential toxicity
Promethazine	C	No teratogenicity, low risk: large database study	No human data: probably compatible
Trimethobenzamide	C	No teratogenicity, low risk: case series	No human data: probably compatible

usually confined to the first trimester, but it is also used to enhance gastric emptying throughout pregnancy. A Danish study identified 309 women over a 5-year period with singleton pregnancies and prescriptions for metoclopramide. As compared with 13,327 controls, there were no major differences in the risk for malformations (OR, 1.11; 95% CI, 0.6–2.1), low birth weight (OR, 1.79; 95% CI, 0.8–3.9), or preterm delivery (OR, 1.02; 95% CI, 0.6–1.7).[48] In a later study, 175 women treated during their first trimester were matched for age, smoking, and alcohol consumption with unexposed pregnant women. There was no difference in major malformations, but there was a higher rate of premature births (8.1% vs 2.4%).[49]

Prochlorperazine

Prochlorperazine, a pregnancy category C drug, readily crosses the placenta. However, most studies have not found an increased risk of adverse outcomes in pregnancy. In the Collaborative Perinatal Project, 877 mothers had first-trimester exposure and a total of 2023 had any time exposure. No evidence was found in either group of malformations or effects on birth weight or intelligence quotient scores up to 4 years of age.[4] In the Michigan Medicaid study, 704 women were exposed to prochlorperazine during the first trimester. There were a total of 24 major birth defects, with 29 expected.[5] There are no data available regarding its use during lactation. Drug excretion should be anticipated, and sedation is a possible effect in the breast-feeding infant.

Promethazine

Promethazine is also a pregnancy category C drug. It is an antihistamine that is occasionally used as an antiemetic during pregnancy and adjunctive therapy for narcotics during labor. The antiemetic effect of promethazine versus placebo was studied during labor.[50] In 477 women, promethazine was compared with metoclopramide for postpartum emesis. While both were superior to placebo, there was more sedation noted in the promethazine group. In the Collaborative Perinatal Project, a total of 746 exposures were reported. There was no evidence to suggest an increased risk of major or minor malformations.[4] In the Michigan Medicaid study, 1197 newborns were exposed to promethazine during the first trimester. There were 61 major birth defects seen, with 51 expected. Seventeen of these were cardiovascular events that were believed to possibly be associated with exposure.[5] There are no human data regarding breast milk levels, because the accurate detection of promethazine and the other phenothiazines is difficult given their rapid metabolism. It is expected to be present in breast milk, and the potential effects of this exposure are unknown.

Trimethobenzamide

Trimethobenzamide is a pregnancy category C drug. There are 3 studies that have followed up outcomes in women who used trimethobenzamide in their first trimester for nausea and vomiting, and there was no increase in the incidence of malformations in all 3 studies.[51–53] There are no data regarding the use of this agent during breast-feeding.

Ondansetron

Ondansetron, a pregnancy category B drug, is used for the prevention and treatment of chemotherapy-induced nausea and vomiting and for hyperemesis gravidarum. A randomized double-blind study compared intravenous ondansetron with promethazine for hyperemesis. It was well tolerated and efficacious with no side effects; however, infant outcomes were not reported in this trial.[54] Results from the Teratogen Information Services database do not demonstrate an increase in major malformations (3.6%) as compared with exposure to other antiemetics or normal controls.[55] There are no human data regarding the use of ondansetron during lactation.

Granisetron and Dolasetron

Granisetron and dolasetron are both pregnancy category B drugs. There have been no studies on pregnant humans exposed to these agents. However, pregnant rats and rabbits administered doses up to 146 times those

Table 4. Medications Used in the Treatment of Gastroesophageal Reflux and Peptic Ulcer Disease

Drug	FDA pregnancy category	Recommendations for pregnancy	Recommendations for breast-feeding[2]
Antacids			
Aluminum containing	None	Most low risk: minimal absorption	Low risk
Calcium containing	None	Most low risk: minimal absorption	Low risk
Magnesium containing	None	Most low risk: minimal absorption	Low risk
Magnesium trisilicates	None	Avoid long-term or high doses	Low risk
Sodium bicarbonate	None	Not safe: alkalosis	Low risk
Mucosal protectants			
Sucralfate	B	Low risk	No human data: probably compatible
H2RAs			
Cimetidine	B	Controlled data: low risk	Compatible
Famotidine	B	Paucity of safety data	Limited human data: probably compatible
Nizatidine	B	Limited human data: low risk in animals	Limited human data: probably compatible
Ranitidine	B	Low risk	Limited human data: probably compatible
Proton pump inhibitors			
Esomeprazole	B	Limited data: low risk	No human data: potential toxicity
Lansoprazole	B	Limited data: low risk	No human data: potential toxicity
Omeprazole	C	Embryonic and fetal toxicity reported, but large data sets suggest low risk	Limited human data: potential toxicity
Pantoprazole	B	Limited data: low risk	No human data: potential toxicity
Rabeprazole	B	Limited data: low risk	No human data: potential toxicity
Promotility agents			
Cisapride	C	Controlled study: low risk, limited availability	Limited human data: probably compatible
Metoclopramide	B	Low risk	Limited human data: potential toxicity
Treatment of *H pylori* infection			
Amoxicillin	B	Low risk	Compatible
Bismuth	C	Not safe: teratogenicity	No human data: potential toxicity
Clarithromycin	C	Avoid in first trimester	No human data: probably compatible
Metronidazole	B	Low risk: avoid in first trimester	Limited human data: potential toxicity
Tetracycline	D	Not safe: teratogenicity	Compatible

used in humans have failed to demonstrate any adverse outcomes.[56] Similarly, there are no data regarding their safety in breast-feeding.

Domperidone

Domperidone, a pregnancy category C drug, is a dopamine antagonist used for short-term treatment of nausea and vomiting and for its prokinetic properties. It is not currently available in the United States by prescription. It is not known whether it crosses the placenta, but its bioavailability after oral ingestion is low. There are no data regarding its use in breast-feeding.

GERD

Heartburn is estimated to occur in 30%–50% of pregnancies. For mild symptoms, lifestyle and dietary modifications may be all that are required. Medications for the treatment of GERD have not been routinely tested in randomized controlled trials in pregnant women. Table 4 summarizes the use of medications for GERD and peptic ulcer disease.

Antacids

Antacids that contain magnesium, aluminum, or calcium are not teratogenic in animal studies.[57] One case-control study reported a significant increase in major and minor congenital abnormalities in infants exposed to antacids during the first trimester of pregnancy.[58] However, no analysis of individual agents was conducted, and presently most antacids are considered acceptable in pregnancy in normal therapeutic doses. Magnesium trisilicate, found in alginic acid, can lead to fetal nephrolithiasis, hypotonia, and respiratory distress if used long-term and in high doses. Antacids containing sodium bicarbonate should not be used because they can cause maternal or fetal metabolic alkalosis and fluid overload. Excessive intake of calcium carbonate can result in the milk-alkali syndrome characterized by hypercalcemia, renal impairment, and metabolic alkalosis.[59] None of the antacids have been shown to concentrate in breast milk and are acceptable when breast-feeding.

Sucralfate

Sucralfate, a pregnancy category B drug, is a nonabsorbable drug that exerts a local rather than systemic effect and has been tested in a prospective randomized controlled trial. Ranchet et al evaluated 66 patients with heartburn during pregnancy.[60] Forty-two women received 1 g of sucralfate 3 times daily versus 24 women who were treated with dietary and lifestyle modifica-

tions. Sucralfate-treated women had a higher frequency of symptomatic remission than controls (90% vs 43%; $P < .05$). In rodent studies, sucralfate did not affect fertility and was not teratogenic with doses up to 50 times those used in humans. There is minimal absorption and therefore minimal excretion into breast milk, making sucralfate acceptable for breast-feeding.[2]

Cimetidine

Cimetidine is a pregnancy category B drug. In the Michigan Medicaid Birth Registry, 460 newborns were exposed to cimetidine during the first trimester and a 4.3% rate of major birth defects was observed, a rate similar to that reported in healthy controls.[5] In the Swedish Medical Birth Registry, 553 babies delivered by 547 women using various acid-suppressing agents found a 3.1% incidence rate of congenital defects compared with 3.9% of women not taking these medications.[61] Two other European databases were combined to study the incidence of congenital malformations in the progeny of women administered cimetidine, ranitidine, or omeprazole during the first trimester of pregnancy compared with unexposed controls.[62] Cimetidine was taken in 333 pregnancies, resulting in 3 stillbirths and one neonatal death; 4.7% of exposed infants had a malformation compared with 4.1% of controls. The calculated relative risk was 1.3 (95% CI, 0.7–2.6). Cimetidine is excreted and concentrated in breast milk but is classified by the AAP as compatible with breast-feeding.[3]

Ranitidine

Ranitidine, like the other H_2 blockers, is also a pregnancy category B drug. Ruigomez et al[62] reported the relative risk of malformation with use of ranitidine as 1.5 (95% CI, 0.9–2.6). In a double-blind placebo-controlled study of ranitidine, Larson et al compared ranitidine once or twice daily with placebo.[63] Twenty women received 150 mg once or twice daily versus placebo after 20 weeks of pregnancy, and heartburn was reduced 55.6% with ranitidine versus 44.2% with placebo ($P = .01$). In the Michigan Medicaid study,[5] 23 of 560 newborns (4.5%) exposed during the first trimester had major birth defects compared with 4.3% of controls. In 1996, Magee et al conducted a prospective cohort study in 178 women exposed to histamine blockers (H_2-receptor antagonists [H2RAs]) and 178 controls matched for age, history of smoking, and history of alcohol use.[64] There were no differences in terms of live births, spontaneous or elective abortions, gestational age, birth weight, or major malformations between the 2 groups. The rate of congenital malformations was 2.1% in exposed women versus 3.0% in nonexposed women. In the most recently published study of ranitidine use during pregnancy, data from a large network database for teratology information were collected prospectively. A total of 335 pregnancies exposed to ranitidine, 113 to cimetidine, 75 to famotidine, and 15 to nizatidine were reported.[65] The incidence of premature deliveries was higher in the exposed group compared with the control group, but there was no increase in the incidence of major malformations. The investigators concluded that there was no indication of an increased risk for major malformations after the use of H_2 blockers during pregnancy. Ranitidine is excreted in a similar fashion into breast milk and considered acceptable for breast-feeding mothers.

Famotidine and Nizatidine

While both famotidine and nizatidine are pregnancy category B drugs, the relatively smaller amount of data available from animal and human studies as compared with other H2RAs makes the choice of another agent prudent. In the Michigan Medicaid study, 2 of 33 fetuses exposed to famotidine developed major malformations compared with the expected number of 1.[5] Of all the H2RAs, famotidine is concentrated the least in breast milk. Animal studies of nizatidine with 300 times the recommended human dose resulted in more abortions, lower fetal weight, and fewer live fetuses. Another study showed a higher rate of abortions in rabbits treated with large doses.[66]

Promotility Agents

Metoclopramide is a pregnancy category B drug. No congenital malformations or other neonatal toxicities have been reported in humans with the use of metoclopramide. In the Michigan Medicaid study, 10 major birth defects were reported in 192 newborns exposed to metoclopramide during the first trimester, with 8 major birth defects expected.[5] Reproductive studies in mice, rats, and rabbits of up to 250 times the recommended human dose have failed to demonstrate any increases in fetal toxicity. Metoclopramide has been used as a lactation stimulant, and the total daily dose that would be consumed by a breast-feeding infant during maternal use of 30 mg/day is much less than the maximum daily dose of 500 μg/kg recommended in infants.[67] Therefore, maternal dosages of ≤45 mg/day should not have adverse effects on the breast-feeding infant.

Cisapride

Cisapride is a pregnancy category C drug. In a prospective, multicenter study, the outcomes of 129 Canadian women who took cisapride between November

1996 and November 1998 were compared with matched controls.[68] The mean daily dose of cisapride was 25 mg (range, 5–120 mg) and mean length of exposure was 4.6 weeks (range, 0.41–41 weeks). Most women were also taking multiple other medications, including H2RAs, proton pump inhibitors, and antacids. There were no differences in rates of major or minor congenital malformations in the cisapride group compared with controls. In July 2000, Janssen removed cisapride from the market due to cardiovascular concerns, and it is available only through a limited-access program.

Omeprazole

Omeprazole was the first proton pump inhibitor and is a pregnancy category C drug. At doses similar to those used in humans, it has been shown to produce dose-related embryonic and fetal mortality in pregnant rats and rabbits.[69] However, several prospective database studies have shown the safety of omeprazole. In the Swedish Medical Birth Registry, it was the only acid-suppression exposure in 262 infants. The rate of birth defects was 3.1% compared with 3.9% in controls. Five of 8 malformations were of the cardiac system.[70] In another cohort study, the outcome of 113 women exposed to omeprazole during pregnancy was compared with 113 disease-matched controls exposed to H2RAs and 113 untreated controls.[71] The incidence of major abnormalities in those exposed to omeprazole was 5.1%, compared with 3.1% in the H2RA group and 3.0% in the untreated group. The relative risk from the previously cited Swedish observational study was 0.9 (95% CI, 0.4–2.4).[70] Two of the 5 reported congenital abnormalities were atrial septal defects. In a recent prospective study, Diav-Citrin et al followed up 295 pregnancies exposed to omeprazole, the majority of which (233) had exposure starting in the first trimester.[72] There was a 3.6% rate of major congenital anomalies compared with 3.8% of healthy controls. In the only report published on breast-feeding, omeprazole was taken by the mother and sequential serum analyses documented infant concentrations lower than maternal concentrations, with no clinical effects to 1 year. However, proton pump inhibitors are not recommended for breast-feeding mothers because of the paucity of data.

Lansoprazole

Lansoprazole is a pregnancy category B drug. In one nonobservational cohort study of lansoprazole, 6 pregnant patients exposed during the first trimester delivered 7 healthy newborns.[73] In a study by Nielsen et al, 35 patients were treated with omeprazole and 3 with lansoprazole.[74] The relative risk for a congenital malformation was 1.6 (95% CI, 0.1–5.2), and the relative risk for low birth weight was 1.8 (95% CI, 0.2–13.1). In the Swedish Medical Birth Registry, lansoprazole was the only acid-suppression exposure in 13 infants, and 2 birth defects were observed.[61] In the study by Diav-Citrin et al, 62 patients were exposed to lansoprazole, with a rate for congenital anomalies of 3.9%.[72]

Pantoprazole

Pantoprazole is also a pregnancy category B drug. In the previously mentioned study by Diav-Citrin et al, 53 pregnancies were exposed to pantoprazole. There was an observed rate of 2.1% for congenital anomalies.[72] Although the newer proton pump inhibitors rabeprazole and esomeprazole are also categorized as pregnancy category B drugs, no controlled data are available for these agents, so their use is not suggested during pregnancy.

