Drugs, Pregnancy, And Lactation

GI Agents: Part I

Gastrointestinal complaints are common in pregnancy and during the postpartum period. They include conditions such as nausea and vomiting, constipation, diarrhea, heartburn, and erosive gastroesophageal reflux disease.

► **Antiemetics.** Nausea and vomiting is the most frequent GI complaint in pregnancy. Many oral and parenteral antiemetics are available to treat nausea and vomiting of pregnancy (NVP). All are considered low risk for developmental toxicity (growth retardation, structural defects, functional and behavioral deficits, or death).

BY GERALD G. BRIGGS, B. PHARM.

The most commonly prescribed over-the-counter agent for this condition is doxylamine (Unisom), usually combined with vitamin B_6 (pyridoxine). These two drugs were the components of Bendectin, which was removed from the market by its manufacturer in 1983, but classified by the Food and Drug Administration as safe and effective. Other commonly used oral medications for NVP include prochlorperazine (Compazine), metoclopramide (Reglan), trimethobenzamide (Tigan), promethazine (Phenergan), and ondansetron (Zofran).

The most severe form of nausea, hyperemesis gravidarum, occurs in less than 1% of pregnancies and requires hospitalization and intravenous antiemetics, such as droperidol (Inapsine), prochlorperazine, and ondansetron.

► **Laxatives.** Seven types of products act as laxatives: saline (phosphates and magnesium hydroxide and its salts); stimulants/irritants (cascara, bisacodyl, casanthranol, senna, and castor oil); bulking agents (methylcellulose, polycarbophil, and psyllium); emollient (mineral oil); fecal softeners (docusate); hyperosmotics (glycerin, lactulose); and tegaserod (Zelnorm).

With the exception of lactulose and tegaserod, all of these products are available over the counter, and most do not cause direct embryo/fetal toxicity. However, castor oil, which is converted to ricinoleic acid in the gut, is an irritant that may induce premature labor. Improper use of saline laxatives can cause electrolyte imbalances, and mineral oil will prevent absorption of fat-soluble vitamins.

Of the laxatives, bulking agents and fecal softeners are the best choices in pregnancy. Cascara sagrada and senna are excreted into breast milk and are compatible with breast-feeding, although they may cause diarrhea in a nursing infant.

Tesgaserod, a serotonin type-4 receptor agonist, is approved for women with irritable bowel syndrome whose primary bowel symptom is constipation (and for idiopathic constipation in those under age 65). Limited animal and human data suggest a low risk for embryo/fetal toxicity, but the drug is best avoided during lactation because of the absence of any human data.

► **Antidiarrheal agents.** The antidiarrheal agents diphenoxylate and its active metabolite, difenoxin, are meperidine-related narcotics. Available as Lomotil and Motofen when combined with atropine to prevent abuse, they present low risk in pregnancy. Although there is potential for toxicity in a nursing infant, infrequent use is probably compatible with nursing. Loperamide (Imodium) is low risk in pregnancy and lactation. Alosetron (Lotronex), a serotonin antagonist, has both antiemetic and antidiarrheal properties. It is indicated only in women with IBS whose primary symptom is severe, chronic diarrhea. Based only on animal data, it is considered low risk in pregnancy. Because severe GI toxicity (constipation, ischemic colitis) has been reported in adults, it should be avoided during lactation. Bismuth subsalicylate, such as Pepto-Bismol and Kaopectate, should not be used in pregnancy or lactation.

► **Antacids.** Antacids available to treat heartburn include calcium carbonate, magnesium hydroxide and oxide, and aluminum hydroxide and carbonate. Systemic absorption of antacids is negligible, so recommended doses are safe in pregnancy and lactation. Sodium bicarbonate should be avoided because it is absorbed systemically and could cause alkalosis.

► **Antisecretory agents.** These agents, used for heartburn and GERD, include the histamine H_2 antagonists cimetidine (Tagamet), famotidine (Pepcid), nizatidine (Axid), and ranitidine (Zantac) and the proton pump inhibitors esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix), and rabeprazole (Aciphex).

Low strengths of the histamine antagonists are available over the counter, but omeprazole is the only PPI available without a prescription. All of these antisecretory agents are low risk in pregnancy. The histamine antagonists are compatible with breast-feeding. In contrast, the PPIs have carcinogenic and mutagenic properties, so prolonged use while breast-feeding should be avoided.

