

DRUGS, PREGNANCY, AND LACTATION

New Asthma Treatment Guidelines

The 2004 asthma treatment guidelines for pregnant women, issued by the National Asthma Education and Prevention Program last month, is an extremely valuable document that meets a great need for guidance in this area.

A better understanding of the inflammatory nature of the disease has promoted a major shift in asthma therapy. Anti-inflammatory medications, most notably corticosteroids, and mast cell stabilizers (leukotriene inhibitors) are the first-line drugs of current treatment. Theophylline is rarely used today to treat asthma, but the guidelines say at recommended doses it has proved safe in pregnancy.

The authors, a multidisciplinary expert panel, performed a systematic review of the available evidence on asthma treatment in pregnancy. Some of the key findings are:

- ▶ Inhaled corticosteroids can reduce the risk of asthma exacerbations and improve lung function. There is no evidence that they are linked to increases in congenital malformations or other adverse outcomes. When taken through the inhaled route, systemic exposure is much less than with oral corticosteroids. Budesonide has the most data backing its safety in pregnancy, making it the "preferred inhaled corticosteroid," but there are no data indicating the other agents are unsafe in pregnancy, according to the guidelines.
- ▶ Oral corticosteroids may be necessary for treating women with severe asthma. While there are conflicting data on their safety in pregnancy, they may be warranted in women with severe disease, the guidelines say. In the general population, there is an association between use of oral corticosteroids in the first trimester and an increased risk for cleft lip and palate, compared with nonuse (0.3% vs. 0.1%), but not many asthmatic pregnant women have been included in these studies.

This risk for oral cleft has been shown in animals and in humans. Our Motherisk Program systematically reviewed studies and found a two- to threefold increase in oral cleft (with first-trimester exposure), which is probably not the case for inhaled steroids because the systemic dose is much smaller. Clearly, patients who are prescribed oral corticosteroids in the first trimester should be informed of this risk, and as the document points out, untreated asthma can be lethal.

During the second and third trimester, oral steroids cannot cause malformations. However, there are studies, which do not include patients with asthma, indicating that systemic exposure to corticosteroids may be associated with some CNS damage in babies.

Most of these data were from studies of premature infants whose mothers received corticosteroids to enhance lung maturation when the risk of prematurity was identified.

There is some evidence that repeating the dose of corticosteroids more than once may increase the risk of adverse brain outcome in premature babies. Although this evidence is not yet conclusive, it is fair to say that if the woman needs high-dose corticosteroids late in pregnancy for asthma, such a possibility should be discussed with her before prescribing these agents.



BY GIDEON
KOREN, M.D.

▶ The short-acting β_2 -agonist albuterol is the preferred drug in this class for treating acute symptoms, and the available data on the safety of β_2 -agonists are reassuring, the guidelines say. Albuterol has been studied in millions of patients worldwide and thousands of pregnant women, and there is no

indication whatsoever that it has any teratogenic effects. Since it is inhaled, systemic exposure is not great.

▶ For women with persistent asthma who are not well controlled on low-dose inhaled corticosteroids, increasing the dose or adding a long-acting β_2 -agonist is recommended, but there are not enough data to indicate which approach is preferable, according to the guidelines. It is fair to say that β_2 -agonists have not been shown to be teratogenic, and I agree with the panel that there is no reason to prefer one treatment option over the other.

▶ Cromolyn as a preventive treatment, appears safe based on the currently available evidence, the guidelines state.

▶ Leukotriene modifiers, the document notes, have "minimal" data available on their use in pregnancy, although there are reassuring animal data. We at Motherisk are prospectively collecting information on cases of pregnant women exposed to these drugs, and so far, they do not appear to be major teratogens.

I would also add that since asthma is often accompanied by allergy, effective management of allergic symptoms can prevent asthmatic attacks in many cases. H_1 blockers are safe in pregnancy.

A copy of the guidelines can be found at www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg.htm.

DR. KOREN is professor of pediatrics, pharmacology, pharmacy, medicine, and medical genetics at the University of Toronto, and holds the Ivey Chair in Molecular Toxicology at the University of Western Ontario, London. He has the Research Leadership in Better Pharmacotherapy During Pregnancy and Lactation at the Hospital for Sick Children, Toronto, where he also serves as director of the Motherisk Program.