Peptic Ulcer Disease

Treatment of patients with peptic ulcer disease involves the use of proton pump inhibitors or H_2 blockers, which are covered in detail in the section on GERD. In the event that peptic ulcer disease is related to *Helicobacter pylori* infection, treatment can be deferred until after pregnancy. The most common regimen involves triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin. Alternatively, metronidazole, bismuth, and tetracycline are used as part of the regimen. In the unusual case when treatment is warranted during the gravid period, tetracycline and bismuth should not be used. These, along with other agents, are discussed in the following text.

Amoxicillin

Amoxicillin is a pregnancy category B drug. A population-based study of maternal use of amoxicillin, a penicillin drug, in 401 women did not show any increased risk of congenital malformation or any other adverse event.[75] Amoxicillin is low risk in lactation according to the AAP.

Clarithromycin

Clarithromycin, a pregnancy category C drug, has a higher placental passage rate than other macrolide antibiotics.[76] In a prospective study of clarithromycin in pregnancy, there was no increased risk of congenital malformations; however, there was a higher rate of spontaneous abortions than in the unexposed group.[77] A retrospective surveillance study of clarithromycin exposure within 270 days of delivery showed no increase in congenital malformations compared with the general population.[78] Clarithromycin has mean peak concentrations in breast milk of 25%

of the maternal serum concentration.[79] The safety of clarithromycin in lactation is unknown.

Tetracycline

Tetracycline is a pregnancy category D drug and is possibly unsafe in lactation. It is covered in more detail in the section on infectious diarrhea.

Metronidazole

Metronidazole is a pregnancy category B drug and presents a low risk in lactation. It is covered in more detail in the section on infectious diarrhea.

Bismuth

Bismuth, a pregnancy category C drug, is one of the most commonly used over-the-counter antacids. Fetotoxicity with bismuth has been described in animals.[80,81] Exposure to bismuth subsalicylate during late pregnancy may increase the risk of closure or constriction of the fetal ductus arteriosus with resultant pulmonary hypertension.[82] Bismuth is considered possibly unsafe in lactation.

Acute and Chronic Pancreatitis

Acute pancreatitis often resolves with supportive care. In the event that analgesia is required, meperidine and fentanyl are the preferred medications and are covered in detail in the section on endoscopy. In acute necrotizing pancreatitis, 3 approaches to decrease bacterial infections include the use of enteral feedings to avoid central line-related infections, selective decontamination of the gut with nonabsorbable antibiotics, and the use of prophylactic systemic antibiotics.

Gut decontamination in the setting of acute pancreatitis is achieved by a combination of norfloxacin, colistin, and amphotericin.[83] Norfloxacin is a pregnancy category C drug. Fluoroquinolone antibiotics cross the placenta and have a high affinity for cartilage, raising concern for fetotoxicity.[84] However, a prospective study of 200 women with fluoroquinolone exposure during the first trimester did not demonstrate an increased risk of major congenital malformations when compared with controls matched for age, tobacco use, and alcohol use.[84] Spontaneous abortions, fetal distress, and prematurity were also similar, but the rate of therapeutic abortion was higher in the fluoroquinolone group. A smaller study using the prescription database in Denmark supported these findings.[85] There are no available data on pregnancy outcomes for colistin (polymyxin E) and no FDA category rating, but polymyxin B is a pregnancy category C drug. Amphotericin is a pregnancy category B drug. The Collaborative Perinatal Project monitored 50,282 mother-child pairs, of whom 9 had first-trimester exposure to amphotericin B. No adverse events were noted.[2] Multiple other studies have also shown no association with congenital malformations, and amphotericin is the antifungal of choice during pregnancy.[86]

Randomized trials and meta-analysis of the benefit of prophylactic antibiotics in the setting of severe acute pancreatitis have been conflicting. If necrotizing pancreatitis is noted, antimicrobial therapy with imipenem is often started. Imipenem/cilastatin is a pregnancy category C drug because animal studies show no teratogenicity, but data in humans are limited. It does cross the placenta in rats, and concentrations in breast milk equal that in the serum.[87] The pharmacokinetics of imipenem change considerably during pregnancy, with larger volumes of distribution and faster total clearance from plasma.[88] Appropriate dose adjustments during pregnancy should be considered. In the event that a pregnant patient has necrotizing pancreatitis, the morbidity from this condition is sufficiently high to warrant imipenem therapy.

Chronic pancreatitis is managed with alcohol cessation, small low-fat meals, analgesia, and pancreatic enzyme supplements. For analgesia, fentanyl (endoscopy) and amitriptyline (irritable bowel syndrome [IBS]) are covered elsewhere. Long-acting morphine is often used in this setting and is a pregnancy category C drug. Six case reports of morphine use for analgesia during pregnancy did not demonstrate any congenital anomalies or neonatal opioid withdrawal.[89] A study of slow-release morphine in pregnant opioid-addicted women noted that all infants were healthy, although some required treatment for neonatal withdrawal.[90] Finally, pancreatic enzymes are classified as pregnancy category C. Animal reproduction studies have not been performed with pancreatic enzymes, and there are limited data on safety during pregnancy and lactation. In general, these medications should be avoided if nonessential. However, in patients with cystic fibrosis and pancreatic insufficiency, maintenance of nutritional status is a critical factor in pregnancy outcome. In a study of 23 women with 33 pregnancies, 91% of the women received pancreatic supplementation during pregnancy. Severity of lung disease predicted preterm delivery, and no congenital malformations were noted.[91] A case series reported 2 women on pancreatic supplementation who had successful pregnancies and breast-fed their infants with appropriate growth.[92]

Biliary Tract Disease

Choledocholithiasis

Laparoscopic cholecystectomy has become the standard of care for the management of cholecystitis and

Table 5. Medications Used in the Treatment of Diseases of the Liver

Drug	FDA pregnancy category	Recommendations for pregnancy	Recommendations for breast-feeding[2]
Adefovir	C	Minimal data: no teratogenicity	No human data: probably compatible (hepatitis B)
Antithymocyte globulin	C	Human specific agent	Safety unknown
Cyclosporin A	C	Safest of immune suppressants	Limited human data: potential toxicity
Entecavir	C	Not recommended unless benefit outweighs risk	Contraindicated
Interferon	C	Not recommended: treatment deferred until after delivery	Limited human data: probably compatible
Lamivudine	C	Low risk	Contraindicated
Mycophenolate mofetil	C	Not recommended	Contraindicated
Nadolol	C: first trimester D: second/third trimesters	Prolonged half-life, use alternative; risk of intrauterine growth retardation in second/third trimesters	Limited human data: potential toxicity
OKT3 (Muromonab-CD3)	C	No pregnancy data but probably low risk	Contraindicated
Penicillamine	D	Significant embryopathy; if required, reduce dose to 250 mg/day 6 weeks before delivery	No human data: potential toxicity
Propranolol	C: first trimester D: second/third trimesters	Fetal bradycardia, intrauterine growth retardation in second/third trimesters	Limited human data: potential toxicity
Ribavirin	X	Contraindicated: severe fetal neurotoxicity	No human data: potential toxicity
Sirolimus	C	Not recommended	No human data: potential toxicity
Tacrolimus	C	Use if mother's health mandates	Limited human data: potential toxicity
Trientine	C	Limited human data: alternative to penicillamine	No human data: potential toxicity
Ursodiol	B	Low risk: used in intrahepatic cholestasis of pregnancy	No human data: probably compatible

symptomatic choledocholithiasis. Surgical intervention during pregnancy does not appear to be associated with increased complications.[93] Nonsurgical approaches, such as oral chenodeoxycholic acid and ursodeoxycholic acid (UDCA) and extracorporeal shock wave lithotripsy, have not been used in pregnancy and are not recommended.[94] Chenodeoxycholic acid and UDCA have been used with limited success in the treatment of cholesterol gallstones in the general population. There are no available data on chenodeoxycholic acid in pregnancy, but UDCA is discussed in the section on primary biliary cirrhosis.

Primary Sclerosing Cholangitis

There is no effective medical therapy for primary sclerosing cholangitis that impacts mortality. The most commonly used medication is UDCA, which can provide symptomatic and serologic improvement. UDCA is a pregnancy category B drug and is discussed in the section on primary biliary cirrhosis. Safety in lactation is unknown. Fetotoxicity of UDCA has not been reported in humans; however, data are insufficient to determine risk in the first trimester.[95] Case reports have noted the safety of UDCA use in primary sclerosing cholangitis,[96,97] primary biliary cirrhosis,[98] and intrahepatic cholestasis of pregnancy.[99] UDCA can be used during pregnancy, especially after the first trimester, to reduce cholestasis and accompanying sequelae such as pruritus.

Diseases of the Liver

Table 5 summarizes the use of medications for diseases of the liver, including liver transplantation.

Viral Hepatitis

Hepatitis A is a self-limited condition, and treatment in pregnancy is similar to that of nonpregnant women. Both the inactivated vaccine against hepatitis A and postexposure immunoglobulin prophylaxis are low risk in pregnancy.[100]

Hepatitis B infection carries a high rate of vertical transmission, and the indications to treat are much greater during pregnancy. The vaccine is low risk to use. Passive and active immunization, given together, are very effective in preventing neonatal transmission, reducing the carrier state of infants born to hepatitis B e antigen/hepatitis B surface antigen–positive women from 70%–90% to almost zero.[101]

Lamivudine. Lamivudine is a pregnancy category C drug. For those women with chronic hepatitis B, studies have documented the safety of lamivudine for continued treatment during pregnancy. Su et al followed up 38 pregnancies in which the mothers were treated with lamivudine and compared the outcomes with a historical control group. Standard doses of lamivudine were continued through pregnancy with a hepatitis B

virus DNA seroconversion rate of 92%. There were no reported complications or congenital abnormalities.[102] In an earlier study, investigators treated 8 highly viremic women with 150 mg of lamivudine in the third trimester of pregnancy in an attempt to prevent perinatal transmission of hepatitis B virus infection.[103] One child was delivered early because of intrauterine growth retardation. All but one woman had a significant decrease in hepatitis B virus DNA levels before delivery, and vertical transmission occurred in only one child.

In the human immunodeficiency virus literature, the Antiretroviral Pregnancy Registry contains 526 live births that were exposed to lamivudine during the first trimester with a congenital defect rate of 1.7%. Twenty-five of 1256 live births had a history of exposure any time during pregnancy and showed a slightly higher rate (2.5% [95% CI, 1.3–3.0]) but not statistically higher than expected.[104] The use of lamivudine is contraindicated during breast-feeding because it is excreted into milk in high concentrations.[105]

Adefovir dipivoxil. There are currently no adequate well-controlled studies of adefovir dipivoxil, a pregnancy category C drug, in pregnant women. Adefovir dipivoxil is indicated for the treatment of chronic hepatitis B in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferase levels or histologically active disease. During clinical trials with this agent, 16 pregnancies with known outcomes were reported. Ten patients had a therapeutic abortion, 2 patients had a spontaneous abortion, 3 patients delivered healthy babies, and one patient delivered a live infant at 25 weeks' gestation that subsequently died 4 days later. Studies conducted with adefovir administered orally in doses up to 23 times that achieved in humans have failed to show any embryotoxicity or teratogenicity in laboratory animals. There are no human studies regarding the use of adefovir during lactation, and its use during this time is not recommended.

Interferon. Interferon, a pregnancy category C drug, is contraindicated during pregnancy because of its antiproliferative activity. When administered to pregnant Rhesus monkeys, there was a statistically significant increase in the number of spontaneous abortions. No teratogenic effects were observed in this species when doses of 1–25 million IU $\cdot$ kg^{-1} $\cdot$ day^{-1} were administered during the early to mid-fetal period.[106] To date, there have only been 26 reported pregnancies following exposure to interferon. Most have been in women treated for essential thrombocythemia and not hepatitis C virus infection. Premature delivery occurred in 15% and intrauterine growth retardation in 6 of 27 (22%) of these patients.[107] A total of 8 children have been born to mothers on interferon believed to be at high risk for chronic hepatitis infection. In patients with chronic infection, it is prudent to delay treatment; in women with active infection, use still should be considered only if the health of the mother mandates therapy, with close and careful monitoring. There is a single case report of its use in a 26-year-old woman diagnosed with acute hepatitis C in the 16th week of pregnancy.[108] She sustained a complete biochemical and virologic response after a total of 72 million units was given over 10 weeks. Therapy was discontinued at that point secondary to maternal side effects. Twin infants were born prematurely but had normal development. The treatment of hepatitis C with interferon in combination with ribavirin is contraindicated because of severe neurotoxicity in children younger than 2 years and its high potential for teratogenicity (see following text).

Ribavirin. Ribavirin is an antiviral agent used in combination with interferon for the treatment of hepatitis C and is a pregnancy category X drug. A dose-related teratogenicity has been demonstrated, as well as embryolethality in all animal species tested.[109] Ribavirin is still present in human blood 4 weeks after dosing, and it is recommended that patients wait at least 6 months following any exposure before conception.

Entecavir. Entecavir is an orally administered cyclopentyl guanosine analogue that has been recently approved for treatment of chronic hepatitis B virus infection in adults with evidence of active viral replication and either evidence of persistent elevation in serum aminotransferase levels or histologically active disease. Approval was based on the results of three phase 3 trials involving a total of 1633 patients aged 16 years and older who had chronic hepatitis B virus infection and persistently elevated serum alanine aminotransferase levels. Although entecavir is a pregnancy category C drug, there are inadequate data from well-controlled studies in pregnancy. Teratogenic effects have been observed in animal studies, and thus entecavir should be used only if benefit outweighs risk.

Wilson's Disease

Penicillamine. Penicillamine, a pregnancy category D drug, is a chelating agent that is first-line therapy for the treatment of Wilson's disease. There are only a few reports regarding the outcomes of pregnancies in women with Wilson's disease. In one series, outcomes of 18 women with 29 normal infants were reported.[110] Patients were treated with 0.75–1 g/day. Another group reported 8 exposed women with 12 normal infants, but all mothers had been taken off

their medications.[111] The largest recent case series in Wilson's disease is from India, where 59 pregnancies in 16 women were studied retrospectively.[112] There were 24 spontaneous abortions, 3 stillbirths, 2 terminations, and 30 successful pregnancies. The majority of the spontaneous abortions were in women not on therapy. Other case reports have documented severe embryopathy characterized by micrognathia, diffuse cutis laxa, and agenesis of the corpus callosum as well as transient fetal myelosuppression.[111] It is controversial whether penicillamine should be continued during pregnancy, and various investigators have disagreed on whether to use the agent and, if so, at the appropriate dosage.[2] The fetus can only remove 0.044 mg of copper per day, which is less than 10% of copper excreted in the urine of a patient receiving 1 g of penicillamine daily. The manufacturer recommends limiting dosages to 1 g/day and if cesarean section is planned to 250 mg/day for 6 weeks before delivery and postoperatively until wound healing is complete. While there have been no reports of adverse effects to infants breast-fed by mothers taking penicillamine, there are no controlled data regarding levels in breast milk, and at this time it is not recommended.