Misoprostol (Cytotec), another antisecretory agent and a prostaglandin E_1 (PGE_1) analogue, is a proven human teratogen. It should only be used in pregnancy for its off-label indications: uterine stimulation and cervical ripening. Although its use during lactation has not been reported, naturally occurring PGE_1 is excreted into milk and may protect the GI tract in nursing infants.

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Birth Defects Decline as Valproate Is Used Less

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

WASHINGTON — Decreased use of valproate to manage epilepsy during pregnancy in Australia has produced a corresponding drop in fetal malformations associated with the drug, Dr. Frank Vajda said at the joint annual meeting of the American Epilepsy Society and the American Clinical Neurophysiology Society.

Dr. Vajda, a physician at the Victorian Epilepsy Centre in Victoria, Australia, presented the most recent data from the Australian Pregnancy Registry for Women on Antiepileptic Medication. The registry, established in 1999, has enrolled 810 women—77% of all Australian women who had taken antiepilepsy drugs (AEDs) for any reason. The 64-month data contained outcome information on 715 births.

Of the women in the registry, most who were taking AEDs (692) were taking the drugs for epilepsy. Other indications were bipolar disorder (11), pain (4), sleep (1), and unspecified (14). Most of the women (504) were on AED monotherapy.

Most of the births (640) were of live infants without congenital malformations. There were 44 births with fetal malformations: 27 live births with defects, 9 live births with defects that emerged by 1 year, and 8 induced abortions of malformed fetuses. Malformations included spina bifida, anencephaly, holoprosencephaly, Dandy-Walker syndrome, and cardiac defects.

There were also 23 spontaneous abortions, one induced abortion for maternal indications, and seven stillbirths; no malformations were noted in these fetuses.

The only significant drug/defect associations occurred in women taking high doses of valproate, either as monotherapy or polytherapy. Women taking more than 1,100 mg/day of valproate as monotherapy had a 13-fold increased risk of fetal malformations, compared with women not taking any AEDs. Women taking similar doses of the drug as polytherapy had a sixfold increased risk of fetal malformations.

The rate of malformation among women taking less than 1,100 mg/day was higher than the 2%-3% that occurs in the general population, but the difference was not statistically significant

Australian physicians appear to be heeding the data linking valproate to birth defects, Dr. Vajda said. The rate of valproate prescribing and dosages prescribed has decreased, as have rates of fetal malformation. In 1999, 26% of women on the registry were on the drug. The rate increased to 33% by 2001 and has since dropped to 21%. The average daily dose has decreased from 1,780 mg in 1999 to 936 mg in 2004.

The rate of malformation associated with valproate monotherapy was 16% before 2004, compared with 7% in 2004; the rate associated with polytherapy was 10% before 2004 and 0% in 2004.

But rates of malformation among women on carbamazepine or lamotrigine monotherapy have increased. For carbamazepine, the pre-2004 rate was 4.8%; it rose to 6.5% in 2004. The rate associated with lamotrigine monotherapy was 4.5% before 2004 and rose to 8.6% in 2004. The average dosages of these drugs increased for 1999-2004 as well.

Valproate is the most frequently prescribed antiepileptic drug in the United States, with 12 million prescriptions written annually for women of childbearing age. ■

Periconceptional OC Use Not Linked to Congenital Defects

ST. PETE BEACH, FLA. — Periconceptional exposure to oral contraceptives was not associated with an increased risk of adverse fetal outcomes in a recent prospective study.

Of the 45 women who participated in the study who were exposed to oral contraceptives during the periconceptional period, and were followed until after delivery, none gave birth to an infant with congenital malformations, compared with 6 of 225 controls.

The difference in the congenital malformation rate between the exposed and control groups was not significant, said Dr. H.K. Ahn and colleagues of the Motherisk Program at Sungkyunkwan University, Seoul, South Korea, during a poster session at the annual meeting of the Teratology Society.

The groups were also similar in regard to mean gestational age at delivery (39 weeks in both groups) and birth weight (3,257 g in the exposed group, and 3,268 g in the controls), the investigators said.

Women in the exposed group took oral contraceptives containing either combined ethinyl estradiol and progesterone, or high-dose progesterone.

Although some earlier studies suggested a link between oral contraceptive use during pregnancy and an increased risk of birth defects, later studies—including the current study—have failed to reproduce these earlier findings.

"Exposure to oral contraceptives, including high doses of progesterone … did not increase adverse fetal outcomes," the investigators said.

—Sharon Worcester