Drugs, Pregnancy, And Lactation

Inhaled Corticosteroids and Fetal Growth

BY GIDEON KOREN, M.D.

The widespread prescribing of corticosteroids in medicine includes many clinical situations during pregnancy, which naturally raises concerns about the safety of these drugs in pregnant women. Over the past several years, information on this topic has begun to accumulate, providing stronger evidence about the safety of inhaled corticosteroids in this population.

Most recently, in October, the largest study to date, conducted by the Organization of Teratology Information Services (OTIS), on the use of medications for asthma during pregnancy and their effects on fetal growth was published. The main finding was that treatment of pregnant women with β_2-agonists and inhaled steroids did not have adverse effects on fetal growth and that systemic corticosteroids had a minimal effect on birth weight and length.

The prospective study compared birth size and the incidence of babies born small for gestational age (SGA) in 654 infants whose mothers had taken inhaled or systemic corticosteroids and β_2-agonists for asthma during pregnancy with birth size and incidence of SGA in 303 infants whose mothers did not have asthma. Women from North America were enrolled between 1998 and 2003. There were no significant differences in the incidence of SGA for weight between the groups. There was a small reduction in birth weight among those exposed to systemic steroids: In this group, the mean birth weight, adjusted for other risk factors, was 3,373 g, compared with a mean of 3,540 g among controls, 3,552 g among those exposed to β_2-agonists only, and 3,524 g among those exposed to inhaled steroids.

Mean birth weight and mean birth length, adjusted for risk factors, among infants whose mothers had been treated with inhaled steroids were not significantly different from those of controls or of infants whose mothers had used β_2-agonists only. The adjusted mean birth lengths were 51.3 cm in the inhaled steroid group and 51.5 cm in the β_2-agonist group.

The authors, from the University of California, San Diego and the OTIS Research Group, concluded that these results were "reassuring and support the recommendations of adequate control of severe asthma during pregnancy," and that "the modest effect of systemic steroids on fetal growth should be weighed against the necessity to achieve adequate control of severe persistent asthma and to prevent hypoxia during pregnancy" (J. Allergy Clin. Immunol. 2005;116:503-9).

While these conclusions are not novel, this study is a major breakthrough because it combines information from teratology information centers in North America to provide much larger numbers than were available previously.

Women and physicians should be informed there are some risks: In 2000, my colleagues and I published a meta-analysis of all available studies of women who were given high-dose steroids during pregnancy for various reasons. The results clearly indicated that the use of systemic steroids during the first trimester was associated with a two- to threefold greater risk of oral clefts. This finding was consistent with extensive animal data that have shown the same association.

However, inhaled corticosteroids, commonly used as first-line therapy for asthma, result in an extremely low systemic dose, and none of the available reviews on the use of inhaled steroids during pregnancy have found any association with a greater risk of oral clefts. The β_2-agonist albuterol is not teratogenic.

There is emerging evidence that repeated weekly corticosteroid injections for fetal lung maturation in cases of premature rupture of the membranes may result in brain damage in some babies. But this is not relevant to the use of inhaled corticosteroids in pregnant women with asthma.

Therefore, based on this recent study and previous data, pregnant women should be encouraged not to neglect their asthma therapy because of concerns about potential effects on the fetus. The risks include higher rates of perinatal complications, mostly prematurity, when asthma is poorly controlled. We are aware of fatal cases of women who stopped much-needed asthma treatment during pregnancy.

The authors of an editorial accompanying the OTIS study state that inhaled steroids "do not seem to significantly impair fetal growth," but add that "before ruling out with confidence any potential adverse effect" of inhaled steroids on fetal growth, "there is a need for larger studies adequately powered to answer this question" (J. Allergy Clin. Immunol. 2005;116:501-2). While I agree that we always need more studies, the risk-benefit ratios should dictate optimal treatment of maternal asthma.

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Maternal Asthma Linked to Risk of Premature Birth

BY PATRICE WENDLING
Chicago Bureau

MIAMI — Maternal asthma was a significant risk factor for premature birth and low birth weight, even if the mother's asthma was diagnosed years before delivery, Dr. Joel Liem reported at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

"Physicians and other health care professionals need to assess present and past asthma, up to 5 years prior, in order to properly assess the risk for premature labor," Dr. Liem told reporters at a press conference at the meeting.

