Drugs, Pregnancy, And Lactation

GI Agents: Part II

The second part of this three-part series examines the safety of drugs used to treat several gastrointestinal diseases that cause significant morbidity in pregnant women.

▶ ***Helicobacter pylori* infection:** Several studies have linked this infection to severe nausea/vomiting of pregnancy. Eradication regimens involve dual, triple, or quadruple therapy, typically for 2 weeks, combining one or two anti-infectives and an antisecretory agent. Bismuth and ranitidine bismuth citrate are sometimes added to the regimen.

BY GERALD G. BRIGGS, B.PHARM.

If clinically acceptable, the best course is to delay therapy until after the first trimester. Of the four anti-infectives used (amoxicillin, clarithromycin, metronidazole, and tetracycline), only tetracycline clearly causes developmental toxicity, but the carcinogenic potential of metronidazole has not been tested adequately.

Two proton pump inhibitors, lansoprazole (Prevacid) and omeprazole (Prilosec, Zegerid), are the antisecretory agents of choice for *H. pylori* eradication as neither appears to pose significant risk in pregnancy. Although ranitidine (Zantac) is compatible with pregnancy, both the salt form ranitidine bismuth citrate (Tritec) and bismuth alone are best avoided because the limited human data prevent an accurate assessment of bismuth's risk to the embryo or fetus. Amoxicillin, clarithromycin, and tetracycline are compatible with breast-feeding. All of the other agents used for *H. pylori* infection are best avoided in lactation.

▶ **Cholelithiasis:** Only one gallstone-solubilizing agent, ursodiol (Actigall, Urso), is available in the United States. Reports of exposure to this agent early in pregnancy are limited, but there are more data on the second half of pregnancy, which indicate that the drug does not appear to represent a risk in pregnancy or lactation.

▶ **Digestive enzymes:** Two digestive pancreatic enzymes—pancreatin and pancrelipase—are used for various conditions that result in deficient pancreatic secretions, such as cystic fibrosis and chronic pancreatitis. Only fragments of pancreatin and pancrelipase are absorbed systemically. Human data are limited, but animal data suggest these enzymes are low risk in pregnancy and lactation. Of note, the enteric coating on many of these products is diethyl phthalate, and high doses of some phthalates may cause developmental toxicity, but the embryo or fetus is exposed to very small quantities.

▶ **Ulcer prophylaxis:** Sucralfate (Carafate) inhibits pepsin activity and protects against ulceration. Only very small amounts of the drug are absorbed systemically, and it is compatible in both pregnancy and lactation. The prostaglandin misoprostol (Cytotec) is also indicated for ulcer prophylaxis, but this use is contraindicated in pregnancy (see GI Agents: Part I, Internal Medicine News, Feb. 15, 2006, p. 47).

▶ **Flatulence:** Two antiflatulents available over the counter are the silicone product simethicone (multiple trade names) and activated charcoal. They also are combined in a single product (Flatulex). Because neither agent is absorbable, they present no risk to the embryo, fetus, or nursing infant.

▶ **Obesity:** There is no human pregnancy experience with the lipase inhibitor, orlistat (Xenical), which inhibits the absorption of dietary fats. The animal reproduction data and minimal systemic bioavailability suggest that the drug represents a low risk in pregnancy and lactation.

▶ **Inflammatory bowel disease:** Mesalamine (5-aminosalicylic acid, 5-ASA) (Asacol, Canasa, Pentasa, Rowasa) is compatible with pregnancy. Reports have described several hundred pregnant women who had taken the drug without apparent harm to embryo or fetus. Two other agents in this class, balsalazide (Colazal) and olsalazine (Dipentum), are broken down in the colon to 5-ASA. Both agents appear to be compatible with pregnancy.

A third drug, sulfasalazine (Azulfidine), is metabolized to 5-ASA plus sulfapyridine. Sulfapyridine readily crosses the placenta to the fetus. When sulfapyridine is used close to delivery, neonatal jaundice and/or kernicterus secondary to displacement of bilirubin from albumin is a theoretical concern but has not been reported. Although human experience is limited, sulfasalazine appears to be compatible with pregnancy.

