DRUGS, PREGNANCY, AND LACTATION

Beta$_2$-Agonists for Asthma

Asthma continues to be one of the most common chronic conditions complicating pregnancy; approximately 8% of pregnant women in the United States report a current diagnosis. Asthmatic women are at increased risk of adverse birth outcomes and perinatal complications, including spontaneous abortion, preterm delivery, reduced birth weight, preeclampsia, and, in selected studies, congenital anomalies. In some cases, these increased risks have been linked to specific medications (for example, oral corticosteroids and orofacial clefts). But much of the current evidence is also consistent with the interpretation that at least some of the excess risk can be attributed to the underlying severity/inadequate control of maternal asthma.

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However, two recently published studies suggest that beta$_2$-agonists – mainstays of treatment and control of asthma symptoms – may be associated with increased risks of congenital anomalies.

The first, an analysis conducted with data from the National Birth Defects Prevention Study, focused specifically on orofacial clefts as the outcome and bronchodilators as the exposure. With a case-control design, 2,711 mothers of infants with oral clefts and 6,482 mothers of infants with no malformations in 10 states were interviewed between 1997 and 2005 about bronchodilator use for asthma during and just before pregnancy. The authors separately evaluated risks for cleft lip alone, cleft lip with cleft palate, and cleft palate alone, as each of these defect categories may have distinct etiologies. Almost 3% (247 women) reported exposure to any bronchodilator in the periconceptional period, with nearly 90% of those exposures limited to the widely used short-acting beta$_2$-agonist, albuterol.

Significantly increased risks were noted for any bronchodilator use (without an additional anti-inflammatory drug) and cleft lip alone (adjusted odds ratio, 1.77; 95% confidence interval, 1.08-2.88); however, with the addition of an anti-inflammatory drug (four cases), the odds were attenuated and no longer statistically significant. If the analysis is limited to only those reporting use of albuterol, the estimated risks for cleft lip alone (adjusted OR, 1.79; 95% CI, 1.07-2.99) and cleft palate alone (adjusted OR, 1.65; 95% CI, 1.06-2.58) were both significantly elevated. No increased risks were noted for use of any bronchodilator and cleft lip with cleft palate. If these findings represent a causal association, the estimated odds ratios would translate to less than one excess case each of cleft lip alone and cleft palate alone for every 1,000 women using albuterol in the first trimester (Hum. Reprod. 2011;26:3147-54).

As the authors pointed out, there was no mechanism in the study to adjust for the contribution of underlying disease severity/asthma symptom control in these mothers. However, the lack of an association between orofacial clefts and bronchodilators among those women who also used an anti-inflammatory drug suggests that perhaps women on polytherapy had more optimum treatment and therefore better control.

The second study used a retrospective cohort design drawing on administrative data collected between 1990 and 2002 in Quebec. The 13,117 pregnancies selected for the analysis were limited to those with a coded diagnosis of asthma and excluded women who received multiple prescriptions for oral corticosteroids in the year before pregnancy. The exposures evaluated were any prescription in the periconceptional period for a short-acting beta$_2$-agonist rescue medication (such as albuterol), and any prescription in the periconceptional period for a long-acting beta$_2$-agonist controller medication (such as salmeterol, available during the years of this study as a single active ingredient medication). In all, 17 categories of major congenital malformations were evaluated as outcomes, including orofacial clefts. More than 50% of pregnant women in the study filled a prescription for a short-acting drug in the first trimester, while only 1.3% received a prescription for one of the long-acting medications.