Trientine. Trientine, a pregnancy category C drug, is used if no other alternatives are appropriate to treat the mother's liver disease. This chelating agent is an alternative to penicillamine and is available only as an orphan drug for use in Wilson's disease. A single published case series described outcomes of 11 pregnancies in 7 women with Wilson's disease.[113] Therapy was continued in 7 cases and interrupted in 2 others. There were 9 live infants, 2 born prematurely and one with isochromosome X, not believed to be secondary to copper deficiency. Given that there are few other options, the benefit is believed to outweigh the risk. There are no human data regarding the levels of trientine in milk or the effect on the breast-feeding infant, and therefore it is not recommended in this setting.

Primary Biliary Cirrhosis

UDCA. UDCA is a pregnancy category B drug. Given the paucity of data regarding its safety in the first trimester, use of UDCA during this time is not recommended unless essential. It has been given to women in the second and third trimesters with no deterioration of liver function noted. No fetal loss or unfavorable outcomes were noted in 10 women receiving UDCA.[114] A recent case report of a woman with primary biliary cirrhosis with exposure to UDCA in the first 20 days after conception did not show any congenital anomalies or adverse birth outcomes.[115] In a randomized controlled trial of UDCA use in intrahepatic cholestasis of pregnancy, it was demonstrated to improve pruritus and liver enzymes and allowed for delivery closer to term.[99] A second randomized controlled trial of UDCA versus cholestyramine found similar results; symptoms were alleviated and babies were delivered significantly closer to term in the UDCA-treated patients.[116] There are no human data available regarding its use during lactation. It is believed to be low risk, however, because only small amounts of UDCA appear in the systemic circulation and these are tightly bound to albumin; thus, it is unlikely to result in a significant amount in breast milk.

Portal Hypertension

Propranolol. Propranolol, a pregnancy category C drug, is a nonselective β-adrenergic blocking agent used for prophylaxis against variceal bleeding in patients with cirrhosis. It has been used during pregnancy to treat maternal thyrotoxicosis, arrhythmias, and hypertension. It readily crosses the placenta and thus is used for fetal arrhythmias as well. Adverse outcomes have not been clearly linked to its use, but daily doses greater than 160 mg seem to produce more serious fetal cardiac complications. There are no data for outcomes in women using propranolol for variceal prophylaxis. In the Michigan Medicaid study, 274 newborns were exposed to propranolol during the first trimester.[5] A total of 11 major birth defects were observed, with 12 expected. Intrauterine growth retardation has been reported but is believed to be secondary to the underlying maternal hypertension. Propranolol is not a teratogen, but fetal and neonatal toxicity may occur. Maternal use after the second trimester can result in significant weight reductions in the infant.[117] It is therefore not recommended for use after the first trimester unless the underlying condition of the mother requires continued β-blockade.

Propranolol is excreted into breast milk, and peak concentrations occur 2–3 hours after a dose. Events secondary to β-blockade have not been reported in the infants breast-fed by mothers on this agent, and the AAP classifies this agent as compatible with breast-feeding.

Nadolol. Nadolol, a pregnancy category C drug, is another nonselective β-adrenergic blocker used as an alternative to propranolol. In the Michigan Medicaid study, 71 newborns were exposed to nadolol during the first trimester.[5] One major birth defect was noted, with 3 expected. Again, this is a medication used predominantly as an antihypertensive, and no data are available when used for variceal prophylaxis. Intrauterine growth retardation was documented in a single case report of a mother with immunoglobulin A nephropathy and hy-

pertension that required treatment throughout pregnancy.[118] Because nadolol has a long half-life, low protein binding, and lack of metabolism, the recommendation is that alternative agents in this class be used if strongly indicated. Like propranolol, nadolol is considered compatible with breast-feeding because of the apparent absence of adverse effects on the breast-feeding infant.

Liver Transplantation

The best data available regarding medications in transplant recipients come from the National Transplantation Pregnancy Registry. Every year, an updated report is presented with the results of a prospective database of all transplant recipients. The most recent published reports are from 2003.[119] To date, 106 liver recipients and 3 liver/kidney recipients were reported to the registry as having had a pregnancy. There were a total of 187 pregnancies in these patients, with known outcomes in 190 births. There was only one death that occurred in a patient on cyclosporin A. The rate of live births was 77% in patients treated with cyclosporin A, 82% in patients treated with cyclosporine, and 72% in patients treated with tacrolimus. Two patients were treated with mycophenolate mofetil and delivered healthy infants. The mean gestational age was 37 weeks, and the rate of low birth weight was 29%–42%. The conclusion of the advisory board was that "the majority of pregnancy outcomes reported to the Registry appear favorable for parent and newborn."[119]

Cyclosporine

Cyclosporine is a pregnancy category C drug. A meta-analysis of 15 studies of pregnancy outcomes after cyclosporine therapy reported a total of 410 patients with data on major malformations.[120] The calculated OR of 3.83 for malformations did not achieve statistical significance (95% CI, 0.75–19.6). The rate of malformations was 4.1%, which is not different from the general population. The conclusion of the study was that cyclosporine did not appear to be a major human teratogen. In a study published in the obstetric literature, a retrospective review of 38 pregnancies in 29 women between 1992 and 2002 was conducted. There were 4 spontaneous abortions and 10 first-trimester terminations for worsening liver function. The mean gestational age was 36.4 weeks, and there were no intrauterine or neonatal deaths. Five minor congenital anomalies were noted. The investigators concluded that planned pregnancy at least 2 years after liver transplantation with stable allograft function and continued immunosuppression had an excellent maternal and neonatal outcome.[121] Cyclosporine is excreted into breast milk in high concentrations. Therefore, the AAP considers cyclosporine contraindicated during breast-feeding due to the potential for immune suppression and neutropenia.

Tacrolimus

Tacrolimus is also a pregnancy category C drug. The earliest experience with this medication was in 1997, with a report of 27 pregnancies with exposure to tacrolimus.[122] Two infants died at weeks 23 and 24, but the mean gestational period was 36.6 weeks. There was a 36% incidence of transient perinatal hyperkalemia. One newborn had unilateral polycystic renal disease. Another study from Germany reported on 100 pregnancies in transplant recipients followed up from 1992 to 1998.[123] There was a 68% live birth rate, 12% spontaneous abortion rate, and 3% stillbirth rate. Fifty-nine percent of the infants were premature. Malformations occurred in 4 neonates with no consistent defects. In a later single-center experience, 49 pregnancies in 37 women over 13 years were followed up prospectively.[124] Thirty-six women survived the pregnancy, and 2 premature babies were seen. One infant died of Alagille syndrome; the rest survived, and 78% were of normal birth weight. No other congenital abnormalities were noted. Tacrolimus is contraindicated in breast-feeding because of the high concentrations found in breast milk.

Sirolimus

Sirolimus is a pregnancy category C drug, but little is known about its true effect in humans. Sirolimus is another agent for immune suppression in the transplant recipient. There were 3 patients treated with sirolimus from the National Transplantation Pregnancy Registry, but these were kidney recipients. A single case report of a patient receiving sirolimus during early pregnancy resulted in a normal infant delivered at 39 weeks.[125] Given the relative paucity of information and the reasonable alternatives for immunosuppression, this agent is not recommended during pregnancy.

Mycophenolate Mofetil

Mycophenolate mofetil is a pregnancy category C drug and has been shown to have teratogenic properties in laboratory animals. Mycophenolate mofetil is a relatively new addition to the armamentarium for immunosuppression in liver transplant recipients. In a single case report from the obstetric literature, a renal transplant recipient was treated with mycophenolate mofetil before conception and during the first trimester of pregnancy.[126] The fetus had facial dysmorphology and multiple midline anomalies. The molecular weight of this agent is low enough that it most

Table 6. Medications Used in the Treatment of IBS

Drug	FDA pregnancy category	Recommendations for pregnancy	Recommendations for breast-feeding[2]
Alosetron	B	Avoid: restricted access	No human data: potential toxicity
Amitriptyline	C	Avoid: no malformations, but worse outcomes	Limited human data: potential toxicity
Bisacodyl	C	Low risk in short-term use	Safety unknown
Bismuth subsalicylate	C	Not safe: teratogenicity	No human data: potential toxicity
Castor oil	X	Uterine contraction and rupture	Possibly unsafe
Cholestyramine	C	Low risk, but can lead to infant coagulopathy	Compatible
Desipramine	C	Avoid: no malformations, but worse outcomes	Limited human data: potential toxicity
Dicyclomine	B	Avoid: possible congenital anomalies	Limited human data: potential toxicity
Diphenoxylate/atropine	C	Teratogenic in animals: no human data	Limited human data: potential toxicity
Docusate	C	Low risk	Compatible
Hyoscyamine	C	No available data	No human data: probably compatible
Imipramine	D	Avoid: no malformations, but worse outcomes	Limited human data: potential toxicity
Kaopectate	C	Unsafe because now contains bismuth	No human data: probably compatible
Lactulose	B	No human studies	No human data: probably compatible
Loperamide	B	Low risk: possible increased cardiovascular defects	Limited human data: probably compatible
Magnesium citrate	B	Avoid long-term use: hypermagnesemia, hyperphosphatemia, dehydration	Compatible
Mineral oil	C	Avoid: neonatal coagulopathy and hemorrhage	Possibly unsafe
Nortriptyline	D	Avoid: no malformations, but worse outcomes	Limited human data: potential toxicity
Paroxetine	D	Avoid: twice as many birth defects as other antidepressants	Potential toxicity
PEG	C	First-choice laxative in pregnancy	Low risk
Senna	C	Low risk in short-term use	Compatible
SSRIs (except paroxetine)	C	Avoid: no malformations, but increased adverse events in fetus	Limited human data: potential toxicity
Simethicone	C	No available data: low risk	No human data: probably compatible
Sodium phosphate		Avoid long-term: hypermagnesemia, hyperphosphatemia, dehydration	Safety unknown
Tegaserod	B	Low risk: human data negative for malformations	Safety unknown

likely crosses the placenta, and it is not recommended for use in pregnancy. The manufacturer recommends women use effective contraception before and during therapy and for 6 weeks after therapy is stopped.

IBS

IBS is a heterogeneous disorder without a standardized therapeutic regimen. No large epidemiologic studies have been conducted in pregnant women with preexisting IBS; however, healthy women report an 11%–38% rate of constipation during pregnancy, most commonly in the third trimester, and 34% report increased stool frequency.[127] If possible, medications should be avoided and dietary alterations and fiber supplementation should be the first step. In the event that medications are required, the following is a summary of available safety data, keeping in mind that most drug therapies for the treatment of IBS have not demonstrated efficacy over placebo. Table 6 summarizes the use of medications for IBS during pregnancy.

Constipation

Symptomatic relief of constipation with laxatives is often adequate for most patients. Osmotic laxatives include saline osmotics (magnesium and sodium salts), saccharated osmotics (lactulose, sorbitol), and PEG. Saline osmotic laxatives such as magnesium citrate (pregnancy category B) and sodium phosphate have a rapid onset of action but are intended for short-term intermittent relief. Long-term use can result in hypermagnesemia, hyperphosphatemia, and dehydration.[128] There are no available human studies on the use of lactulose (pregnancy category B) during pregnancy. PEG (pregnancy category C) is negligibly absorbed and metabolized in humans, making it unlikely to cause malformations. It is also effective and well tolerated compared with lactulose.[129] Results of animal teratogenesis studies have been negative. A consensus meeting on the management of constipation in pregnancy[128] considered PEG to meet the criteria for an ideal laxative in pregnancy:

effective, not absorbed (nonteratogenic), well tolerated, and low risk. However, it was believed that present data were insufficient to conclusively demonstrate whether absorption of PEG affects the fetus. Stimulant laxatives such as senna (pregnancy category C) and bisacodyl (pregnancy category C) are considered low risk for short-term use, but long-term use is not recommended.[128] Senna is excreted in breast milk and should therefore be used with caution during lactation.[130] Docusate (pregnancy category C), a stool softener, is generally considered to be low risk.[127] Castor oil (pregnancy category X) should be avoided because it is associated with uterine contraction and even rupture.[131] Mineral oil should also be avoided because it can impair maternal fat-soluble vitamin absorption, leading to neonatal coagulopathy and hemorrhage.[127]

Tegaserod (pregnancy category B), a serotonin 5-HT_4 receptor agonist, is approved for the treatment of constipation-type IBS and chronic constipation. As of December 2004, 74 pregnancies were reported in studies on tegaserod (data on file, Novartis, 2005). Pregnancy outcome was similar between the placebo and tegaserod groups. There were no congenital anomalies reported. Reproductive studies in rats and rabbits revealed no evidence of impaired fertility or fetal malformation.

In the pregnant patient with constipation, fiber supplements introduced gradually to avoid excessive gas and bloating and adequate water intake should be the first line of therapy. Often, new-onset constipation during early pregnancy is due to iron therapy and symptomatic relief can be achieved with docusate, now a component of some prenatal vitamins. When these methods are inadequate, an osmotic laxative should be considered, particularly a PEG solution.

Diarrhea

Loperamide (pregnancy category B) was not found to be associated with an increased risk of congenital malformations in a trial of 105 women exposed to the drug during pregnancy, although 20% of the infants were 200 grams smaller than infants in the control group.[132] However, a study of Michigan Medicaid recipients noted 108 infants exposed to loperamide in the first trimester, of which 6 (5.6%) had major birth defects (5 expected).[2] Three of the 5 were cardiovascular defects (one expected), raising concern about a possible link. This may be an errant signal, and the drug is probably low risk in pregnancy. Diphenoxylate with atropine (pregnancy category C) has been found to be teratogenic in animals.[133] At least 187 cases of first-trimester exposure have been reported with no evidence of developmental toxicity.[2] Cholestyramine (pregnancy category C), an anion exchange resin, is often used to treat cholestasis of pregnancy[134] and can be used to manage diarrhea resulting from ileal resection or cholecystectomy. However, fat-soluble vitamin deficiency including coagulopathy can occur, so it should be used with caution. Kaolin and pectin or Kaopectate (Pfizer, Morris Plains, NJ) (pregnancy category B) was an antidiarrheal of choice because it was not absorbed and did not cross the placenta.[133] Concern did arise over the potential for kaolin-induced iron deficiency anemia.[135] In 2003, Kaopectate was reformulated to contain bismuth subsalicylate (pregnancy category C). Bismuth subsalicylate, alone or in Kaopectate, should be avoided in pregnancy because the salicylates can be absorbed and lead to increased perinatal mortality, premature closure of the ductus arteriosus, neonatal hemorrhage, decreased birth weight, prolonged gestation and labor, and possible teratogenicity.[136] Alosetron (pregnancy category B) has restricted access due to concerns over ischemic colitis and should generally be avoided during pregnancy.