All of the inflammatory bowel disease agents should be used cautiously during lactation. Multiple episodes of diarrhea were reported in one nursing infant that appeared to be related to the mesalamine rectal suppositories used by the mother. In another case, persistent bloody diarrhea was attributed to the mother's use of sulfasalazine. Because of these cases, close observation of the nursing infant is required if the mother is taking any of these agents.

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Data Back Letrozole's Safety For Ovulation Induction

BY KATE JOHNSON
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Letrozole safely and effectively induces ovulation, according to the findings of a retrospective study of data from five Canadian fertility centers.

The findings contradict a report presented at last year's conjoint annual meeting of the American Society for Reproductive Medicine and the Canadian Fertility and Andrology Society suggesting that the aromatase inhibitor could cause serious fetal anomalies when used off-label for ovulation induction.

Novartis, which markets the drug as Femara for the treatment of breast cancer, issued global warnings to health care professionals about the potential for embryo and fetus toxicity.

"The concern that letrozole use for ovulation induction could be teratogenic is unfounded based on our data," wrote Dr. Togas Tulandi and Dr. Robert F. Casper, professors of obstetrics and gynecology at McGill University in Montreal and the University of Toronto, respectively. Both physicians pioneered the use of the drug for ovulation induction.

The Canadian team examined the rates of congenital malformations among 911 newborns of women who conceived using either clomiphene citrate (n = 397) or letrozole (n = 514) and compared them with known malformation rates in the general population (Fertil. Steril. 2006;doi:10.1016/j.fertnstert.2006.03.014).

There were no significant differences among the malformation rates in the letrozole group (2.4%), the clomiphene citrate group (4.8%), and the general population (2%-3%). Congenital cardiac anomalies appeared to be less common in the letrozole-treated group (0.2%) than in the clomiphene group (1.8%).

Dr. Marinko M. Biljan of the Montreal Fertility Center previously found a significantly higher rate of major fetal anomalies among 150 babies conceived with letrozole (4.7%), than among babies of 36,000 control patients (1.8%) (ASRM 2005 abstract #O-231).

Dr. Tulandi and his colleagues wrote, "We believe there were several methodologic problems with the ASRM abstract as presented that led to an erroneous conclusion."

It was "an apples-and-oranges comparison, because there are always fewer birth defects in children conceived spontaneously," he said. Also, there is no biologic plausibility for the drug causing birth defects, coauthor Dr. Casper said in an interview. "With the short half-life of letrozole, it should be completely cleared before implantation."

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DR. TULANDI

In response, Dr. Biljan reiterated his opinion that letrozole is teratogenic for ovulation induction. "I personally received numerous messages from Femara-treated individuals expressing their personal accounts of similar malformations," he said in an interview.

The Novartis warning has been endorsed by Health Canada, but the U.S. Food and Drug Administration has not yet followed suit. Yet even with the new data, few fertility doctors will feel comfortable using the drug, Dr. Tulandi said. "We still can't use it. Physicians use a lot of off-label drugs. But when someone specifically advises you against it, it becomes a legal issue."

Dr. Tulandi remains hopeful that physicians might successfully appeal to Novartis. "I hope the company reads our paper and reconsiders their stand on this," he said in an interview.

Novartis spokesperson Kim Fox said that the company stands by its warning. "Femara is classified as Pregnancy Category D and is not indicated for the induction of ovulation," according to a statement posted on the company's Web site for health care professionals (www.oncologymedicalservices.com).

Dr. Casper has a licensing agreement with Ares-Serono for the use of aromatase inhibitors for ovulation induction; the company markets clomiphene. Dr. Tulandi reported no financial conflicts of interest. ■

CDC Advises Routine Preconception Counseling, With Insurance Coverage

Primary care physicians should offer risk assessment and counseling to all women of childbearing age to improve pregnancy outcomes, according to new recommendations from the Centers for Disease Control and Prevention.

The 10 recommendations for improvement of preconception health care were published in the April 21 issue of the Morbidity and Mortality Weekly Report Recommendations and Reports. This type of routine preconception counseling should include discussion of child spacing, family planning, and prevention of unintended pregnancy. In addition, physicians should advise women about healthy diet, folic acid supplementation, immunization, and healthy weight.

But not all of the burden for improving preconception care is placed on physicians and other health care providers. The CDC recommendations also call on insurers to change their payment policies to reimburse for one prepregnancy visit per pregnancy.

—Mary Ellen Schneider