Several Crohn's Drugs Safe During Pregnancy, Lactation

BY DOUG BRUNK
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LOS ANGELES — Mesalamine, sulfasalazine, and prednisone are safe to use in Crohn's disease patients who are pregnant or nursing, a European expert panel has concluded.

"The panel position was, however, cautious and mainly based on label recommendations despite an accumulation of evidence from databases on the safety of Aza/6-MP [azathioprine/6-mercaptopurine] and infliximab before conception and during the first trimester," researchers led by Dr. Christian Mottet wrote in a poster presented at the annual Digestive Disease Week.

The European Panel on the Appropriateness of Crohn's Disease Therapy (EPACT) convened in Lausanne, Switzerland, to look into Crohn's disease therapy, including safety of available therapies for patients who are pregnant or nursing. The panel consisted of 10 gastroenterologists, 3 surgeons, and 2 general practitioners from 12 European countries.

Dr. Mottet of the division of gastroenterology and hepatology at Lausanne University Medical Center, Switzerland, and his fellow panel members used a 9-point scale to judge the appropriateness of treatment options in women before conception and the first trimester, in late pregnancy, and during nursing. In the scale, 1 was considered "very unsafe" while 9 was considered "extremely safe." The researchers defined a median rating of 7-9 as safe, a rating of 4-6 as equivocal, and a rating of 1-3 as unsafe.

The panelists rated mesalamine, sulfasalazine, and prednisone as safe to use during pregnancy and nursing. For their ratings of other drugs, see the related table. Safety criteria can also be found on the EPACT Web site at www.epact.ch. ■

Crohn's Therapy for Pregnant and Nursing Patients

Drug	Early Pregnancy And Before	Late Pregnancy	Nursing	Pregnancy Risk Category
Aza/6-MP	○	●	○	D
Budesonide	○	○	○	C
Ciproxine	●	○	●	C
Cyclosporine	●	●	●	C
Infliximab	○	○	○	B
Mesalamine	●	●	●	B
Metronidazole	●	○	●	B
Prednisone	●	●	●	B
Sulfasalazine	●	●	●	B

Source: Dr. Mottet

Key ● = Safe ○ = Equivocal ● = Unsafe

ELSEVIER GLOBAL MEDICAL NEWS

In Maternal Lupus, Minor Birth Defects Linked to Alcohol, Not SLE

Minor physical anomalies are not increased in infants born to women with systemic lupus erythematosus, according to the results of a new study.

"Our findings suggest that the potential risk factors for [minor physical anomalies] in this population were exposure to alcohol and tobacco," wrote Dr. Phyllis N. Bonaminio of Northwestern University, Chicago, and her colleagues. "Infants exposed to prednisone or aspirin in utero and whose mothers had a disease flare during pregnancy did not have an increased risk" (Ann. Rheum. Dis. 2006;65:246-8).

Their study followed 44 women with SLE through their pregnancies to assess the incidence and type of minor physical anomalies in their offspring. Examinations were performed on 30 infants between 1 and 245 days of age. Of the 30 infants, 22 (73%) were born at full term, 6 (20%) were preterm, and 2 (7%) were small for gestational age. Overall, the incidence of minor physical anomalies was 43% "which is consistent with the incidence in the general population," they reported.

The minor physical anomalies involved mostly the face and included flat nasal bridge (five), hypoplastic nose (four), long philtrum (three), high-arched palate (three), and thin vermillion, posterior-rotated ears, low-set ears, and protruding ears in one infant each. Limb anomalies included syndactyly and polydactyly in one infant each, and length discrepancies in the second and third toes of two infants.

Flat nasal bridge, hypoplastic nose, and long philtrum are associated with fetal alcohol exposure and were found in infants whose mothers reported alcohol use during their pregnancies. In fact, 10 of the 30 women whose infants were examined reported using alcohol (13%), tobacco (23%), and/or illicit drugs (13%) during their pregnancies, the authors noted.

Neither prednisone use (reported by 50%), nor aspirin use (reported by 20%), nor the presence of maternal disease flare during pregnancy were associated with minor physical anomalies, the authors reported.