In the pregnant patient with diarrhea, dietary modification, with reduction of fat and dairy consumption, can improve symptoms. Although the human data are limited, both loperamide and diphenoxylate are considered low risk and can be used with discretion. Patients with a history of eating disorders can have a very difficult time during pregnancy and should be observed carefully and provided with adequate counseling and psychiatric support.

Antidepressants

Tricyclic antidepressants (amitriptyline [pregnancy category C], desipramine [pregnancy category C], nortriptyline [pregnancy category D], and imipramine [pregnancy category D]) and selective serotonin reuptake inhibitors (SSRIs) (generally pregnancy category C) are frequently used in the management of IBS. Overall, the newer antidepressants (citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, reboxetine, venlafaxine, nefazodone, trazodone, mirtazapine, and bupropion) are not associated with an increased rate of major malformations compared with the general population.[137,138] However, recently, an unpublished study by GlaxoSmithKline[139] of 3500 pregnant women noted twice as many birth defects with paroxetine compared with other antidepressants (Table 7). The absolute rate of major congenital malformations seen in the first trimester for paroxetine users was 4%, and the rate of cardiovascular malformations was 2%.[140] Infants exposed to antidepressants are also at higher risk for other adverse events. A large Swedish study of 997 infants exposed to

Table 7. The Risk of Major Congenital Malformation in Infants According to the Antidepressant Medication Used Maternally During the First Trimester[139]

Drug	Maternal Users	Infant Malformations	Malformations per 1000 live births	Adjusted OR (95% CI)
Amitriptyline	146	1	6.8	0.27 (0.04–1.96)
Bupropion	248	6	24.2	0.99 (0.42–2.30)
Citalopram	188	7	37.2	1.39 (0.62–3.11)
Fluoxetine	820	18	22.0	0.82 (0.48–1.39)
Nefazodone	41	1	24.4	0.94 (0.13–6.96)
Paroxetine	527	23	43.6	2.20 (1.34–3.63)
Sertraline	507	7	13.8	0.48 (0.22–1.05)
Trazodone	49	2	40.8	1.98 (0.47–8.39)
Venlafaxine	129	2	15.5	0.59 (0.14–2.42)
>1 type of antidepressant	406	14	34.5	1.41 (0.79–2.55)

antidepressants during pregnancy noted an increased risk of preterm birth, low birth weight, low Apgar score, respiratory distress, neonatal convulsions, and hypoglycemia.[141] There was a trend toward worse outcome with tricyclic antidepressants versus SSRIs. Multiple studies with SSRIs confirm a similar rate of congenital malformations compared with the general population[142] but do note a higher rate of premature delivery, respiratory difficulty, cyanosis on feeding, and jitteriness[143] as well as low birth weight[144] and neonatal convulsions.[145] The effects of SSRI exposure via the placenta on neonatal adaptation and long-term neurocognitive development remain controversial.[146] Given these findings, if the antidepressant is being used solely for the treatment of symptoms of IBS, as opposed to treatment of an associated significant depression, cessation of the drug during the gravid period should be strongly considered.

Tricyclic antidepressants and SSRIs are excreted in breast milk to varying degrees. The potential for neurobehavioral abnormalities in the chronically exposed infant is not known. The AAP classifies the drugs as having an unknown effect on the breast-feeding infant with potential for concern. They should not be used during breast-feeding in the mother with IBS.

Other Medications

Antispasmodics are frequently prescribed for the management of abdominal pain in IBS. Dicyclomine (pregnancy category B), in combination with Bendectin, was associated with multiple congenital anomalies, although studies have not been conclusive.[147] Hyoscyamine (pregnancy category C) has not been studied in pregnancy.[127] Simethicone (pregnancy category C) has also not been studied in pregnancy. See the section on endoscopy for further details on simethicone.

Infectious Diarrhea

Diarrhea can be described as acute (<14 days), persistent (>14 days), or chronic (>30 days).[148] Although most episodes of diarrhea are self-limited and treatment is not required, certain pathogens require treatment. The medications commonly used to treat infectious diarrhea are listed in the following text and are summarized in Table 8.

Albendazole

Albendazole, a pregnancy category C drug, is used in the treatment of microsporidia, cystericercosis, helminths, and hydatid disease. The drug is embryotoxic and teratogenic (skeletal malformations) in rats and rabbits.[149] Human data are limited. A study in Ghana on inadvertent exposure of pregnant women to ivermectin and albendazole did not find an increased risk of spontaneous abortion or congenital malformation.[150] Albendazole therapy for the eradication of helminths during pregnancy is associated with significantly less maternal anemia[151] and no increase in adverse pregnancy outcomes,[152] prompting the World Health Organization to recommend antihelminthic therapy in pregnancy.[151]

Ampicillin

Ampicillin is a pregnancy category B drug and is not considered teratogenic. It is covered further in the section on endoscopy. It is a second-line treatment of *Shigella* infection. In the Collaborative Perinatal Project, 3546 mothers took penicillin derivatives in the first trimester of pregnancy with no increased risk of anomalies.[153] Ampicillin passes through the placenta by simple diffusion and is excreted into breast milk in low concentrations. Although antibiotic transmission to the neonate may result in modification of bowel flora or allergic response, the benefits of breast milk are generally believed to outweigh the relatively small risk.[153]

Table 8. Medications Used in the Treatment of Infectious Diarrhea

Drug	FDA pregnancy category	Recommendations for pregnancy	Recommendations for breast-feeding[2]
Albendazole	C	Embryotoxic in animals; avoid in first trimester; human data support improved pregnancy outcomes with helminth eradication	No human data: probably compatible
Ampicillin	B	Low risk	Compatible
Azithromycin	B	Low risk	Limited human data: probably compatible
Ciprofloxacin (all quinolones)	C	Potential toxicity to cartilage: avoid	Limited human data: probably compatible
Doxycycline	D	Contraindicated: teratogenic	Compatible
Furazolidone	C	Low risk; limited data	No human data: potential toxicity
Metronidazole	B	Low risk:? Cleft lip/palate	Limited human data: potential toxicity
Rifaximin	C	Animal teratogen: no human data	No human data: probably compatible
Tetracycline	D	Not safe: teratogenicity	Compatible
Tinidazole	C	Low risk: limited data	Unsafe
Trimethoprim-sulfamethoxazole	C	Teratogenic	Compatible
Vancomycin	C	Low risk	Limited human data: probably compatible

Azithromycin

Azithromycin, a macrolide antibiotic, is a pregnancy category B drug and is a second-line treatment of *Cryptosporidium* and *Entamoeba histolytica* infection. A study of 20 women who received the drug for *Chlamydia trachomatis* noted that 40% reported moderate to severe gastrointestinal side effects.[154] A trial of 94 pregnant women with *Trichomonas vaginalis* treated with a combination of azithromycin, cefixime, and metronidazole demonstrated increased rates of infant low birth weight, preterm birth, and 2-year mortality compared with the children of 112 infected mothers who were not treated for the same infection.[155] Whether it was a single antibiotic or the combination of antibiotics that led to this result is not clear. The drug does accumulate in breast milk but presents a low risk in breast-feeding.

Doxycycline/Tetracycline

Doxycycline and tetracycline are pregnancy category D drugs. Doxycycline is used as second-line treatment of *Vibrio cholera*, *Campylobacter*, and enterotoxigenic *Escherichia coli* infection. Along with tetracycline, this class of medications crosses the placenta and is bound by chelating to calcium in developing bone and teeth.[156] This results in discoloration of the teeth, hypoplasia of enamel, and inhibition of skeletal growth. A population-based study found a higher rate of congenital anomalies in the infants of mothers treated with doxycycline during pregnancy; however, the case-control pair analysis did not show a significantly higher rate of doxycycline treatment in the second and third months of gestation in any group of congenital abnormalities.[157]

Doxycycline and tetracycline are compatible with breast-feeding. Although there is a potential for dental staining and inhibition of bone growth, this possibility is remote given the undetectable serum levels of tetracycline found in exposed infants.

Furazolidone

Furazolidone is a pregnancy category C drug and is a second-line treatment of giardiasis. There are limited data on its safety in pregnancy. The Collaborative Perinatal Project monitored 50,282 mother-child pairs, of whom 132 had first-trimester exposure to furazolidone. There was no association with congenital malformations.[158] There are no human data in breast-feeding, and it may be potentially toxic.

Metronidazole

Metronidazole is a pregnancy category B drug and is used in the treatment of *Clostridium difficile* infection, amebiasis, and giardiasis. Multiple studies have suggested that prenatal use of metronidazole is not associated with birth defects. These studies include 2 meta-analyses,[159,160] 2 retrospective cohort studies,[161,162] and a prospective controlled study of 228 women exposed to metronidazole during pregnancy.[163] A population-based case-control study found that overall teratogenic risk was low, but infants of women exposed to metronidazole in the second to third months of pregnancy had higher rates of cleft lip with or without cleft palate.[164] This increase was slight and not believed to be clinically significant.

Metronidazole is excreted in breast milk. If a single dose of metronidazole is given, as for the treatment of trichomoniasis, the AAP recommends that breast-feeding should be suspended for 12–24 hours.[3] Potential toxicity exists for longer-term use of metronidazole, and it is not compatible with breast-feeding.

Quinolones

Quinolones (eg, ciprofloxacin, levofloxacin, norfloxacin) are pregnancy category C drugs and are used in the treatment of *Shigella*, *Campylobacter*, *Yersinia*, enterotoxigenic and enteroinvasive *E coli*, and *Vibrio cholerae* infection. Quinolones have a high affinity for bone tissue and cartilage and may cause arthropathies in children.[153] The manufacturer reports damage to cartilage in weight-bearing joints after quinolone exposure in immature rats and dogs. However, a prospective controlled study of 200 women exposed to quinolones[84] and a population-based cohort study of 57 women exposed to quinolones[85] did not find an increased risk of congenital malformations. Overall, the risk is believed to be minimal, but given safer alternatives, the drug should be avoided in pregnancy.

The data in breast-feeding are limited, but quinolones are probably compatible with use.[2]

Rifaximin

Rifaximin is a pregnancy category C drug and is used in the treatment of traveler's diarrhea. This is a new agent, and little information exists on safety in pregnancy. Rifaximin has not been found to affect fertility or pregnancy outcome in rats[165] or cause teratogenic complications in rats and rabbits in one study,[166] although other studies have noted teratogenicity in rats and rabbits, including cleft palate and incomplete ossification.[167] Safety in breast-feeding is unknown.

Tinidazole

Tinidazole, a pregnancy category C drug, is a second-line treatment for giardiasis and amebiasis. Placental transfer of tinidazole does occur early in pregnancy,[168] raising concerns for its use in the first trimester. A population-based study from Hungary did not note an increased rate of congenital malformations when used in pregnancy; however, the numbers were small.[169] Limited human data are available, and the drug is considered unsafe in breast-feeding.[170]

Trimethoprim-sulfamethoxazole

Trimethoprim-sulfamethoxazole, a pregnancy category C drug, is first-line treatment of *Isospora* and *Cyclospora* infection and second-line treatment of *Shigella*, *Yersinia*, and enterotoxigenic *E coli* infection. Trimethoprim has antifolate effects, increasing the potential of congenital anomalies. A study of 2296 Michigan Medicaid recipients with first-trimester exposure to trimethoprim noted an increased risk of birth defects, particularly cardiovascular defects.[5] A population-based case-control study in Hungary noted a higher rate of multiple congenital anomalies and cardiovascular malformations.[171] Trimethoprim-sulfamethoxazole should be avoided in pregnancy based on these data.

Trimethoprim-sulfamethoxazole is excreted in low concentrations in breast milk. The AAP classifies this drug as compatible with breast-feeding.[3]

Vancomycin

Vancomycin, a pregnancy category C drug, is used in the treatment of *C difficile* colitis refractory to therapy with metronidazole. Reproduction studies in rats and rabbits have not demonstrated teratogenic effects.[172] Vancomycin did not result in sensorineural hearing loss or nephrotoxicity in 10 infants whose mothers were treated with the drug during pregnancy.[173] No cases of congenital defects attributable to vancomycin have been located to date,[2] and it is considered low risk in pregnancy. There are limited human data in breast-feeding, but it is probably compatible.

Inflammatory Bowel Disease

For patients with Crohn's disease and ulcerative colitis, disease activity at the time of conception can be associated with a higher risk of spontaneous abortions; disease activity during the course of pregnancy can be associated with higher rates of low birth weight and premature infants.[174] It is advisable that patients be in remission when considering pregnancy, and for the majority, this requires continuing their medications. Medications used in the treatment of inflammatory bowel disease (IBD) are summarized in Table 9.

Aminosalicylates

All aminosalicylates (sulfasalazine, mesalamine, balsalazide) are pregnancy category B except olsalazine, which is pregnancy category C. Sulfasalazine is composed of 5-aminosalicylic acid azo-bonded to sulfapyridine. Initial case reports suggested sulfasalazine teratogenicity with evidence of cardiovascular, genitourinary, and neurologic defects.[175–177] However, a larger series of 181 pregnant women did not note an increase in congenital anomalies.[178] A population-based study using the Hungarian Case Control Surveillance of Congenital Abnormalities database[179] also did not find a significant increase in the prevalence of congenital abnormalities in the children of women treated with sulfasalazine. Given the concern over potential antifolate effects of the drug, it is recommended that women take folic acid 1 mg twice daily in the prenatal period and throughout pregnancy. Breast-feeding is also considered low risk with sulfasala-

Table 9. Medications Used in the Treatment of IBD

Drug	FDA pregnancy category	Recommendations for pregnancy	Recommendations for breast-feeding[2]
Adalimumab	B	Limited human data: low risk	No human data: probably compatible
Amoxicillin/clavulanic acid	B	Low risk	Probably compatible
Azathioprine/6-mercaptopurine	D	Data in IBD, transplant literature suggest low risk	No human data: potential toxicity
Balsalazide	B	Low risk	No human data: potential diarrhea
Ciprofloxacin	C	Avoid: potential toxicity to cartilage	Limited human data: probably compatible
Corticosteroids	C	Low risk; possible increased risk: cleft palate, adrenal insufficiency, premature rupture of membranes	Compatible
Cyclosporine	C	Low risk	Limited human data: potential toxicity
Fish oil supplements	—	Low risk: possibly beneficial	No human data
Infliximab	B	Low risk	No human data: probably compatible
Mesalamine	B	Low risk	Limited human data: potential diarrhea
Methotrexate	X	Contraindicated: teratogenic	Contraindicated
Metronidazole	B	Given limited efficacy in IBD, risk of cleft palate, would avoid	Limited human data: potential toxicity
Olsalazine	C	Low risk	Limited human data: potential diarrhea
Rifaximin	C	Animal teratogen: no human data	No human data: probably compatible
Sulfasalazine	B	Considered low risk; give folate 2 mg daily	Limited human data: potential diarrhea
Tacrolimus	C	Use if mother's health mandates	Limited human data: potential toxicity
Thalidomide	X	Contraindicated: teratogenic	No human data: potential toxicity

zine. Unlike other sulfonamides, bilirubin displacement, and therefore kernicterus, does not occur in the infant.[180] This may be due to negligible transfer via breast milk.

