AMERICAN GASTROENTEROLOGICAL ASSOCIATION INSTITUTE

American Gastroenterological Association Institute Medical Position Statement on the Use of Gastrointestinal Medications in Pregnancy

This document presents the official recommendations of the American Gastroenterological Association (AGA) Institute on "Use of Gastrointestinal Medications in Pregnancy." It was approved by the Clinical Practice and Economics Committee on February 22, 2006, and by the AGA Institute Governing Board on April 20, 2006.

Pharmacotherapy for the management of gastrointestinal disease has evolved dramatically in the past 10 years. Women with chronic illnesses who would have been unwilling or unable to conceive in the past are now healthy enough to consider pregnancy. In addition, many women are deferring childbearing until later in life, when polypharmacy and illness may be more common. This medical position statement provides recommendations to gastroenterologists on the use of medications during pregnancy based on the best available evidence, primarily from large retrospective databases and case series. Because the amount of high-quality controlled data in pregnancy is limited, absolute safety is not guaranteed for any medication. Instead, the risk of the underlying condition versus the safety of the medications used to treat the condition should be balanced against the overall health of the mother and the fetus in each individual case. The risks and benefits of treatment and the consequences of withholding treatment should be discussed with the patient and the obstetrician and carefully documented. This statement covers the treatment of common gastrointestinal and liver diseases, the management of common gastrointestinal symptoms, and the use of medications during endoscopy.

Recommendations

In general, deferring treatment until after pregnancy is preferred when possible. While this would be sensible with respect to the eradication of *Helicobacter pylori*, it would be detrimental in settings such as inflammatory bowel disease (IBD), where disease activity may lead to adverse pregnancy outcomes.

The majority of medications can be categorized as "low risk" or "should be avoided" and are listed by disease category in the following text and in Table 1. The following medications should never be used during pregnancy due to the clear risk of teratogenicity or adverse events: bismuth, castor oil, sodium bicarbonate, methotrexate, ribavirin, doxycycline, tetracycline, and thalidomide.

Endoscopy

If endoscopy with sedation is necessary during pregnancy, fetal monitoring may be prudent during the third trimester. When sedation is needed, meperidine appears to be low risk at doses commonly used for endoscopy and may provide adequate comfort. If a benzodiazepine is required, then the smallest dose of midazolam to achieve calmness as opposed to somnolence is recommended. Fentanyl may also be used in low doses. Propofol has not been studied during the first and second trimester and therefore should be avoided. For deeper sedation, as in endoscopic retrograde cholangiopancreatography, consultation with anesthesiology and obstetrics is recommended. Naloxone and flumazenil should be used only if prompt reversal of clinically significant maternal sedation is necessary. Glucagon and simethicone are low-risk drugs but in most instances not required for successful endoscopy. Preprocedure prophylaxis with ampicillin is low risk, but gentamicin should be used only for patients who demonstrate biliary sepsis. For colonic lavage, tap water enemas and polyethylene glycol solutions are low-risk treatments. Sodium phosphate should be avoided. Any therapeutic intervention should be with bipolar cautery that does not require placement of a grounding pad.

Nausea and Vomiting

Metoclopramide, prochlorperazine, promethazine, trimethobenzamide, and ondansetron are considered low-risk drugs based on studies in pregnant women and can be used for nausea and vomiting and for hyperemesis gravidarum. Granisetron and dolasetron have not been studied in human pregnancies.

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Gastroesophageal Reflux Disease and Peptic Ulcer Disease

Heartburn occurs in a significant number of pregnancies, and primary interventions such as dietary modifications and lifestyle changes are less likely to be successful due to the pressure the gravid uterus imposes. Over-the-counter calcium-based antacids are low risk and should be the first-line therapy, although excessive intake of calcium carbonate can lead to the milk-alkali syndrome. Aluminum- and magnesium-containing antacids are also low-risk treatments. Magnesium trisilicates and sodium bicarbonate should not be used. Safety data for sucralfate, histamine blockers, and the majority of the proton pump inhibitors come from prospective studies, and at therapeutic doses these drugs do not appear to increase the risk of adverse events even when used in the first trimester. Famotidine and nizatidine have limited human pregnancy safety data, making cimetidine and ranitidine preferred agents in this setting. Omeprazole has demonstrated embryonic and fetal toxicity, although the risk is low and it remains the agent of choice.

