# Preemie Asthma Tied to Mom's Chorioamnionitis

BY MITCHEL L. ZOLER
*Philadelphia Bureau*

PHILADELPHIA — Children born prematurely to mothers who developed chorioamnionitis during pregnancy were about fourfold more likely to develop asthma and wheezing during the first 2 years of life, compared with term infants born to mothers without chorioamnionitis, based on data collected on nearly 1,100 children.

The finding needs to be extended by following the children to an older age and by studying other populations. If the findings are confirmed in such studies, earlier treatment and resolution of chorioamnionitis may have important implications for the future respiratory health of affected children, Dr. Rajesh Kumar said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

"What was surprising was the degree of association that chorioamnionitis had with wheezing and asthma," whereas no link was seen between prematurity, chorioamnionitis, and food allergy or eczema, said Dr. Kumar, a pediatric allergy and asthma specialist at Children's Memorial Hospital and Northwestern University, both in Chicago. Atopy does not appear to play a role in the association.

An alternative, physiological explanation is that chorioamnionitis produces a strong, proinflammatory response that boosts levels of various cytokines, such as tumor necrosis factor–α, and interleukin-6 and -8. Cytokines like these may trigger premature birth, and may also lead to chronic respiratory disease in the fetus.

Dr. Kumar's analysis was based on data from children in the Boston Birth Cohort, an ongoing study at Boston Medical Center that began in 1998. Included were 771 term and 325 preterm infants who completed at least one postnatal examination. These numbers make the analysis one of the few prospective studies large enough to allow stratification of the infants in groups according to the severity of prematurity and the presence of chorioamnionitis, he noted. The average age of the children at their last follow-up visit was 2.2 years.

The analysis adjusted for several infant and maternal variables, including breast-feeding, postnatal passive smoking, maternal smoking during pregnancy, and maternal educational status. Infants born at less than 33 weeks' gestation to mothers who had chorioamnionitis were 4.0-fold more likely to wheeze and 4.4-fold more likely to have asthma, compared with infants born at 37 weeks or beyond to mothers without chorioamnionitis. (See box.) Both differences were highly statistically significant.

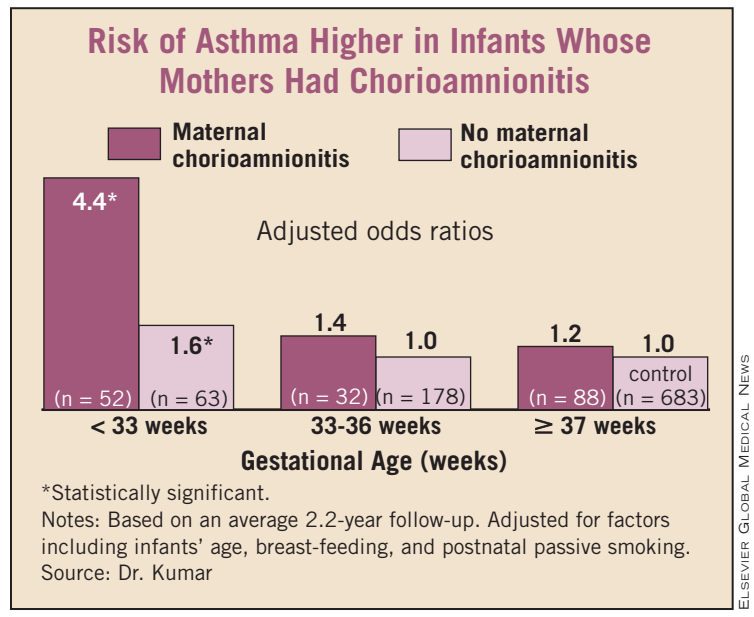
**Treating chorioamnionitis earlier could have important implications for affected children's respiratory health.**

**DR. KUMAR**

In contrast, infants born before 33 weeks to mothers without chorioamnionitis were 2.7-fold more likely to wheeze (a significant difference), but were no more likely to have asthma than were term infants.

"One of the major issues in our study was that our primary outcome was recurrent wheezing of early childhood. We also evaluated physician-diagnosed asthma, but this is a bit less clear of a diagnosis at a young age. We will continue to follow these children [until] they are 6 years of age to see if the effects of chorioamnionitis on physician-diagnosed asthma will truly equate to persistent asthma by the time the children are older," Dr. Kumar said.

The associations were even stronger in infants born to African American mothers, who made up about 62% of the study cohort. In this subgroup, infants born at less than 33 weeks' gestation to mothers with chorioamnionitis were 5.4-fold more likely to have wheezing and 5.2-fold more likely to have asthma, compared with infants born at term to African American mothers without chorioamnionitis. Both differences were highly significant. Infants born at less than 33 weeks to mothers without chorioamnionitis were 3.8-fold more likely to wheeze, but did not have a significantly increased risk for developing asthma. ■




ELSEVIER GLOBAL MEDICAL NEWS

# *Oral Drug for Cystic Fibrosis Shows Promise in Early Trials*

BY TERRY RUDD
*Senior Editor*

A drug for fixing a crucial defective protein in cystic fibrosis improved patients' lung function and sweat chloride levels, according to early results from a small randomized study.