Sulfasalazine has been clearly associated with infertility in men. Abnormalities in sperm number, motility, and morphology have been noted.[181,182] The effect appears to be reversible; when men were switched from sulfasalazine to mesalamine, semen quality returned to normal.[183,184] An association between sulfasalazine use in the parent and congenital malformations in the progeny has been described.[185] Because the life span of sperm is 120 days, men desiring conception should either discontinue sulfasalazine or switch to mesalamine at least 3 months before attempting conception.

Case series of mesalamine use in pregnancy do not suggest an increased risk to the fetus.[186–188] This has been supported by a prospective controlled trial of 165 women exposed to mesalamine compared with matched controls with no exposure[189] and a population-based cohort study from Denmark.[190] Neither trial demonstrated teratogenic risk, but there was an increased risk of premature birth, low birth weight, and stillbirth. The latter complications may reflect disease effect because the mesalamine group had IBD and the nonexposed group was from the general population.

Breast-feeding while on aminosalicylates has been associated with diarrhea in the infant.[191] Women can breast-feed while being treated with 5-aminosalicylates, but infants should be observed for a persistent change in stool frequency.

Antibiotics

Metronidazole, the quinolones, and rifaximin are covered in the section on infectious diarrhea. In general, given the limited evidence of benefit of these agents in IBD and the extended duration of use in the treatment of Crohn's disease and ulcerative colitis, they should be avoided during pregnancy. Short courses for the treatment of pouchitis can be considered based on the safety data presented previously. An alternative antibiotic for pouchitis is amoxicillin/clavulanic acid, a pregnancy category B drug. A population-based case-control study[192] and a prospective controlled study[193] did not show evidence of increased teratogenic risk, and it is compatible with breast-feeding.

Corticosteroids

Corticosteroids are pregnancy category C drugs. A case-control study of corticosteroid use during the first trimester of pregnancy noted an increased risk of oral clefts in the newborn.[194] This was confirmed by a large case-control study[195] and a meta-analysis that reported a summary OR for case-control studies examining the risk of oral clefts (3.35 [95% CI, 1.97–5.69]).[196] However, the overall risk of major malformations was low (1.45 [95% CI, 0.80–2.60]). A prospective controlled study of 311 women who received glucocorticosteroids during the first trimester did not note an increased rate of major anomalies and no cases of oral cleft were noted.[197] The study was powered to find a 2.5-fold increase in the

overall rate of major anomalies. An increased risk of premature rupture of membranes and adrenal insufficiency in the newborn has been reported in the transplant setting.[198] Overall, the use of corticosteroids poses a small risk to the developing infant and the mother needs to be informed of both the benefits and the risks of therapy. Prednisone and prednisolone are compatible with breast-feeding.

There are no published data on the safety of oral budesonide in pregnancy. A retrospective review of 4 patients with IBD treated with budesonide during pregnancy did not demonstrate congenital malformations or an increase in adverse outcomes (personal communication, D. Binion, July 2005). Inhaled or intranasal budesonide is not associated with adverse fetal outcomes based on large clinical series.[199,200] Safety in lactation is not known.

Bisphosphonates

The bisphosphonates alendronate and risedronate are pregnancy category C drugs, and the safety in breast-feeding is unknown. Many patients with IBD are started on these medications in conjunction with corticosteroids for prevention of bone loss. Both agents should be avoided in pregnancy because animal studies show that alendronate does cross the placenta and store in fetal bone, causing anatomic changes.[201] The effects on human fetal bone development are unknown. The half-life of alendronate is more than 10 years, and it accumulates in bone. The concern in giving this agent to a woman of child-bearing potential is that the drug is slowly released from bone and may result in a low level of continuous exposure to the fetus throughout gestation. Risedronate has a reported half-life of 20 days. However, an ongoing study by the manufacturer suggests that the half-life may be significantly longer. The long-term use of bisphosphonates in women of child-bearing potential should be done with caution and under the guidance of an endocrinologist or rheumatologist.

Immunomodulators

The immunomodulators are the most controversial agents used in the treatment of the pregnant woman with IBD.

Methotrexate. Methotrexate, a pregnancy category X drug, is clearly teratogenic and should not be used in women or men considering conception. Methotrexate is a folic acid antagonist, and use during the critical period of organogenesis (6–8 weeks postconception) is associated with multiple congenital anomalies collectively called methotrexate embryopathy or the fetal aminopterin-methotrexate syndrome.[2] The syndrome is characterized by intrauterine growth retardation; decreased ossification of the calvarium; hypoplastic supraorbital ridges; small, low-set ears; micrognathia; limb abnormalities; and sometimes mental retardation.[202] Exposure in the second and third trimesters may be associated with fetal toxicity and mortality.[2] Methotrexate may cause reversible oligospermia in men.[203] There are no case reports to date of resultant congenital anomalies in the offspring of men treated with methotrexate. Methotrexate may persist in tissues for long periods, and it is suggested that patients wait at least 3–6 months from the discontinuation of the drug before attempting conception.

Methotrexate is excreted in breast milk and may accumulate in neonatal tissues. The AAP classifies methotrexate as a cytotoxic drug with the potential to interfere with cellular metabolism.[3] It is contraindicated in breast-feeding.

Azathioprine/6-mercaptopurine. 6-Mercaptopurine and its prodrug azathioprine are pregnancy category D drugs. Animal studies have demonstrated teratogenicity with increased frequencies of cleft palate, open-eye, and skeletal anomalies seen in mice exposed to azathioprine and cleft palate, skeletal anomalies, and urogenital anomalies seen in rats.[204] Transplacental and transamniotic transmission of azathioprine and its metabolites from the mother to the fetus can occur.[205] The oral bioavailability of azathioprine (47%) and 6-mercaptopurine (16%) is low,[204] and the early fetal liver lacks the enzyme inosinate pyrophosphorylase needed to convert azathioprine to 6-mercaptopurine. Both features may protect the fetus from toxic drug exposure during the crucial period of organogenesis. The largest evidence on safety comes from transplantation studies where rates of anomalies ranged from 0 to 11.8% and no evidence of recurrent patterns of congenital anomalies emerged.[204] A population-based cohort study from Denmark compared 11 women exposed to azathioprine or 6-mercaptopurine with the general population.[206] The adjusted OR for congenital malformations was 6.7 (95% CI, 1.4–32.4). However, when a single severely ill patient with autoimmune hepatitis and multiple other medications was removed from the cohort, the OR was 3.4 (95% CI, 0.4–27.3). In IBD, multiple case series have not noted an increase in congenital anomalies.[207–210] Based on the large experience in transplant recipients and the body of evidence in IBD, the drugs are often continued during pregnancy to keep the mother in remission. A flare of disease during pregnancy may be more deleterious to neonatal outcome than any potential risk from the medication.

Studies are currently being performed on mercaptopurine levels in breast milk. Given the potential for severe toxicity in the breast-feeding infant, breast-feeding is not recommended.[2]

Cyclosporine and tacrolimus. These agents are covered in depth in the section on liver transplantation. A case report notes the successful use of cyclosporine in a 27-week pregnant woman with fulminant ulcerative colitis.[211] In the setting of severe, corticosteroid-refractory ulcerative colitis, cyclosporine may be a better option than colectomy, which is associated with a 50%–60% rate of fetal mortality.[212] A single case report of a patient with ulcerative colitis who had a successful pregnancy on maintenance tacrolimus was recently published.[213] No other data in IBD are published at this time.

Thalidomide. Thalidomide, a pregnancy category X drug, has some anti–tumor necrosis factor effects and has been used successfully for the treatment of Crohn's disease.[214] However, its teratogenicity has been extensively documented and includes limb defects, central nervous system effects, and abnormalities of the respiratory, cardiovascular, gastrointestinal, and genitourinary system.[2] Thalidomide is contraindicated during pregnancy and in women of childbearing age who are not using 2 reliable methods of contraception for 1 month before starting therapy, during therapy, and for 1 month after stopping therapy.[215] There are no human data on breast-feeding, but it is not advised given the potential toxicity.

Biologic Therapy

Infliximab. Infliximab, a pregnancy category B drug, is used for the management of Crohn's disease[216] and ulcerative colitis.[217] There is a growing body of evidence that suggests infliximab is low risk in pregnancy. There were 4 early case reports in patients with Crohn's disease. In one case,[218] the mother received infliximab during the conception period and first trimester, had active disease throughout, and was also on azathioprine, metronidazole, and mesalamine. The pregnancy ended in premature birth at 24 weeks and death of the infant 3 days later of intracerebral and intrapulmonary bleeding. In the 3 other cases, the pregnancy ended in a live birth; 2 infants were full-term and one was preterm at 36 weeks, and the infants were healthy at last follow-up.[219–221]

The 2 largest studies are from the TREAT Registry[222] and the Infliximab Safety Database[223] maintained by Centocor (Malvern, PA). The TREAT Registry is a prospective registry of patients with Crohn's disease. Patients may or may not be treated with infliximab. Of the 5807 patients enrolled, 66 pregnancies were reported, 36 with prior infliximab exposure. Fetal malformations have not occurred in any of the pregnancies. The rates of miscarriage (11.1% vs 7.1%; $P = .53$) and neonatal complications (8.3% vs 7.1%; $P = .78$) are not significantly different between infliximab-treated and infliximab-naïve patients, respectively.

The Infliximab Safety Database is a retrospective data collection instrument. Pregnancy outcome data are available for 96 women with direct exposure to infliximab.[223] The 96 pregnancies resulted in 100 births. The expected versus observed outcomes among women exposed to infliximab were not different from those of the general population. A series of 10 women with maintenance infliximab use throughout pregnancy was reported.[224] All 10 pregnancies ended in live births, with no reported congenital malformations.

Infliximab probably crosses the placenta. A recent case report[225] noted higher than detectable infliximab levels in an infant born to a mother on infliximab therapy every 4 weeks. The mother breast-fed and continued to receive infliximab but the infant's infliximab level dropped over 6 months, suggesting placental rather than breast milk transfer. The effect of the high infliximab levels on the infant's developing immune system is not known, although at 7 months the infant had appropriate responses to vaccination.

It is not known whether infliximab is excreted in human milk or absorbed systemically after ingestion. The only available study on infliximab in breast milk found that levels were either not present or were too low to be detected in the single patient studied.[226] Case reports of women who breast-fed while on infliximab do not suggest toxicity,[224,225] and it is probably compatible with breast-feeding.

Adalimumab. Adalimumab, a pregnancy category B drug, has recently demonstrated safety and efficacy for induction of remission in Crohn's disease.[227] Currently the drug is FDA approved for the treatment of rheumatoid arthritis; however, it is being administered off-label to patients with Crohn's disease who are intolerant of infliximab. A case report documents a successful pregnancy in a woman with long-standing Crohn's disease who began treatment with adalimumab 1 month before conception and received a total of 38 doses during her pregnancy.[228]

Fish Oil Supplements

Many patients with IBD use fish oil supplements as an adjunct to standard medical therapy. Because this is a supplement and not a drug, it is not rated by the FDA. A randomized controlled trial of fish oil supplementation

demonstrated a prolongation of pregnancy without detrimental effects on the growth of the fetus or on the course of labor.[229] Fish oil supplementation may also play a role in preventing miscarriage associated with the antiphospholipid antibody syndrome.[230] In women with IBD who may be at increased risk for preterm birth and miscarriage, fish oil supplementation is not harmful and may be of some benefit.

Summary

The majority of the medications used in commonly treated gastrointestinal and hepatological conditions are relatively low risk for use during pregnancy and lactation. In all cases, the benefit of the drug for the treatment of the underlying condition versus the potential toxicity to the infant needs to be carefully considered. The mother should be informed of the available data, and the obstetrician and pediatrician, where indicated, should be involved in the decision-making process. When possible, a proactive approach should be taken for pregnancy and childbearing because the best outcomes will be when appropriate medications can be stopped before exposure in the first trimester when organogenesis is occurring.

Future Directions

The ethical concerns regarding enrollment of pregnant women in clinical trials will always be present. Collaborative studies from multiple centers and population-based databases will continue to provide the best evidence and the means with which to collect safety data on pregnant patients. Clinicians who care for pregnant patients should be made aware of local and national resources to report outcomes of their patients. Particularly, any patient who becomes pregnant on prescription medications and has an adverse outcome should be reported to the manufacturer of the drug and to the FDA's Medwatch (http://www.fda.gov/medwatch). Teratogenic studies on laboratory animals will continue to be important as new medications become available. Finally, milk-based assays for drug concentrations need to be developed to determine the true risk to the breast-feeding infant.