Fish Intake in Pregnancy Affects Child's Asthma

BY DEBRA WOOD
Contributing Writer

ORLANDO, FLA. — The type of fish a woman consumes during pregnancy may affect the risk of her child developing asthma, Frank D. Gilliland, M.D., said at the 100th International Conference of the American Thoracic Society.

"We found maternal oily-fish intake was strongly protective in mothers who had a family history of asthma," Dr. Gilliland, of the department of preventive medicine at the University of Southern California, Los Angeles said during a press conference at the meeting. The children "had a 70% reduction in their risk of asthma, and this was not observed in children with no family history."

Oily fish, which are rich in omega-3 fatty acids, include yellowtail and cold-water fish like salmon, trout, and orange roughy. Eating oily fish on a regular basis a few times a month seemed sufficient to confer benefit, and the more oily fish a pregnant woman ate, the lower the risk of asthma in her child.

Using data from the Children's Health Study, a population-based study of school-aged children in 12 Southern California communities, Dr. Gilliland and associates conducted a nested, counter-matched, case-control study to evaluate whether maternal fish consumption affected their

children's asthma risk. Cases included those of children diagnosed with asthma by age 5; asthma-free children served as controls. The researchers completed telephone interviews with the children's mothers, collecting dietary and environmental exposure information.

Last year the Food and Drug Administration issued a consumer advisory about methylmercury in fish and shellfish. The advisory recommends that pregnant women strictly avoid fish that are high in mercury, and limit consumption of fish that are low in mercury, like salmon, to 12 ounces per week. Nearly all fish and shellfish contain trace amounts of mercury, but swordfish, shark, and other large fish tend to have greater amounts of the neurotoxin. Women could follow the FDA guidelines and still obtain the asthma-protective effect seen in this study. Favorable results were observed in women who ate as few as two servings of oily fish per month.

Dr. Gilliland suggested that omega-3's anti-inflammatory properties might reduce the child's asthma risk by decreasing inflammation in the developing fetus. "Some data suggest maternal omega-3 fatty-acid intake alters the immune phenotype of the fetus at birth," Dr. Gilliland said.

The results did not hold when women consumed canned or non-oily fish during pregnancy. ■

Female Fetuses May Increase Maternal Asthma Symptoms

BY DEBRA WOOD
Contributing Writer

ORLANDO, FLA. — Fetal gender may affect maternal asthma symptoms during pregnancy, according to results of a prospective study of 153 pregnant women.

"We found if you had female baby, things were happening, and the asthma tended to be worse. We found lung function was reduced in the last trimester if the woman was pregnant with a baby girl, and that she needed more



inhaled steroids to control the asthma," study investigator Peter G. Gibson, M.B., said at a press conference during the 100th International Conference of the American Thoracic Society.

The study, presented in poster form at the meeting, included 120 asthmatic women and 33 women without asthma. The team assessed patients at 18 and 30 weeks' gestation and recorded their use of inhaled corticosteroids, lung function, morning and night symptoms, use of reliever medications, and activity limitations. Sixty percent of women pregnant with

a male fetus remained free of asthma symptoms throughout gestation. Although 61% of women with a female fetus were symptom free at 18 weeks, by week 30 only 28% of the women were still symptom free. Nighttime symptoms and use of inhaled glucocorticoids increased significantly during the 12-week period, said Dr.

Gibson, professor in the department of respiratory and sleep medicine at Hunter Medical Research Institute at John Hunter Hospital in Newcastle, Australia.

DR. GIBSON
Dr. Gibson noted that women carrying female fetuses had elevated monocyte counts and suggested that female fetuses may somehow trigger increased inflammation in pregnant women.

In a prior study, Dr. Gibson found that girls born to asthmatic mothers who did not use inhaled steroids during pregnancy suffered from low birth weight, which did not happen if the mother used inhaled steroids or delivered a male child. "Guidelines for management of asthma in pregnancy recommend the use of inhaled steroids for women who have sufficient symptoms," Dr. Gibson said. ■