Complete Summary

GUIDELINE TITLE

American Gastroenterological Association Institute medical position statement on the use of gastrointestinal medications in pregnancy.

BIBLIOGRAPHIC SOURCE(S)

Mahadevan U, Kane S. American Gastroenterological Association Institute medical position statement on the use of gastrointestinal medications in pregnancy. Gastroenterology 2006 Jul;131(1):278-82. PubMed

GUIDELINE STATUS

This is the current release of the guideline.

According to the guideline developer, the Clinical Practice Committee meets three times a year to review all American Gastroenterological Association Institute (AGAI) guidelines. This review includes new literature searches of electronic databases followed by expert committee review of new evidence that has emerged since the original publication date.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

Drug Withdrawal

- July 27, 2007, Zelnorm (Tegaserod) (Update): U.S. Food and Drug Administration (FDA) announced that it is permitting the restricted use of Zelnorm under a treatment investigational new drug (IND) protocol to treat irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in women younger than 55 who meet specific guidelines. See the U.S. Food and Drug Administration (FDA) Web site for more information.
- March 30, 2007, Zelnorm (tegaserod): Voluntary market withdrawal due to serious cardiovascular adverse events, including angina, heart attacks, and stroke. See the U.S. Food and Drug Administration (FDA) Web site for more information.

Additional Notices

- July 08, 2008, Fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, levofloxacin, moxifloxacin, gemifloxacin): A BOXED WARNING and Medication Guide are to be added to the prescribing information to strengthen existing warnings about the increased risk of developing tendinitis and tendon rupture in patients taking fluoroquinolones for systemic use.
- June 30, 2008, CellCept (mycophenolate mofetil) and Myfortic (mycophenolate acid): Novartis and Roche have agreed to include additional labeling revisions to the WARNINGS and ADVERSE REACTIONS sections of the Myfortic and CellCept prescribing information, based on post-marketing data regarding cases of Progressive Multifocal Leukoencephalopathy (PML) in patients treated with these drugs.
- October 29, 2007, CellCept (mycophenolate mofetil): Roche has agreed to include additional labeling revisions to the BOXED WARNING, WARNINGS/Pregnancy and Pregnancy Exposure Prevention, PRECAUTIONS/Information for Patients, and ADVERSE REACTIONS/Postmarketing Experience sections.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **
SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
CONTRAINDICATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Pregnancy and:

- Gastrointestinal diseases and symptoms, including nausea and vomiting, infectious diarrhea, inflammatory bowel disease, gastroesophageal reflux disease and peptic ulcer disease, irritable bowel syndrome
- Liver diseases, including viral hepatitis, Wilson's disease, primary biliary cirrhosis/primary sclerosing cholangitis, portal hypertension, liver transplantation
- Conditions requiring endoscopy

Note: Recommendations regarding the use of medications during breastfeeding/lactation are included in Table 1 of the original guideline document but are not the focus of the guideline.

GUIDELINE CATEGORY

Evaluation
Management
Treatment

CLINICAL SPECIALTY

Family Practice
Gastroenterology
Internal Medicine
Obstetrics and Gynecology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide recommendations to gastroenterologists on the use of medications during pregnancy

TARGET POPULATION

Pregnant women with gastrointestinal or liver diseases/conditions or conditions requiring endoscopy

INTERVENTIONS AND PRACTICES CONSIDERED

1. Deferral of treatment until after pregnancy, when possible
2. Consideration of the risks versus benefits of treatment (including discussion with the patient and obstetrician) for the following conditions and medications
    - *Endoscopy*
        - Meperidine, midazolam, fentanyl (sedation)
        - Naloxone and flumazenil (sedation reversal)
        - Consultation with anesthesiology and obstetrics as appropriate
        - Ampicillin, gentamicin (preprocedure prophylaxis)
        - Tap water enemas, polyethylene glycol solutions (colonic lavage)
    - *Nausea and vomiting*
        - Metoclopramide
        - Prochlorperazine
        - Promethazine
        - Trimethobenzamide
        - Ondansetron
    - *Gastroesophageal reflux disease and peptic ulcer disease*
        - Over-the-counter calcium-based antacids
        - Aluminum- and magnesium-containing antacids
        - Sucralfate, histamine blockers, proton pump inhibitors, including cimetidine, ranitidine, omeprazole
    - *Viral hepatitis*
        - Hepatitis A and B vaccines
        - Lamivudine (for hepatitis B)

- *Wilson's disease*
  - Penicillamine
  - Trientine
- *Primary biliary cirrhosis/primary sclerosing cholangitis*
  - Ursodeoxycholic acid
- *Portal hypertension*
  - Propranolol (for the first trimester)
- *Liver transplantation*
  - Immunosuppressive agents (cyclosporine and tacrolimus)
- *Irritable bowel syndrome*
  - Dietary modification (increased fiber and water intake for constipation and reduced fat and dairy consumption for diarrhea)
- *Constipation*
  - Osmotic laxatives, including polyethylene glycol
  - Docusate, senna, bisacodyl (short-term use)
  - Tegaserod*

    ***Note from the National Guideline Clearinghouse (NGC)**: On March 30, 2007, Zelnorm (tegaserod) was withdrawn from the market due to serious cardiovascular adverse events, including angina, heart attacks, and stroke. See the U.S. Food and Drug Administration (FDA) Web site for more information.