Liver Diseases

Viral hepatitis. Hepatitis A and B vaccines are low risk to use in pregnancy if needed. Lamivudine for hepatitis B has not been found to increase the rate of congenital abnormalities. Minimal data exist on adefovir and entecavir. The treatment of active hepatitis C with interferon and ribavirin during pregnancy is contraindicated and should not be undertaken.

Wilson's disease. Use of penicillamine during pregnancy is controversial. For patients who require continued penicillamine therapy, dosing needs to be reduced in the third trimester to 250 mg/day to prevent impaired wound healing. An alternative therapy, trientine, appears to be low risk.

Primary biliary cirrhosis/primary sclerosing cholangitis. Ursodeoxycholic acid has been used with success in patients with cholestasis of pregnancy and has not been associated with any increase in adverse events. Its use in pregnant patients with primary liver disease should continue if a therapeutic benefit has been confirmed.

Portal hypertension. The use of propranolol is discouraged after the first trimester because of impaired fetal growth associated with this class of medicines. Nadolol should also be avoided during pregnancy.

Liver transplantation. The National Transplant Registry has prospectively collected data on immunosuppressive agents during pregnancy. Cyclosporine and tacrolimus are considered low-risk drugs and have not been associated with an increased rate of congenital abnormalities at doses required for graft survival. The data for sirolimus and mycophenolate are limited, and their use is not encouraged during pregnancy.

Irritable Bowel Syndrome

Dietary modification, such as increased fiber and water intake for constipation and reduced fat and dairy consumption for diarrhea, should be the first-line therapy for irritable bowel syndrome.

Constipation. Osmotic laxatives are considered low-risk therapy in pregnancy. However, long-term use of saline osmotic laxatives such as magnesium citrate and sodium phosphate can be harmful and should be avoided. Polyethylene glycol is considered low-risk treatment and is the preferred treatment for chronic constipation in pregnancy. Docusate is a low-risk treatment, as are senna and bisacodyl for short-term use. Castor oil and mineral oil are harmful and should not be used. Tegaserod is a low-risk drug, although human data are limited.

Diarrhea. Loperamide and diphenoxylate with atropine are low-risk drugs but should be avoided due to a potential risk of fetotoxicity. Bismuth-containing compounds (including Kaopectate) should not be used in pregnancy due to fetotoxicity. Alosetron should be avoided during pregnancy, although there are no reports of fetotoxicity.

Abdominal pain. Tricyclic antidepressants and selective serotonin reuptake inhibitors are associated with worse fetal outcomes; however, only paroxetine is associated with increased congenital malformations. Given the paucity of efficacy data in irritable bowel syndrome, they should not be used during pregnancy for this indication. Dicyclomine and hyoscyamine should be avoided as well.

Infectious Diarrhea

Most episodes of infectious diarrhea are self-limited, and supportive care should be provided. If antibiotics are necessary, the following recommendations apply. Albendazole is teratogenic in animals, but human studies suggest that its use to eradicate helminths is beneficial to pregnancy outcomes. Ampicillin and vancomycin are considered low-risk drugs. Azithromycin may cause gastrointestinal distress during pregnancy but is not associated with congenital defects. The limited human data on furazolidone and tinidazole during pregnancy do not suggest an increased risk of birth defects. Metronidazole is a low-risk drug when used in the short-term, although there may be a slightly increased risk of cleft lip and cleft palate. Quinolones are associated with arthropathies in children and cartilage defects in animal studies. Although actual fetal risk is believed to be minimal, the drug should be avoided if possible. Rifaxi-