UMA MAHADEVAN
Division of Gastroenterology
Department of Medicine
University of California, San Francisco
San Francisco, California

SUNANDA KANE
Division of Gastroenterology
Department of Medicine
University of Chicago
Chicago, Illinois

References

1. Jefferies JA, Robboy SJ, O'Brien PC, Bergstralh EJ, Labarthe DR, Barnes AB, Noller KL, Hatab PA, Kaufman RH, Townsend DE. Structural anomalies of the cervix and vagina in women enrolled in the Diethylstilbestrol Adenosis (DESAD) Project. Am J Obstet Gynecol 1984;148:59–66.
2. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation. 7th ed. Philadelphia, PA: Lippincott, Williams & Wilkins, 2005.
3. American Academy of Pediatrics Committee on Drugs. The transfer of drugs and other chemicals into human milk. Pediatrics 2001;108:776–789.
4. U.S. Department of Education and Welfare PHS, National Institutes of Health. The Collaborative Study of the National Institute of Neurological Diseases: The Women and Their Pregnancies. DHEW Publication No. (NIH) 73-379, 1972.
5. Schwethelm B, Margolis LH, Miller C, Smith S. Risk status and pregnancy outcome among Medicaid recipients. Am J Prev Med 1989;5:157–163.
6. Fairlie FM, Marshall L, Walker JJ, Elbourne D. Intramuscular opioids for maternal pain relief in labour: a randomised controlled trial comparing pethidine with diamorphine. Br J Obstet Gynaecol 1999;106:1181–1187.
7. Tsui MH, Ngan Kee WD, Ng FF, Lau TK. A double blinded randomised placebo-controlled study of intramuscular pethidine for pain relief in the first stage of labour. BJOG 2004;111:648–655.
8. Barrett JM, Boehm FH. Fetal heart rate responses to meperidine alone and in combination with propiomazine. South Med J 1983; 76:1480–1483.
9. Peiker G, Muller B, Ihn W, Noschel H. [Excretion of pethidine in mother's milk (author's transl)]. Zentralbl Gynakol 1980;102: 537–541.
10. Quinn PG, Kuhnert BR, Kaine CJ, Syracuse CD. Measurement of meperidine and normeperidine in human breast milk by selected ion monitoring. Biomed Environ Mass Spectrom 1986; 13:133–135.
11. Martin LV, Jurand A. The absence of teratogenic effects of some analgesics used in anaesthesia. Additional evidence from a mouse model. Anaesthesia 1992;47:473–476.
12. Fernando R, Bonello E, Gill P, Urquhart J, Reynolds F, Morgan B. Neonatal welfare and placental transfer of fentanyl and bupivacaine during ambulatory combined spinal epidural analgesia for labour. Anaesthesia 1997;52:517–524.
13. Morley-Forster PK, Reid DW, Vandeberghe H. A comparison of patient-controlled analgesia fentanyl and alfentanil for labour analgesia. Can J Anaesth 2000;47:113–119.
14. Nelson KE, Rauch T, Terebuh V, D'Angelo R. A comparison of intrathecal fentanyl and sufentanil for labor analgesia. Anesthesiology 2002;96:1070–1073.
15. Rayburn W, Rathke A, Leuschen MP, Chleborad J, Weidner W. Fentanyl citrate analgesia during labor. Am J Obstet Gynecol 1989;161:202–206.
16. Carrie LE, O'Sullivan GM, Seegobin R. Epidural fentanyl in labour. Anaesthesia 1981;36:965–969.
17. Lindemann R. Respiratory muscle rigidity in a preterm infant after use of fentanyl during Caesarean section. Eur J Pediatr 1998;157:1012–1013.

18. Regan J, Chambers F, Gorman W, MacSullivan R. Neonatal abstinence syndrome due to prolonged administration of fentanyl in pregnancy. BJOG 2000;107:570–572.
19. Celleno D, Capogna G, Tomassetti M, Costantino P, Di Feo G, Nisini R. Neurobehavioural effects of propofol on the neonate following elective caesarean section. Br J Anaesth 1989;62: 649–654.
20. Abboud TK, Zhu J, Richardson M, Peres Da Silva E, Donovan M. Intravenous propofol vs thiamylal-isoflurane for caesarean section, comparative maternal and neonatal effects. Acta Anaesthesiol Scand 1995;39:205–209.
21. Cheng YJ, Wang YP, Fan SZ, Liu CC. Intravenous infusion of low dose propofol for conscious sedation in cesarean section before spinal anesthesia. Acta Anaesthesiol Sin 1997;35:79–84.
22. Gregory MA, Gin T, Yau G, Leung RK, Chan K, Oh TE. Propofol infusion anaesthesia for caesarean section. Can J Anaesth 1990;37:514–520.
23. Dailland P, Cockshott ID, Lirzin JD, Jacquinot P, Jorrot JC, Devery J, Harmey JL, Conseiller C. Intravenous propofol during cesarean section: placental transfer, concentrations in breast milk, and neonatal effects. A preliminary study. Anesthesiology 1989; 71:827–834.
24. American Academy of Pediatrics Committee on Drugs. Naloxone use in newborns. Pediatrics 1980;65:667–669.
25. Smotherman WP, Robinson SR. Prenatal experience with milk: fetal behavior and endogenous opioid systems. Neurosci Biobehav Rev 1992;16:351–364.
26. Safra MJ, Oakley GP Jr. Association between cleft lip with or without cleft palate and prenatal exposure to diazepam. Lancet 1975;2:478–480.
27. Czeizel A. Lack of evidence of teratogenicity of benzodiazepine drugs in Hungary. Reprod Toxicol 1987;1:183–188.
28. Bracken MB, Holford TR. Exposure to prescribed drugs in pregnancy and association with congenital malformations. Obstet Gynecol 1981;58:336–344.
29. Rothman KJ, Fyler DC, Goldblatt A, Kreidberg MB. Exogenous hormones and other drug exposures of children with congenital heart disease. Am J Epidemiol 1979;109:433–439.
30. Ornoy A, Arnon J, Shechtman S, Moerman L, Lukashova I. Is benzodiazepine use during pregnancy really teratogenic? Reprod Toxicol 1998;12:511–515.
31. Dolovich LR, Addis A, Vaillancourt JM, Power JD, Koren G, Einarson TR. Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. BMJ 1998;317:839–843.
32. Wesson DR, Camber S, Harkey M, Smith DE. Diazepam and desmethyldiazepam in breast milk. J Psychoactive Drugs 1985; 17:55–56.
33. Bland BA, Lawes EG, Duncan PW, Warnell I, Downing JW. Comparison of midazolam and thiopental for rapid sequence anesthetic induction for elective cesarean section. Anesth Analg 1987;66:1165–1168.
34. Celleno D, Capogna G, Emanuelli M, Varrassi G, Muratori F, Costantino P, Sebastiani M. Which induction drug for cesarean section? A comparison of thiopental sodium, propofol, and midazolam. J Clin Anesth 1993;5:284–288.
35. Cappell MS, Colon VJ, Sidhom OA. A study at 10 medical centers of the safety and efficacy of 48 flexible sigmoidoscopies and 8 colonoscopies during pregnancy with follow-up of fetal outcome and with comparison to control groups. Dig Dis Sci 1996;41:2353–2361.
36. Cappell MS, Colon VJ, Sidhom OA. A study of eight medical centers of the safety and clinical efficacy of esophagogastroduodenoscopy in 83 pregnant females with follow-up of fetal outcome with comparison control groups. Am J Gastroenterol 1996;91:348–354.
37. Matheson I, Lunde PK, Bredesen JE. Midazolam and nitrazepam in the maternity ward: milk concentrations and clinical effects. Br J Clin Pharmacol 1990;30:787–793.
38. Stahl MM, Saldeen P, Vinge E. Reversal of fetal benzodiazepine intoxication using flumazenil. Br J Obstet Gynaecol 1993;100: 185–188.
39. Shin YK, Collea JV, Kim YD. The effect of glucagon on spontaneous contractility of isolated pregnant uterine muscle. Obstet Gynecol 1996;88:867–871.
40. Rayburn W, Piehl E, Sanfield J, Compton A. Reversing severe hypoglycemia during pregnancy with glucagon therapy. Am J Perinatol 1987;4:259–261.
41. Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. A population-based case-control teratologic study of ampicillin treatment during pregnancy. Am J Obstet Gynecol 2001;185:140–147.
42. Matsuda S. Transfer of antibiotics into maternal milk. Biol Res Pregnancy Perinatol 1984;5:57–60.
43. Czeizel AE, Rockenbauer M, Olsen J, Sorensen HT. A teratological study of aminoglycoside antibiotic treatment during pregnancy. Scand J Infect Dis 2000;32:309–313.
44. Celiloglu M, Celiker S, Guven H, Tuncok Y, Demir N, Erten O. Gentamicin excretion and uptake from breast milk by nursing infants. Obstet Gynecol 1994;84:263–265.
45. Nardulli G, Limongi F, Sue G, Zapata L, Bompart I. [Use of polyethylene glycol in the treatment of puerperal constipation]. G. E. N. 1995;49:224–226.
46. Rimensberger P, Schubiger G, Willi U. Connatal rickets following repeated administration of phosphate enemas in pregnancy: a case report. Eur J Pediatr 1992;151:54–56.
47. Morrison JC, Boyd M, Friedman BI, Bucovaz ET, Whybrew WD, Koury DN, Wiser WL, Fish SA. The effects of Renografin-60 on the fetal thyroid. Obstet Gynecol 1973;42:99–103.
48. Sorensen HT, Nielsen GL, Christensen K, Tage-Jensen U, Ekbom A, Baron J. Birth outcome following maternal use of metoclopramide. The Euromap study group. Br J Clin Pharmacol 2000;49:264–268.
49. Berkovitch M, Mazzota P, Greenberg R, Elbirt D, Addis A, Schuler-Faccini L, Merlob P, Arnon J, Stahl B, Magee L, Moretti M, Ornoy A. Metoclopramide for nausea and vomiting of pregnancy: a prospective multicenter international study. Am J Perinatol 2002;19:311–316.
50. Vella L, Francis D, Houlton P, Reynolds F. Comparison of the antiemetics metoclopramide and promethazine in labour. Br Med J (Clin Res Ed) 1985;290:1173–1175.
51. Breslow S, Belafsky HA, Shangold JE, Hirsch LM, Stahl MB. Antiemetic effect of trimethobenzamide in pregnant patients. Clin Otorinolaringoiatr 1961;8:2153–2155.
52. Miklovich L, van den Berg BJ. An evaluation of the teratogenicity of certain antinauseant drugs. Am J Obstet Gynecol 1976;125: 244–248.
53. Winters HS. Antiemetics in nausea and vomiting of pregnancy. Obstet Gynecol 1961;18:753–756.
54. Sullivan CA, Johnson CA, Roach H, Martin RW, Stewart DK, Morrison JC. A pilot study of intravenous ondansetron for hyperemesis gravidarum. Am J Obstet Gynecol 1996;174:1565–1568.
55. Einarson A, Maltepe C, Navioz Y, Kennedy D, Tan MP, Koren G. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. BJOG 2004;111:940–943.
56. Kytril [package insert]. Philadelphia, PA: SmithKline Beecham, 1997.
57. Ching CK, Lam SK. Antacids. Indications and limitations. Drugs 1994;47:305–317.
58. Witter FR, King TM, Blake DA. The effects of chronic gastrointestinal medication on the fetus and neonate. Obstet Gynecol 1981;58:79S–84S.

59. McGuinness B, Logan JI. Milk alkali syndrome. Ulster Med J 2002;71:132–135.
60. Ranchet G, Gangemi O, Petrone M. Sucralfate in the treatment of gravid pyrosis. G Ital Ostericia Ginecol 1990;12:1–16.
61. Kallen B. Delivery outcome after the use of acid-suppressing drugs in early pregnancy with special reference to omeprazole. Br J Obstet Gynaecol 1998;105:877–881.
62. Ruigomez A, Garcia Rodriguez LA, Cattaruzzi C, Troncon MG, Agostinis L, Wallander MA, Johansson S. Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. Am J Epidemiol 1999;150:476–481.
63. Larson JD, Patatanian E, Miner PB Jr, Rayburn WF, Robinson MG. Double-blind, placebo-controlled study of ranitidine for gastroesophageal reflux symptoms during pregnancy. Obstet Gynecol 1997;90:83–87.
64. Magee LA, Inocencion G, Kamboj L, Rosetti F, Koren G. Safety of first trimester exposure to histamine H2 blockers. A prospective cohort study. Dig Dis Sci 1996;41:1145–1149.
65. Garbis H, Elefant E, Diav-Citrin O, Mastroiacovo P, Schaefer C, Vial T, Clementi M, Valti E, McElhatton P, Smorlesi C, Rodriguez EP, Robert-Gnansia E, Merlob P, Peiker G, Pexieder T, Schueler L, Ritvanen A, Mathieu-Nolf M. Pregnancy outcome after exposure to ranitidine and other H2-blockers. A collaborative study of the European Network of Teratology Information Services. Reprod Toxicol 2005;19:453–458.
66. Morton DM. Pharmacology and toxicology of nizatidine. Scand J Gastroenterol Suppl 1987;136:1–8.
67. Sankaran K, Yeboah E, Bingham WT, Ninan A. Use of metoclopramide in preterm infants. Dev Pharmacol Ther 1982;5:114–119.
68. Bailey B, Addis A, Lee A, Sanghvi K, Mastroiacovo P, Mazzone T, Bonati M, Paolini C, Garbis H, Val T, De Souza CF, Matsui D, Schechtman AS, Conover B, Lau M, Koren G. Cisapride use during human pregnancy: a prospective, controlled multicenter study. Dig Dis Sci 1997;42:1848–1852.
69. Prilosec [package insert]. Wilmington, DE: AstraZeneca, 2001.
70. Kallen BA. Use of omeprazole during pregnancy—no hazard demonstrated in 955 infants exposed during pregnancy. Eur J Obstet Gynecol Reprod Biol 2001;96:63–68.
71. Lalkin A, Loebstein R, Addis A, Ramezani-Namin F, Mastroiacovo P, Mazzone T, Vial T, Bonati M, Koren G. The safety of omeprazole during pregnancy: a multicenter prospective controlled study. Am J Obstet Gynecol 1998;179:727–730.
72. Diav-Citrin O, Arnon J, Shechtman S, Schaefer C, van Tonningen MR, Clementi M, De Santis M, Robert-Gnansia E, Valti E, Malm H, Ornoy A. The safety of proton pump inhibitors in pregnancy: a multicentre prospective controlled study. Aliment Pharmacol Ther 2005;21:269–275.
73. Wilton LV, Pearce GL, Martin RM, Mackay FJ, Mann RD. The outcomes of pregnancy in women exposed to newly marketed drugs in general practice in England. Br J Obstet Gynaecol 1998;105:882–889.
74. Nielsen GL, Sorensen HT, Thulstrup AM, Tage-Jensen U, Olesen C, Ekbom A. The safety of proton pump inhibitors in pregnancy. Aliment Pharmacol Ther 1999;13:1085–1089.
75. Jepsen P, Skriver MV, Floyd A, Lipworth L, Schonheyder HC, Sorensen HT. A population-based study of maternal use of amoxicillin and pregnancy outcome in Denmark. Br J Clin Pharmacol 2003;55:216–221.
76. Witt A, Sommer EM, Cichna M, Postlbauer K, Widhalm A, Gregor H, Reisenberger K. Placental passage of clarithromycin surpasses other macrolide antibiotics. Am J Obstet Gynecol 2003;188:816–819.
77. Einarson A, Phillips E, Mawji F, D'Alimonte D, Schick B, Addis A, Mastroiacova P, Mazzone T, Matsui D, Koren G. A prospective controlled multicentre study of clarithromycin in pregnancy. Am J Perinatol 1998;15:523–525.
78. Drinkard CR, Shatin D, Clouse J. Postmarketing surveillance of medications and pregnancy outcomes: clarithromycin and birth malformations. Pharmacoepidemiol Drug Saf 2000;9:549–556.
79. Sedlmayr T, Peters F, Raasch W, Kees F. [Clarithromycin, a new macrolide antibiotic. Effectiveness in puerperal infections and pharmacokinetics in breast milk]. Geburtshilfe Frauenheilkd 1993;53:488–491.
80. James LF, Lazar VA, Binns W. Effects of sublethal doses of certain minerals on pregnant ewes and fetal development. Am J Vet Res 1966;27:132–135.
81. Ridgway LP, Karnofsky DA. The effects of metals on the chick embryo: toxicity and production of abnormalities in development. Ann N Y Acad Sci 1952;55:203–215.
82. Lione A. Nonprescription drugs as a source of aluminum, bismuth, and iodine during pregnancy. Reprod Toxicol 1987;1:243–252.
83. Luiten EJ, Hop WC, Lange JF, Bruining HA. Controlled clinical trial of selective decontamination for the treatment of severe acute pancreatitis. Ann Surg 1995;222:57–65.
84. Loebstein R, Addis A, Ho E, Andreou R, Sage S, Donnenfeld AE, Schick B, Bonati M, Moretti M, Lalkin A, Pastuszak A, Koren G. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. Antimicrob Agents Chemother 1998;42:1336–1339.
85. Larsen H, Nielsen GL, Schonheyder HC, Olesen C, Sorensen HT. Birth outcome following maternal use of fluoroquinolones. Int J Antimicrob Agents 2001;18:259–262.
86. Moudgal VV, Sobel JD. Antifungal drugs in pregnancy: a review. Expert Opin Drug Saf 2003;2:475–483.
87. Dinsmoor MJ. Imipenem-cilastatin. Obstet Gynecol Clin North Am 1992;19:475–482.
88. Heikkila A, Renkonen OV, Erkkola R. Pharmacokinetics and transplacental passage of imipenem during pregnancy. Antimicrob Agents Chemother 1992;36:2652–2655.
89. Wunsch MJ, Stanard V, Schnoll SH. Treatment of pain in pregnancy. Clin J Pain 2003;19:148–155.
90. Fischer G, Johnson RE, Eder H, Jagsch R, Peternell A, Weninger M, Langer M, Aschauer HN. Treatment of opioid-dependent pregnant women with buprenorphine. Addiction 2000;95:239–244.
91. Odegaard I, Stray-Pedersen B, Hallberg K, Haanaes OC, Storrosten OT, Johannesson M. Maternal and fetal morbidity in pregnancies of Norwegian and Swedish women with cystic fibrosis. Acta Obstet Gynecol Scand 2002;81:698–705.
92. Michel SH, Mueller DH. Impact of lactation on women with cystic fibrosis and their infants: a review of five cases. J Am Diet Assoc 1994;94:159–165.
93. Lu EJ, Curet MJ, El-Sayed YY, Kirkwood KS. Medical versus surgical management of biliary tract disease in pregnancy. Am J Surg 2004;188:755–759.
94. Ramin KD, Ramsey PS. Disease of the gallbladder and pancreas in pregnancy. Obstet Gynecol Clin North Am 2001;28:571–580.
95. Hempfling W, Dilger K, Beuers U. Systematic review: ursodeoxycholic acid—adverse effects and drug interactions. Aliment Pharmacol Ther 2003;18:963–972.
96. Christensen KL, Andersen BN, Vilstrup H. [Primary sclerosing cholangitis with itching treated during pregnancy with ursodeoxycholic acid]. Ugeskr Laeger 1997;159:7151–7153.
97. Gossard AA, Lindor KD. Pregnancy in a patient with primary sclerosing cholangitis. J Clin Gastroenterol 2002;35:353–355.
98. Poupon R, Chretien Y, Chazouilleres O, Poupon RE. Pregnancy in women with ursodeoxycholic acid-treated primary biliary cirrhosis. J Hepatol 2005;42:418–419.
99. Palma J, Reyes H, Ribalta J, Hernandez I, Sandoval L, Almuna R, Liepins J, Lira F, Sedano M, Silva O, Toha D, Silva JJ. Ursodeoxycholic acid in the treatment of cholestasis of pregnancy: a