- *Infectious diarrhea*
  - Antibiotics, including albendazole, ampicillin, vancomycin, azithromycin, furazolidone, tinidazole, and metronidazole (short-term)
- *Inflammatory bowel disease*
  - 5-Aminosalicylates
  - Sulfasalazine (with folic acid)
  - Antibiotics, including metronidazole and ciprofloxacin (for short intervals only), amoxicillin/clavulanic acid (for pouchitis)
  - Corticosteroids
  - Immunomodulators (azathioprine, 6-mercaptopurine, cyclosporine and tacrolimus, infliximab, adalimumab)

MAJOR OUTCOMES CONSIDERED

- Embryonic and fetal toxicity
- Maternal symptom control
- Adverse effects of pharmacological agents

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

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 U.S. 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 in the original guideline document and are noted for each drug discussed. Recommendations on breast-feeding come from literature review, the textbook *Drugs in Pregnancy and Lactation* (Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation. 7th ed. Philadelphia, PA: Lippincott, Williams & Wilkins, 2005), and the American Academy of Pediatrics (AAP) guidelines, updated on the AAP Web site on June 15, 2005.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The Medical Position Statements (MPS) developed under the aegis of the American Gastroenterological Association (AGA) Institute and its Clinical Practice and Economics Committee (CPEC) were approved by the AGA Institute Governing Board.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse: Recommendations regarding the use of medications during breastfeeding/lactation are included in Table 1 of the original guideline document but are not the focus of the guideline.

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 in the original guideline document. 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.

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.

> ***Note from the National Guideline Clearinghouse (NGC)**: On March 30, 2007, Zelnorm (tegaserod) was withdrawn from the market due to serious cardiovascular adverse events, including angina, heart attacks, and stroke. See the U.S. Food and Drug Administration (FDA) Web site for more information.

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. Rifaximin 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.

Inflammatory Bowel Disease (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 U.S. 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.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of gastrointestinal medications during pregnancy to maximize the health benefit and minimize the health risks to fetus and mother

POTENTIAL HARMS

See the original guideline document and the technical review companion (see "Availability of Companion Documents" field) for information about potential adverse effects of gastrointestinal medications during pregnancy.

CONTRAINDICATIONS

CONTRAINDICATIONS

See the original guideline document and the technical review companion (see "Availability of Companion Documents" field) for information about gastrointestinal medications that are contraindicated during pregnancy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The Medical Position Statements (MPS) developed under the aegis of the American Gastroenterological Association (AGA) Institute and its Clinical Practice and Economics Committee (CPEC) were approved by the AGA Institute Governing Board. The data used to formulate these recommendations are derived from the data available at the time of their creation and may be supplemented and updated as new information is assimilated. These recommendations are intended for adult

patients, with the intent of suggesting preferred approaches to specific medical issues or problems. They are based upon the interpretation and assimilation of scientifically valid research, derived from a comprehensive review of published literature. Ideally, the intent is to provide evidence based upon prospective, randomized placebo-controlled trials; however, when this is not possible the use of experts' consensus may occur. The recommendations are intended to apply to healthcare providers of all specialties. It is important to stress that these recommendations should not be construed as a standard of care. The AGA Institute stresses that the final decision regarding the care of the patient should be made by the physician with a focus on all aspects of the patient's current medical situation.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Mahadevan U, Kane S. American Gastroenterological Association Institute medical position statement on the use of gastrointestinal medications in pregnancy. Gastroenterology 2006 Jul;131(1):278-82. PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Jul

GUIDELINE DEVELOPER(S)

American Gastroenterological Association Institute - Medical Specialty Society

SOURCE(S) OF FUNDING

American Gastroenterological Association Institute

GUIDELINE COMMITTEE

American Gastroenterological Association Institute Clinical Practice Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

According to the guideline developer, the Clinical Practice Committee meets three times a year to review all American Gastroenterological Association Institute (AGAI) guidelines. This review includes new literature searches of electronic databases followed by expert committee review of new evidence that has emerged since the original publication date.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Gastroenterological Association Institute (AGAI) *Gastroenterology* journal Web site.

Print copies: Available from the American Gastroenterological Association Institute, 4930 Del Ray Avenue, Bethesda, MD 20814.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- American Gastroenterological Association Institute technical review on the use of gastrointestinal medications in pregnancy. Gastroenterology 2006 July;131(1);238-311.

Electronic copies: Available from the American Gastroenterological Association Institute (AGAI) *Gastroenterology* journal Web site.

Print copies: Available from American Gastroenterological Association Institute, 4930 Del Ray Avenue, Bethesda, MD 20814.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on September 6, 2006. The information was verified by the guideline developer on September 21, 2006. This summary was updated by ECRI Institute on April 20, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Tigan (trimethobenzamide hydrochloride). This summary was updated by ECRI Institute on August 7, 2007 following the U.S. Food and Drug Administration (FDA) updated advisory on Zelnorm (tegaserod maleate). This summary was updated by ECRI Institute on November 6, 2007, following the U.S. Food and Drug Administration advisory on CellCept (mycophenolate mofetil). This summary was updated by ECRI Institute on July 8, 2008, following the updated U.S. Food and Drug Administration (FDA) advisory on CellCept (mycophenolate mofetil) and Myfortic (mycophenolate acid). This summary was updated by ECRI Institute on July 28, 2008 following the U.S. Food and Drug Administration advisory on fluoroquinolone antimicrobial drugs.

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