Table 1. Gastrointestinal Medications During Pregnancy and Lactation

Drug	Food and Drug Administration pregnancy category	Recommendations for pregnancy	Recommendations for breast-feeding
Adalimumab	B	Limited human data: low risk	No human data: probably compatible
Adefovir	C	Minimal data: no teratogenicity	No human data: probably compatible
Alosetron	B	Avoid: restricted access	No human data: potential toxicity
Aluminum-based antacids	None	Most low risk: minimal absorption	Low risk
Amitriptyline	C	Avoid: no malformations, but worse outcomes	Limited human data: potential toxicity
Amoxicillin/clavulanic acid	B	Low risk	Probably compatible
Ampicillin	B	Low risk	Compatible
Antithymocyte globulin	C	Human specific agent	Safety unknown
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
Bisacodyl	C	Low risk in short-term use	Safety unknown
Bismuth subsalicylate	C	Not safe: teratogenicity	No human data: potential toxicity
Calcium-based antacids	None	Most low risk: minimal absorption	Probably compatible
Cholestyramine	C	Low risk, but can lead to infant coagulopathy	Compatible
Cimetidine	B	Controlled data: low risk	Compatible
Ciprofloxacin (all quinolones)	C	Potential toxicity to cartilage: avoid	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
Desipramine	C	Avoid: no malformations, but worse outcomes	Limited human data: potential toxicity
Diazepam	D	Midazolam preferred benzodiazepine	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
Doxycycline	D	Contraindicated: teratogenic	Compatible
Epinephrine	C	Avoid unless for hemostasis	No human data: potential toxicity
Esomeprazole	B	Limited data: low risk	No human data: potential toxicity
Entecavir	C	No human data	No human data: potential toxicity
Famotidine	B	Paucity of safety data	Limited human data: probably compatible
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 >48 hours	Compatible
Hyoscyamine	C	No available data	No human data: probably compatible
Imipramine	D	Avoid: no malformations, but worse outcomes	Limited human data: potential toxicity
Infliximab	B	Low risk	No human data: probably compatible
Interferon	C	Not recommended: treatment deferred until after delivery	Limited human data: probably compatible
Kaopectate	C	Unsafe because now contains bismuth	No human data: probably compatible
Lactulose	B	No human studies	No human data: probably compatible
Lamivudine	C	Low risk	Contraindicated
Lansoprazole	B	Limited data: low risk	No human data: potential toxicity
Loperamide	B	Low risk: possible increased cardiovascular defects	Limited human data: probably compatible
Magnesium-based antacids	None	Most low risk: minimal absorption	Probably compatible
Magnesium citrate	B	Avoid long-term use: hypermagnesemia, hyperphosphatemia, dehydration	Compatible
Meperidine	B	Use in low doses	Compatible
Mesalamine	B	Low risk	Limited human data: potential diarrhea
Methotrexate	X	Contraindicated: teratogenic	Contraindicated
Metoclopramide	B	Low risk	Limited human data: potential toxicity
Metronidazole	B	Low risk: avoid in first trimester	Limited human data: potential toxicity
Midazolam	D	Use in low doses	Limited human data: potential toxicity
Mineral oil	C	Avoid: neonatal coagulopathy and hemorrhage	Possibly unsafe
Mycophenolate mofetil	C	Not recommended	Contraindicated

(continued on following page)