randomized, double-blind study controlled with placebo. J Hepatol 1997;27:1022–1028.
100. Magriples U. Hepatitis in pregnancy. Semin Perinatol 1998;22: 112–117.
101. Jonas MM, Reddy RK, DeMedina M, Schiff ER. Hepatitis B infection in a large municipal obstetrical population: characterization and prevention of perinatal transmission. Am J Gastroenterol 1990;85:277–280.
102. Su GG, Pan KH, Zhao NF, Fang SH, Yang DH, Zhou Y. Efficacy and safety of lamivudine treatment for chronic hepatitis B in pregnancy. World J Gastroenterol 2004;10:910–912.
103. van Zonneveld M, van Nunen AB, Niesters HG, de Man RA, Schalm SW, Janssen HL. Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. J Viral Hepat 2003;10:294–297.
104. Antiretroviral Pregnancy Registry. The Antiretroviral Pregnancy Registry for abacavir, amprenavir, delavirdine, didanosine, efavirenz, indinavir, lamivudine, lamivudine/zidovudine, nelfinavir, nevirapine, ritonavir, saquinavir, saquinavir mesylate, stavudine, zalcitavine, zidovudine, Interim report 1 January 1989 though 31 July 2000. Antiretroviral Pregnancy Registry 2000: 1–55.
105. Moodley J, Moodley D, Pillay K, Coovadia H, Saba J, van Leeuwen R, Goodwin C, Harrigan PR, Moore KH, Stone C, Plumb R, Johnson MA. Pharmacokinetics and antiretroviral activity of lamivudine alone or when coadministered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring. J Infect Dis 1998;178:1327–1333.
106. Chard T. Interferon in pregnancy. J Dev Physiol 1989;11:271–276.
107. Hiratsuka M, Minakami H, Koshizuka S, Sato I. Administration of interferon-alpha during pregnancy: effects on fetus. J Perinat Med 2000;28:372–376.
108. Ozaslan E, Yilmaz R, Simsek H, Tatar G. Interferon therapy for acute hepatitis C during pregnancy. Ann Pharmacother 2002; 36:1715–1718.
109. Rebetol [package insert]. Kenilworth, NJ: Schering, 2004.
110. Scheinberg IH, Sternlieb I. Pregnancy in penicillamine-treated patients with Wilson's disease. N Engl J Med 1975;293:1300–1302.
111. Marecek Z, Graf M. Pregnancy in penicillamine-treated patients with Wilson's disease (letter). N Engl J Med 1976;295:841–842.
112. Sinha S, Taly AB, Prashanth LK, Arunodaya GR, Swamy HS. Successful pregnancies and abortions in symptomatic and asymptomatic Wilson's disease. J Neurol Sci 2004;217:37–40.
113. Walshe JM. The management of pregnancy in Wilson's disease treated with trientine. Q J Med 1986;58:81–87.
114. Janczewska I, Olsson R, Hultcrantz R, Broome U. Pregnancy in patients with primary sclerosing cholangitis. Liver 1996;16: 326–330.
115. Korkut E, Kisacik B, Akcan Y, Belenli O, Bicik Z, Yucel O. Two successive pregnancies after ursodeoxycholic acid therapy in a previously infertile woman with antimitochondrial antibody-negative primary biliary cirrhosis. Fertil Steril 2005;83:761–763.
116. Kondrackiene J, Beuers U, Kupcinskas L. Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. Gastroenterology 2005;129:894–901.
117. Pruyn SC, Phelan JP, Buchanan GC. Long-term propranolol therapy in pregnancy: maternal and fetal outcome. Am J Obstet Gynecol 1979;135:485–489.
118. Fox RE, Marx C, Stark AR. Neonatal effects of maternal nadolol therapy. Am J Obstet Gynecol 1985;152:1045–1046.
119. Armenti VT, Radomski JS, Moritz MJ, Gaughan WJ, McGrory CH, Coscia LA. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl 2003:131–141.
120. Bar Oz B, Hackman R, Einarson T, Koren G. Pregnancy outcome after cyclosporine therapy during pregnancy: a meta-analysis. Transplantation 2001;71:1051–1055.
121. Nagy S, Bush MC, Berkowitz R, Fishbein TM, Gomez-Lobo V. Pregnancy outcome in liver transplant recipients. Obstet Gynecol 2003;102:121–128.
122. Jain A, Venkataramanan R, Fung JJ, Gartner JC, Lever J, Balan V, Warty V, Starzl TE. Pregnancy after liver transplantation under tacrolimus. Transplantation 1997;64:559–565.
123. Kainz A, Harabacz I, Cowlrick IS, Gadgil S, Hagiwara D. Analysis of 100 pregnancy outcomes in women treated systemically with tacrolimus. Transpl Int 2000;13(Suppl 1):S299–S300.
124. Jain AB, Reyes J, Marcos A, Mazariegos G, Eghtesad B, Fontes PA, Cacciarelli TV, Marsh JW, de Vera ME, Rafail A, Starzl TE, Fung JJ. Pregnancy after liver transplantation with tacrolimus immunosuppression: a single center's experience update at 13 years. Transplantation 2003;76:827–832.
125. Jankowska I, Oldakowska-Jedynak U, Jabiry-Zieniewicz Z, Cyganek A, Pawlowska J, Teisseyre M, Kalicinski P, Markiewicz M, Paczek L, Socha J. Absence of teratogenicity of sirolimus used during early pregnancy in a liver transplant recipient. Transplant Proc 2004;36:3232–3233.
126. Le Ray C, Coulomb A, Elefant E, Frydman R, Audibert F. Mycophenolate mofetil in pregnancy after renal transplantation: a case of major fetal malformations. Obstet Gynecol 2004;103: 1091–1094.
127. Hasler WL. The irritable bowel syndrome during pregnancy. Gastroenterol Clin North Am 2003;32:385–406, viii.
128. Tytgat GN, Heading RC, Muller-Lissner S, Kamm MA, Scholmerich J, Berstad A, Fried M, Chaussade S, Jewell D, Briggs A. Contemporary understanding and management of reflux and constipation in the general population and pregnancy: a consensus meeting. Aliment Pharmacol Ther 2003;18:291–301.
129. Attar A, Lemann M, Ferguson A, Halphen M, Boutron MC, Flourie B, Alix E, Salmeron M, Guillemot F, Chaussade S, Menard AM, Moreau J, Naudin G, Barthet M. Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation. Gut 1999;44:226–230.
130. Cameron BD, Phillips MW, Fenerty CA. Milk transfer of rhein in the rhesus monkey. Pharmacology 1988;36(Suppl 1):221–225.
131. Sicuranza GB, Figueroa R. Uterine rupture associated with castor oil ingestion. J Matern Fetal Neonatal Med 2003;13:133–134.
132. Einarson A, Mastroiacovo P, Arnon J, Ornoy A, Addis A, Malm H, Koren G. Prospective, controlled, multicentre study of loperamide in pregnancy. Can J Gastroenterol 2000;14:185–187.
133. Black RA, Hill DA. Over-the-counter medications in pregnancy. Am Fam Physician 2003;67:2517–2524.
134. Jenkins JK, Boothby LA. Treatment of itching associated with intrahepatic cholestasis of pregnancy. Ann Pharmacother 2002;36:1462–1465.
135. Patterson EC, Staszak DJ. Effects of geophagia (kaolin ingestion) on the maternal blood and embryonic development in the pregnant rat. J Nutr 1977;107:2020–2025.
136. Collins E. Maternal and fetal effects of acetaminophen and salicylates in pregnancy. Obstet Gynecol 1981;58:57S–62S.
137. Chun-Fai-Chan B, Koren G, Fayez I, Kalra S, Voyer-Lavigne S, Boshier A, Shakir S, Einarson A. Pregnancy outcome of women exposed to bupropion during pregnancy: a prospective comparative study. Am J Obstet Gynecol 2005;192:932–936.
138. Einarson TR, Einarson A. Newer antidepressants in pregnancy and rates of major malformations: a meta-analysis of prospective comparative studies. Pharmacoepidemiol Drug Saf 2005; 14:823–827.