The investigational oral drug, VX-770, is still in phase II trials. But preliminary findings in 20 patients—particularly the impact on sweat chloride levels—are drawing cautious optimism.

"These [results] are an extraordinary endorsement of our hypothesis—that small molecules can correct the basic defect and affect the clinical indicators of cystic fibrosis," said Robert J. Beall, Ph.D., president and CEO of the Cystic Fibrosis Foundation, in a statement.

VX-770 targets defective Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) proteins in sweat duct epithelial cells. Dysfunctional CFTR proteins are believed to cause the fluid and salt imbalance that characterizes CF patients' airways.

The first part of the phase IIa trial included 20 patients who carry the G551D mutation in the CFTR gene. About 4% of CF patients in the United States carry the G551D mutation. Patients participated in two 14-day treatment periods. In addition to standard CF therapies, they received either placebo or one of three VX-770 dosage levels during each 14-day period.

At the end of 14 days, patients who received the highest dose of VX-770 (150 mg twice daily) experienced an average 10.1% increase in forced expiratory volume in 1 second ($FEV_1$), compared with an average $FEV_1$ decrease of less than 1% in placebo patients.

For patients on high-dose VX-770, sweat chloride levels fell from an average 95.5 mmol/L at baseline to 53.2 mmol/L after 14 days of treatment. Patients on placebo had no significant change in sweat chloride levels. Sweat chloride levels for CF patients typically are greater than 60 mmol/L, compared with normal values of less than 40 mmol/L in people without CF. The adverse events rate was similar between the groups. One patient had two serious adverse events, which researchers deemed were not related to VX-770.

The second stage of the drug's phase IIa trial is slated to begin later this year, and will enroll 16 patients for 28 days of randomized, placebo-controlled treatment. A phase IIb trial may begin in 2009, said the foundation. Vertex Pharmaceutical Inc. is developing VX-770 and a second compound, VX-809, with funding support from the Cystic Fibrosis Foundation. ■

# Genetic Marker May Flag Risk Of Asthma, Poor Lung Function

BY ELIZABETH MECHCATIE
*Senior Writer*

A protein linked to inflammation and tissue remodeling is a significant biomarker for asthma and poor lung function, and a variation in that protein's genetic code is also associated with asthma risk and bronchial hyperresponsiveness.

A single-nucleotide polymorphism (SNP) was associated with elevated serum levels of the protein, YKL-40, in several populations, and both the genetic variation and elevated YKL-40 levels were associated with asthma, bronchial hyperresponsiveness, and reduced lung function, according to Carol Ober, Ph.D., of the University of Chicago and her associates in the United States and Germany (N. Engl. J. Med. 2008;358:1682-91).

In an earlier study, some of the same investigators had reported that serum levels of YKL-40 were elevated in patients with asthma. Serum YKL-40 levels also were associated with asthma severity, thickness of the subepithelial basement membrane, and pulmonary function, suggesting that YKL-40 levels could be a biomarker for asthma.

The investigators conducted a genomewide association study in a group of 632 related Hutterites aged 6-92 years (mean age 33) living on communal farms in South Dakota. They also included studies of children with and without asthma.

The Hutterites' mean YKL-40 levels were 15% higher among those with asthma and 10% higher among those with bronchial hyperresponsiveness, compared with controls. They also found a significant association between an SNP in CHI3L1, a gene encoding for YKL-40, and elevated serum YKL-40 levels, asthma, bronchial hyperresponsiveness, and measures of pulmonary function.

The researchers also determined that the same SNP was predictive of asthma from birth through age 5 years in a study of 638 German children at about age 10 years, and in a study of 296 adults and children in Chicago.

The result "shows that serum YKL-40 level is a highly heritable, quantitative trait in humans and confirms that YKL-40 is a significant biomarker for asthma susceptibility and reduced lung function," the authors wrote. Genetic variation in CHI3L1 "influences serum YKL-40 levels and is associated with the risk of asthma, bronchial hyperresponsiveness, and reduced lung function."

Identifying the rest of the genetic loci that contribute to the differences in serum YKL-40 levels and related proteins "could identify additional genes with a significant effect on the risk of asthma and lung function," the researchers added.

These results need to be confirmed with large studies, Miriam Moffatt, D.Phil., and Dr. William O.C.M. Cookson of the National Heart and Lung Institute at Imperial College London, said in an accompanying editorial (N. Engl. J. Med. 2008;358:1725-6). ■