The investigators used information from the Manitoba Health Services Insurance Plan database, a population-based health care administrative and prescription database that has records of every child born in the province of Manitoba, Canada, as well as their mothers' records. Maternal asthma was defined two ways: as an ICD-9 code of 493 (asthma) in 1995 or a prescription for an asthma medication in 1995; or an ICD-9 code 493 in 1990-1995 or an asthma medication prescription in 1995.

With the first definition, the prevalence of asthma among the mothers was 5.5%. But there was no statistically significant association between maternal asthma and prematurity or low birth weight, said Dr. Liem, an epidemiologist with the University of Manitoba, Winnipeg.

When the second definition covering a longer time period was applied, maternal asthma was found to be a significant risk factor for the development and degree of prematurity and low birth weight, with a prevalence rate of 10.4%, he said.

A total of 881 babies (6.3%) were born at a gestational age of less than 37 weeks, and 691 babies (4.9%) had a birth weight of less than 2,500 g.

Compared with nonasthmatic mothers, asthmatic mothers were 2.8 times more likely to give birth to a premature child at less than 28 weeks, and 3 times more likely to give birth at less than 32 weeks. The relative risk of asthmatic mothers giving birth at less than 37 weeks was 1.13, while their relative risk of having a postterm baby at more than 42 weeks' gestation was 0.63.

The relative risks of an asthmatic mother having a low-birth-weight baby of less than 1,000 g, 1,500 g, 2,000 g, and 2,500 g were 3.8, 3.23, 1.9, and 1.3, respectively, Dr. Liem reported.

The investigators are analyzing the type and frequency of maternal prescriptions and hospitalizations to assess what influence asthma control and severity may have had on outcomes. ■

Large Study Questions Possible Link Between Steroids and Orofacial Cleft

ST. PETE BEACH, FLA. — The use of oral steroids for asthma during pregnancy has long been cited as a possible cause of orofacial clefts in newborns, but findings from a large cohort study suggest this is not the case.

In nearly 82,000 mother/infant pairs, not a single infant with an orofacial cleft was born to any of the more than 400 women who received at least one oral steroid prescription in the 90 days before pregnancy or during early pregnancy, Janet R. Hardy, Ph.D., reported at the annual meeting of the Teratology Society.

The findings could put an end to long-held beliefs—based on findings in laboratory animals decades ago—that a link exists between the medication and an increased risk for such defects.

About 6% of mothers in the retrospective population-based cohort study were asthmatic, and nearly 2% had other respiratory conditions. A total of 130 babies included in the study were born with orofacial cleft; only 6 of these were born to asthmatic mothers, and 3 others were born to women with other respiratory conditions. None of the nine mothers had received a prescription for an oral steroid during pregnancy, said Dr. Hardy, of the University of Massachusetts, Worcester.

The relative risk of cleft overall in this study was 1.30; the relative risk in babies born to women who received a prescription for any type of steroid drug was 1.26.

Dr. Hardy noted that the study, based on data in automated medical records from 1991 to 1999, is limited by its basis on prescribed medications. Medications prescribed do not necessarily equate to medications taken, she said, noting that she also was unable to study asthma severity, maternal smoking, family history, and racial and ethnic background. Adjustment for other possible confounders, including other medications used, did not affect the results, however, she said.

Asthma complicates 3.7%-8.4% of pregnancies, and these findings suggest that any steroid use is associated with only a slightly increased risk of orofacial clefts.

Given the small overall risk with any steroid use and the apparent absence of risk with oral steroids, it is of concern that the data show a decline in the prescribing of oral steroids for the treatment of asthma in the first trimester, Dr. Hardy said.

In the prepregnancy period, 318 mothers (including 203 who were asthmatic) received at least one oral steroid prescription. In early pregnancy, however, only 149 (including 89 who were asthmatic) received at least one oral steroid prescription.

The risks associated with uncontrolled asthma are likely to be worse for the fetus than the risks of asthma medications, she concluded.

—Sharon Worcester