Pregnant women with SLE must be counseled for substance abuse in addition to lupus-related concerns, Dr. Bonaminio advised.

—Kate Johnson

DRUGS, PREGNANCY, AND LACTATION

Gastrointestinal Agents: Part III

The final part of this series covers the use of infliximab, anticholinergics/antispasmodics, gastrointestinal stimulants, and anorectal preparations in pregnant and lactating women.

▶ **Infliximab (Remicade):** Infliximab is a monoclonal antibody used to treat severe Crohn's disease and autoimmune diseases such as ankylosing spondylitis, rheumatoid arthritis, and psoriasis. It binds to and inhibits human tumor necrosis factor–α (TNF-α). Animal reproduction studies have not been conducted with the agent because it does not react with animal TNF-α. Human pregnancy exposure consists of about 30 cases, which are limited to case reports and observational studies. The drug does not appear to represent a significant risk for developmental toxicity. Still, if possible, the best course is to avoid its use in pregnancy. If pregnancy exposure does occur, health care providers are encouraged to register these patients in the Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases in Pregnancy study by calling the toll-free number, 877-311-8972.

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▶ **Anticholinergics/antispasmodics:** These agents have been used for many years for peptic ulcer and functional GI disorders such as diarrhea, hypermotility, neurogenic colon, irritable bowel syndrome, ulcerative colitis, biliary tract spasm, and similar conditions. The agents—available under many trade names—include atropine, belladonna, dicyclomine, glycopyrrolate, L-hyoscyamine, mepenzolate, methscopolamine, propantheline, and scopolamine.

Only atropine, scopolamine, and dicyclomine have sufficient data in pregnancy. There are no reports suggesting that these agents cause birth defects. However, an excessive dose of scopolamine in labor has been associated with newborn toxicity. The other drugs are also probably low risk, but cannot be classified as such because of the very limited or complete lack of human pregnancy experience. However, anticholinergic combinations formulated with phenobarbital or other sedatives should be avoided in pregnancy and lactation. Although the data are very limited, all anticholinergics, except dicyclomine, appear to be compatible with breast-feeding. Dicyclomine is concentrated in milk and has been associated with apnea in one nursing infant.

▶ **GI stimulants:** Dexpanthenol (Ilopan) is given by intramuscular injection to prevent paralytic ileus after abdominal surgery. Although the drug has been promoted for constipation in pregnant women, there are no reports of its use or studies in pregnant or lactating animals or humans. Thus, the drug should not be given during pregnancy or breast-feeding.

In contrast, another GI stimulant, metoclopramide (Reglan, Maxolon), has substantial human pregnancy experience, primarily as an antiemetic. Although it is considered compatible with pregnancy, its use during breast-feeding is controversial. It has been successfully used as a lactation stimulant at doses of 20-45 mg/day. The drug is excreted into milk, but the estimated dose ingested by a nursing infant from milk is much lower than the therapeutic infant dose. However, mild intestinal discomfort has been observed in two infants. Because of its dopaminergic blocking action, the American Academy of Pediatrics classifies metoclopramide as a drug of potential concern during breast-feeding.

▶ **Anorectal preparations:** These include a large group of agents that are available in various topical formulations such as creams, ointments, foams, lotions, tissues and pads, and suppositories. With the exception of the hydrocortisone products, all are available over the counter, so you might not know that your patient is using them unless a careful history is taken. The OTC preparations are formulated with low concentrations of various drug mixtures, such as local anesthetics, vasoconstrictors, astringents, antiseptics, emollients/protectants, counterirritants, keratolytics, and wound healing agents. Only a few of these products and drugs have been studied in human pregnancy or lactation, but these preparations are used for their local effects and clinically significant systemic levels are not expected.

Of the drugs covered in this series, misoprostol and tetracycline cause structural defects, castor oil can induce labor, and mesalamine-containing agents and dicyclomine have caused toxicity in nursing infants. Most GI agents are safe in pregnancy and lactation, but many have insufficient data to judge their risk.

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