Table 1 (continued). Gastrointestinal Medications During Pregnancy and Lactation

Drug	Food and Drug Administration pregnancy category	Recommendations for pregnancy	Recommendations for breast-feeding
Nadolol	C: first trimester D: second/third trimester	Prolonged half-life, use alternative: risk of intrauterine growth retardation in second/third trimester	Limited human data: potential toxicity
Naloxone	B	Only for severe narcotic overdoses	No human data: probably compatible
Nizatidine	B	Limited human data: low risk in animals	Limited human data: probably compatible
Nortriptyline	D	Avoid: no malformations, but worse outcomes	Limited human data: potential toxicity
OKT3 (Muromonab-CD3)	C	No pregnancy data but probably low risk	Contraindicated
Olsalazine	C	Low risk	Limited human data: potential diarrhea
Omeprazole	C	Embryonic and fetal toxicity, but large data sets suggest low risk	Limited human data: potential toxicity
Ondansetron	B	Low risk	No human data: probably compatible
Pantoprazole	B	Limited data: low risk	No human data: potential toxicity
Paroxetine	D	Avoid: twice as many birth defects as other antidepressants	Potential toxicity
Polyethylene glycol	C	First-choice laxative in pregnancy	Low risk
Prochlorperazine	C	Low risk	No human data: potential toxicity
Promethazine	C	No teratogenicity: large database study	No human data: probably compatible
Propofol	B	Avoid in first trimester	Limited human data: probably compatible
Propranolol	C: first trimester D: second/third trimester	Fetal bradycardia, intrauterine growth retardation in second/third trimesters	Limited human data: potential toxicity
Rabeprazole	B	Limited data: low risk	No human data: potential toxicity
Ranitidine	B	Low risk	Limited human data: probably compatible
Ribavirin	X	Contraindicated: severe fetal neurotoxicity	No human data: potential toxicity
Rifaximin	C	Animal teratogen: no human data	No human data: probably compatible
Senna	C	Low risk in short-term use	Compatible
Selective serotonin reuptake inhibitors (except paroxetine)	C	Avoid: no malformations, but increased adverse events in fetus	Limited human data: potential toxicity
Simethicone	C	Can be avoided but low risk	No human data: probably compatible
Sirolimus	C	Not recommended	No human data: potential toxicity
Sodium bicarbonate	None	Not safe: alkalosis	Probably compatible
Sodium phosphate		Avoid long-term: hypermagnesemia, hyperphosphatemia, dehydration	Safety unknown
Sucralfate	B	Low risk	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
Tegaserod	B	Probably low risk: human data negative for malformations	Safety unknown
Tetracycline	D	Teratogenic	Compatible
Trimethoprim-sulfamethoxazole	C	Teratogenic	Compatible
Ursodiol	B	Low risk: used in intrahepatic cholestasis of pregnancy	No human data: probably compatible
Vancomycin	C	Low risk	Limited human data: probably compatible

min has been associated with birth defects in animals. Doxycycline and tetracycline are contraindicated during pregnancy due to teratogenicity. Trimethoprim-sulfamethoxazole has clearly demonstrated teratogenicity and should not be used during pregnancy.

IBD

Optimally, women with IBD should be in remission before considering conception because this improves their chances of a successful pregnancy. To achieve and

maintain remission, patients usually need to continue their medications. 5-Aminosalicylates are considered low-risk drugs in pregnancy. Sulfasalazine, which has antifolate effects, should be given with 2 mg/day of folic acid. Antibiotics are of questionable efficacy in IBD, and treatment duration is often several weeks. Metronidazole may be associated with cleft lip and cleft palate, and ciprofloxacin may be associated with skeletal abnormalities. These agents should not be used unless truly indicated in IBD and, if so, only for short intervals. For the treatment of pouchitis, an alternative antibiotic such as amoxicillin/clavulanic acid can be considered. Corticosteroids are used for the management of disease flares and therefore may be unavoidable. Although there may be an increased risk of oral clefts and premature rupture of the membranes, the overall risk to the fetus is believed to be minimal. Immunomodulators are the most controversial agents used in the pregnant patient with IBD. Methotrexate and thalidomide are clearly teratogenic and should not be used for at least 3 months before conception. Azathioprine and 6-mercaptopurine are embryotoxic in animals, but human data in both IBD and transplantation do not suggest an increased risk of teratogenicity. These agents are low-risk drugs and can be continued to maintain remission during pregnancy. Cyclosporine and tacrolimus are low-risk drugs, but use should be avoided unless clearly indicated. Biologic therapy with infliximab and adalimumab is low risk in pregnancy. Given the importance of maintaining remission, the benefits of continuing these agents seem to outweigh any known risk to the infant or mother.

Conclusion

Treatment of the pregnant patient presents unique challenges. Current Food and Drug Administration classifications do not necessarily reflect clinical experience or recent literature. Using the lowest-risk drug possible, with attention to the appropriate level of efficacy for the patient's condition, is prudent. Other factors include the stage of pregnancy and possible dosing adjustments. Every treatment decision should be fully discussed with the patient and obstetrician before initiation.

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