139. GlaxoSmithKline. Study EPIP083. GSK medicine: bupropion and paroxetine. Epidemiology study: preliminary report on bupropion in pregnancy and the occurrence of cardiovascular and major congenital malformation. Available at: http://ctr.gsk.co.uk/summary/paroxetine/epip083.pdf. Accessed October 26, 2005.
140. Williams M, Wooltorton E. Paroxetine (Paxil) and congenital malformations. CMAJ 2005;173:1320–1321.
141. Kallen B. Neonate characteristics after maternal use of antidepressants in late pregnancy. Arch Pediatr Adolesc Med 2004;158:312–316.
142. Kulin NA, Pastuszak A, Sage SR, Schick-Boschetto B, Spivey G, Feldkamp M, Ormond K, Matsui D, Stein-Schechman AK, Cook L, Brochu J, Rieder M, Koren G. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. JAMA 1998;279:609–610.
143. Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 1996;335:1010–1015.
144. Hendrick V, Smith LM, Suri R, Hwang S, Haynes D, Altshuler L. Birth outcomes after prenatal exposure to antidepressant medication. Am J Obstet Gynecol 2003;188:812–815.
145. Sanz EJ, De-las-Cuevas C, Kiuru A, Bate A, Edwards R. Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis. Lancet 2005;365:482–487.
146. Gentile S. The safety of newer antidepressants in pregnancy and breastfeeding. Drug Saf 2005;28:137–152.
147. McKeigue PM, Lamm SH, Linn S, Kutcher JS. Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies. Teratology 1994;50:27–37.
148. Guerrant RL, Van Gilder T, Steiner TS, Thielman NM, Slutsker L, Tauxe RV, Hennessy T, Griffin PM, DuPont H, Sack RB, Tarr P, Neill M, Nachamkin I, Reller LB, Osterholm MT, Bennish ML, Pickering LK. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis 2001;32:331–351.
149. Albenza [package insert]. Philadelphia, PA: SmithKline Beecham Pharmaceuticals, 2001.
150. Gyapong JO, Chinbuah MA, Gyapong M. Inadvertent exposure of pregnant women to ivermectin and albendazole during mass drug administration for lymphatic filariasis. Trop Med Int Health 2003;8:1093–1101.
151. Torlesse H, Hodges M. Albendazole therapy and reduced decline in haemoglobin concentration during pregnancy (Sierra Leone). Trans R Soc Trop Med Hyg 2001;95:195–201.
152. Torlesse H, Hodges M. Anthelminthic treatment and haemoglobin concentrations during pregnancy. Lancet 2000;356:1083.
153. Niebyl JR. Antibiotics and other anti-infective agents in pregnancy and lactation. Am J Perinatol 2003;20:405–414.
154. Kacmar J, Cheh E, Montagno A, Peipert JF. A randomized trial of azithromycin versus amoxicillin for the treatment of Chlamydia trachomatis in pregnancy. Infect Dis Obstet Gynecol 2001;9:197–202.
155. Kigozi GG, Brahmbhatt H, Wabwire-Mangen F, Wawer MJ, Serwadda D, Sewankambo N, Gray RH. Treatment of Trichomonas in pregnancy and adverse outcomes of pregnancy: a subanalysis of a randomized trial in Rakai, Uganda. Am J Obstet Gynecol 2003;189:1398–1400.
156. Kline AH, Blattner RJ, Lunin M. Transplacental effect of tetracyclines of teeth. JAMA 1964;188:178–180.
157. Czeizel AE, Rockenbauer M. Teratogenic study of doxycycline. Obstet Gynecol 1997;89:524–528.
158. Heinonen OP, Slone D, Shaprio S. Birth defects and drug in pregnancy. Littleton, MA: Publishing Sciences Group, 1977.
159. Burtin P, Taddio A, Ariburnu O, Einarson TR, Koren G. Safety of metronidazole in pregnancy: a meta-analysis. Am J Obstet Gynecol 1995;172:525–529.
160. Caro-Paton T, Carvajal A, Martin de Diego I, Martin-Arias LH, Alvarez Requejo A, Rodriguez Pinilla E. Is metronidazole teratogenic? A meta-analysis. Br J Clin Pharmacol 1997;44:179–182.
161. Piper JM, Mitchel EF, Ray WA. Prenatal use of metronidazole and birth defects: no association. Obstet Gynecol 1993;82:348–352.
162. Sorensen HT, Larsen H, Jensen ES, Thulstrup AM, Schonheyder HC, Nielsen GL, Czeizel A. Safety of metronidazole during pregnancy: a cohort study of risk of congenital abnormalities, preterm delivery and low birth weight in 124 women. J Antimicrob Chemother 1999;44:854–856.
163. Diav-Citrin O, Shechtman S, Gotteiner T, Arnon J, Ornoy A. Pregnancy outcome after gestational exposure to metronidazole: a prospective controlled cohort study. Teratology 2001;63:186–192.
164. Czeizel AE, Rockenbauer M. A population based case-control teratologic study of oral metronidazole treatment during pregnancy. Br J Obstet Gynaecol 1998;105:322–327.
165. Bertoli D, Borelli G. Fertility study of rifaximin (L/105) in rats. Chemioterapia 1986;5:204–207.
166. Bertoli D, Borelli G. [Teratogenic action of Rifaximin in the rat and rabbit and its effect on perinatal development in the rat]. Boll Soc Ital Biol Sper 1984;60:1079–1085.
167. Xifaxan [package insert]. Morrisville, NC: Salix Pharmaceuticals, 2005.
168. Karhunen M. Placental transfer of metronidazole and tinidazole in early human pregnancy after a single infusion. Br J Clin Pharmacol 1984;18:254–257.
169. Czeizel AE, Kazy Z, Vargha P. Oral tinidazole treatment during pregnancy and teratogenesis. Int J Gynaecol Obstet 2003;83:305–306.
170. Evaldson GR, Lindgren S, Nord CE, Rane AT. Tinidazole milk excretion and pharmacokinetics in lactating women. Br J Clin Pharmacol 1985;19:503–507.
171. Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study. Reprod Toxicol 2001;15:637–646.
172. Vancocin [package insert]. Indianapolis, IN: Eli Lilly, 2000.
173. Reyes MP, Ostrea EM Jr, Cabinian AE, Schmitt C, Rintelmann W. Vancomycin during pregnancy: does it cause hearing loss or nephrotoxicity in the infant? Am J Obstet Gynecol 1989;161:977–981.
174. Woolfson K, Cohen Z, McLeod RS. Crohn's disease and pregnancy. Dis Colon Rectum 1990;33:869–873.
175. Craxi A, Pagliarello F. Possible embryotoxicity of sulfasalazine. Arch Intern Med 1980;140:1674.
176. Hoo JJ, Hadro TA, Von Behren P. Possible teratogenicity of sulfasalazine. N Engl J Med 1988;318:1128.
177. Newman NM, Correy JF. Possible teratogenicity of sulphasalazine. Med J Aust 1983;1:528–529.
178. Mogadam M, Dobbins WO III, Korelitz BI, Ahmed SW. Pregnancy in inflammatory bowel disease: effect of sulfasalazine and corticosteroids on fetal outcome. Gastroenterology 1981;80:72–76.
179. Norgard B, Czeizel AE, Rockenbauer M, Olsen J, Sorensen HT. Population-based case control study of the safety of sulfasalazine use during pregnancy. Aliment Pharmacol Ther 2001;15:483–486.
180. Esbjorner E, Jarnerot G, Wranne L. Sulphasalazine and sulphapyridine serum levels in children to mothers treated with sulphasalazine during pregnancy and lactation. Acta Paediatr Scand 1987;76:137–142.

181. Levi AJ, Fisher AM, Hughes L, Hendry WF. Male infertility due to sulphasalazine. Lancet 1979;2:276–278.
182. Toovey S, Hudson E, Hendry WF, Levi AJ. Sulphasalazine and male infertility: reversibility and possible mechanism. Gut 1981;22:445–451.
183. Chatzinoff M, Guarino JM, Corson SL, Batzer FR, Friedman LS. Sulfasalazine-induced abnormal sperm penetration assay reversed on changing to 5-aminosalicylic acid enemas. Dig Dis Sci 1988;33:108–110.
184. Kjaergaard N, Christensen LA, Lauritsen JG, Rasmussen SN, Hansen SH. Effects of mesalazine substitution on salicylazosulfapyridine-induced seminal abnormalities in men with ulcerative colitis. Scand J Gastroenterol 1989;24:891–896.
185. Moody GA, Probert C, Jayanthi V, Mayberry JF. The effects of chronic ill health and treatment with sulphasalazine on fertility amongst men and women with inflammatory bowel disease in Leicestershire. Int J Colorectal Dis 1997;12:220–224.
186. Habal FM, Hui G, Greenberg GR. Oral 5-aminosalicylic acid for inflammatory bowel disease in pregnancy: safety and clinical course. Gastroenterology 1993;105:1057–1060.
187. Marteau P, Tennenbaum R, Elefant E, Lemann M, Cosnes J. Foetal outcome in women with inflammatory bowel disease treated during pregnancy with oral mesalazine microgranules. Aliment Pharmacol Ther 1998;12:1101–1108.
188. Trallori G, d'Albasio G, Bardazzi G, Bonanomi AG, Amorosi A, Del Carlo P, Palli D, Galli M, Pacini F. 5-Aminosalicylic acid in pregnancy: clinical report. Ital J Gastroenterol 1994;26:75–78.
189. Diav-Citrin O, Park YH, Veerasuntharam G, Polachek H, Bologa M, Pastuszak A, Koren G. The safety of mesalamine in human pregnancy: a prospective controlled cohort study. Gastroenterology 1998;114:23–28.
190. Norgard B, Fonager K, Pedersen L, Jacobsen BA, Sorensen HT. Birth outcome in women exposed to 5-aminosalicylic acid during pregnancy: a Danish cohort study. Gut 2003;52:243–247.
191. Nelis GF. Diarrhoea due to 5-aminosalicylic acid in breast milk. Lancet 1989;1:383.
192. Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. Augmentin treatment during pregnancy and the prevalence of congenital abnormalities: a population-based case-control teratologic study. Eur J Obstet Gynecol Reprod Biol 2001;97:188–192.
193. Berkovitch M, Diav-Citrin O, Greenberg R, Cohen M, Bulkowstein M, Shechtman S, Bortnik O, Arnon J, Ornoy A. First-trimester exposure to amoxycillin/clavulanic acid: a prospective, controlled study. Br J Clin Pharmacol 2004;58:298–302.
194. Rodriguez-Pinilla E, Martinez-Frias ML. Corticosteroids during pregnancy and oral clefts: a case-control study. Teratology 1998;58:2–5.
195. Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. Am J Med Genet 1999;86: 242–244.
196. Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, Friesen MH, Jacobson S, Kasapinovic S, Chang D, Diav-Citrin O, Chitayat D, Nulman I, Einarson TR, Koren G. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology 2000;62:385–392.
197. Gur C, Diav-Citrin O, Shechtman S, Arnon J, Ornoy A. Pregnancy outcome after first trimester exposure to corticosteroids: a prospective controlled study. Reprod Toxicol 2004;18:93–101.
198. Armenti VT, Moritz MJ, Cardonick EH, Davison JM. Immunosuppression in pregnancy: choices for infant and maternal health. Drugs 2002;62:2361–2375.
199. Gluck PA, Gluck JC. A review of pregnancy outcomes after exposure to orally inhaled or intranasal budesonide. Curr Med Res Opin 2005;21:1075–1084.
200. Norjavaara E, de Verdier MG. Normal pregnancy outcomes in a population-based study including 2,968 pregnant women exposed to budesonide. J Allergy Clin Immunol 2003; 111:736–742.
201. Patlas N, Golomb G, Yaffe P, Pinto T, Breuer E, Ornoy A. Transplacental effects of bisphosphonates on fetal skeletal ossification and mineralization in rats. Teratology 1999;60:68–73.
202. Del Campo M, Kosaki K, Bennett FC, Jones KL. Developmental delay in fetal aminopterin/methotrexate syndrome. Teratology 1999;60:10–12.
203. French AE, Koren G. Effect of methotrexate on male fertility. Can Fam Physician 2003;49:577–578.
204. Polifka JE, Friedman JM. Teratogen update: azathioprine and 6-mercaptopurine. Teratology 2002;65:240–261.
205. Saarikoski S, Seppala M. Immunosuppression during pregnancy: transmission of azathioprine and its metabolites from the mother to the fetus. Am J Obstet Gynecol 1973;115:1100–1106.
206. Norgard B, Pedersen L, Fonager K, Rasmussen SN, Sorensen HT. Azathioprine, mercaptopurine and birth outcome: a population-based cohort study. Aliment Pharmacol Ther 2003; 17:827–834.
207. Alstead EM, Ritchie JK, Lennard-Jones JE, Farthing MJ, Clark ML. Safety of azathioprine in pregnancy in inflammatory bowel disease. Gastroenterology 1990;99:443–446.
208. Francella A, Dyan A, Bodian C, Rubin P, Chapman M, Present DH. The safety of 6-mercaptopurine for childbearing patients with inflammatory bowel disease: a retrospective cohort study. Gastroenterology 2003;124:9–17.
209. Khan ZH, Mayberry JF, Spiers N, Wicks AC. Retrospective case series analysis of patients with inflammatory bowel disease on azathioprine. A district general hospital experience. Digestion 2000;62:249–254.
210. Moskovitz DN, Bodian C, Chapman ML, Marion JF, Rubin PH, Scherl E, Present DH. The effect on the fetus of medications used to treat pregnant inflammatory bowel-disease patients. Am J Gastroenterol 2004;99:656–661.
211. Bertschinger P, Himmelmann A, Risti B, Follath F. Cyclosporine treatment of severe ulcerative colitis during pregnancy. Am J Gastroenterol 1995;90:330.
212. Anderson JB, Turner GM, Williamson RC. Fulminant ulcerative colitis in late pregnancy and the puerperium. J R Soc Med 1987;80:492–494.
213. Baumgart DC, Sturm A, Wiedenmann B, Dignass AU. Uneventful pregnancy and neonatal outcome with tacrolimus in refractory ulcerative colitis. Gut 2005;54:1822–1823.
214. Ehrenpreis ED, Kane SV, Cohen LB, Cohen RD, Hanauer SB. Thalidomide therapy for patients with refractory Crohn's disease: an open-label trial. Gastroenterology 1999;117:1271–1277.
215. Thalomid [package insert]. Summit, NJ: Celgene Corp, 2000.
216. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541–1549.
217. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462–2476.
218. Srinivasan R. Infliximab treatment and pregnancy outcome in active Crohn's disease. Am J Gastroenterol 2001;96:2274–2275.
219. James RL, Pearson LL. Successful treatment of pregnancy-triggered Crohn's disease complicated by severe recurrent life-threatening gastrointestinal bleeding (abstr). Am J Gastroenterol 2001;96:S295.
220. Bank L, Hunt B. Unexpected dramatic clinical response of psoriasis lesions and unexpected pregnancy in an infertile patient in

response to treatment with anti-tumor necrosis factor monoclonal antibody for Crohn's disease (abstr). Am J Gastroenterol 2002;97:S260.
221. Burt MJ, Frizelle FA, Barbezat GO. Pregnancy and exposure to infliximab (anti-tumor necrosis factor-alpha monoclonal antibody). J Gastroenterol Hepatol 2003;18:465–466.
222. Lichtenstein G, Cohen RD, Feagan BG, et al. Safety of infliximab in Crohn's disease: data from the 5000-patient TREAT Registry (abstr). Gastroenterology 2004;126:A54.
223. Katz JA, Antoni C, Keenan GF, Smith DE, Jacobs SJ, Lichtenstein GR. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. Am J Gastroenterol 2004;99:2385–2392.
224. Mahadevan U, Kane S, Sandborn WJ, Cohen RD, Hanson K, Terdiman JP, Binion DG. Intentional infliximab use during pregnancy for induction or maintenance of remission in Crohn's disease. Aliment Pharmacol Ther 2005;21:733–738.
225. Vasiliauskas EDM, Barry M, Dubinsky M, et al. High serum levels of infliximab detected in the newborn of a mother receiving infliximab during pregnancy (abstr). Gastroenterology 2005;128:P33.
226. Peltier M, James D, Ford J, et al. Infliximab levels in breast-milk of a nursing Crohn's patient (abstr). Am J Gastroenterol 2001; 96:P258.
227. Hanauer SB, Lukas M, MacIntosh D, et al. A randomized, double-blind, placebo controlled trial of the human anti-TNF alpha monoclonal antibody adalimumab for the induction of remission in patients with moderate to severely active Crohn's disease (abstr). Gastroenterology 2004;127:332.
228. Vesga L, Terdiman JP, Mahadevan U. Adalimumab use in pregnancy. Gut 2005;54:890.
229. Olsen SF, Sorensen JD, Secher NJ, Hedegaard M, Henriksen TB, Hansen HS, Grant A. Randomised controlled trial of effect of fish-oil supplementation on pregnancy duration. Lancet 1992; 339:1003–1007.
230. Rossi E, Costa M. Fish oil derivatives as a prophylaxis of recurrent miscarriage associated with antiphospholipid antibodies (APL): a pilot study. Lupus 1993;2:319–323.
231. Food and Drug Administration. Regulations. 1980;44:37434–37467.

Address requests for reprints to: Chair, Clinical Practice and Economics Committee, AGA Institute National Office, c/o Membership Department, 4930 Del Ray Avenue, Bethesda, Maryland 20814. Fax: (301) 654-5920.

The Clinical Practice and Economics Committee acknowledges the following individuals whose critiques of this review paper provided valuable guidance to the authors: Grace Elta, MD, Rosemarie Fisher, MD, Stephen B. Hanauer, MD, and Kim Isaacs, MD. The authors thank Marcia Cruz-Correa, MD (Cleveland Clinic, Cleveland, OH) for materials provided toward the creation of this report and Gerald Briggs, BPharm, for graciously agreeing to review this report.