The authors found no significant associations with short-acting beta$_2$-agonists for any of the congenital defect categories. Cases of cleft lip and cleft palate were combined, and the odds ratio after considering adjustment factors, was 1.50 (95% CI, 0.72-3.14). However, the authors did report that first-trimester prescription for long-acting beta$_2$-agonists was associated with significantly increased risks for major cardiac malformations (adjusted OR, 2.30; 95% CI, 1.11-5.10) based on seven infants exposed and "other or unspecified major malformations" (adjusted OR, 3.97; 95% CI, 1.29-12.20) based on three infants exposed (Birth Defects Res. Clin. Molec. Teratol. 2011;91:937-47). In this study, the authors attempted to control for underlying disease severity using Canadian treatment guidelines as well as emergency room and other hospital admissions for asthma. However, no direct measure of disease severity or symptom control was collected, and unfortunately, the "lumping" of orofacial clefts (likely due to the small number of affected infants) makes comparison to the above-described study difficult. The findings with long-acting beta$_2$-agonists, as the authors point out, could be influenced by the higher rate of more severe and less well-controlled asthma among these women, the expected higher rate of preterm delivery with associated prematurity-related defects, and/or multiple testing/chance. Finally, it has been suggested that some asthmatic women will reduce or discontinue medication in the first trimester of pregnancy based on fear of fetal exposure, not on remission of symptoms. If in fact this is the case, prescriptions filled may not reflect true usage of the drug. With respect to previously published studies, an increased risk for congenital anomalies in general or orofacial clefts in particular, has not been suggested for albuterol. There is a lack of published data on long-acting beta$_2$-agonists and pregnancy outcome. Thus, although neither of the two new studies reviewed above will likely change clinical practice, they both point out the need for further study of commonly-used asthma medications, and specifically, studies that incorporate direct measures of disease severity/symptom control. Reports of even small increased risks for asthma medications during pregnancy can further deter women from appropriate treatment, which in turn may result in unintended risks for both mother and baby. ■

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Fibroids Foretell Worse Maternal and Fetal Outcomes

BY DAMIAN McNAMARA

FROM THE ANNUAL MEETING OF THE AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

ORLANDO – Uterine fibroids are bad for pregnancy and neonatal outcomes, and a new study shows just how bad.

Women diagnosed with fibroids on their first obstetric ultrasound examination, for example, were significantly more likely to experience preterm labor or preterm premature rupture of the membranes (pPROM). Also, significantly more deliver before 37 weeks' gestation or via cesarean section, compared with a group of women without these noncancerous growths of the uterus.

Dr. Radwan Asaad and his colleagues compared 152 women with fibroids to another 165 matched controls in a retrospective cohort analysis conducted at Wayne State University, Detroit. They also found fibroids weren't good news for the baby either.

"Uterine fibroids complicate the pregnancy course as evidenced by a considerable impact on the obstetrical and neonatal outcomes," Dr. Asaad said at the meeting.

In terms of the significantly different maternal numbers, women with fibroids were more likely to experience preterm labor (16.4% vs. 2.4% of controls), and pPROM (15.8% vs. 3.6%), and to deliver preterm (33.3% vs. 10.1%).

Fetal malpresentation also was significantly more likely in the fibroid group (22% vs. 6% in controls). Cesarean delivery occurred in 54.3% of the fibroid group vs. 28.0% of the control group, another significant difference.

Gestational age at delivery was significantly less when the mother had fibroids (mean 35.3 weeks) vs. without (38.6 weeks).

Children born to women in the fibroid group had a mean birth weight of 2,634 g, compared with 3,181 g for those born to control group women. Apgar scores at 1 minute were a mean 6.7 vs. 7.8 in the control group and at 5 minutes were a mean 7.9 vs. 8.8.

Pregnancy loss was higher in the fibroid group during the first trimester (7.9% vs. 3.6% in controls) and during the second trimester (5.9% vs. 1.2%), but these differences were not statistically significant to the *P* less than .001 level. A trend toward more arrested dilation in the fibroid group likewise did not reach significance.

"Uterine myomas are the most common pelvic tumor in reproductive-age women," said Dr. Asaad, a laparoscopic and minimally invasive surgeon in the department of obstetrics and gynecology at Hutzel Women's Hospital and Wayne State University/Detroit Medical Center. Prevalence in published studies varies from 2% to 11%, depending on the trimester in which they are measured and the size threshold chosen by researchers.

A meeting attendee asked for information on the size and anatomic location of the fibroids. Dr. Asaad replied that he was only able to categorize women dichotomously as yes/no for presence of fibroids in this retrospective study.

Dr. Asaad and his associates reviewed all department ultrasounds from 1998 to 2006 at their tertiary care center. Women with complete records in the fibroid group were matched to controls for age, gravidity, parity, and year of delivery.

He said he had no relevant financial disclosures. ■