

Agonizing over Beta 2 Agonists and Autism

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Practice Options from Beyond Our Pages focuses on identifying, critiquing, and placing into context research studies published in other journals that have the potential to change our clinical practices. It is written by Allergy-Immunology Fellows partnered with faculty members, and does not require an invitation for submission. This feature is coordinated by Editorial Board members Matthew Rank, MD and Julie Wang, MD.

REFERENCE

Gidaya NB, Lee BK, Burstyn I, Michael Y, Newschaffer CJ, Mortensen EL. In utero exposure to β -2-adrenergic receptor agonist drugs and risk for autism spectrum disorders. *Pediatrics* 2016;137:e20151316.

BACKGROUND

Recent reports indicate a high prevalence of autism with 1 in 68 children meeting the criteria for autism spectrum disorders (ASD).¹ ASD is reported to occur in all racial, ethnic, and socioeconomic groups.¹ ASD is approximately 4.5 times more common among boys (1 in 42) than girls (1 in 189).¹ The etiologies for ASD are heterogeneous; genetic factors play a major role in many patients.² The role of environmental factors has been a key area for research.³ *In utero* exposure with drugs such as valproate and thalidomide has been linked to ASD.^{4,5} One epidemiological study in 2011 reported a possible role of *in utero* exposure of beta-2 adrenergic receptor (B2AR) agonists in causation of ASD.⁶ In this study, Croen et al⁶ reported that ASD was 4 times more likely in those with IV terbutaline exposure during third trimester but did not find a significant risk with other B2AR agonists. This study was not population based and had only 284 controls and 291 ASD cases; this small sample size led to “statistically imprecise effect estimates.” With this background, Gidaya et al conducted a case-control study to investigate if there was increased risk for autism when inhaled B2AR agonists were used during pregnancy.

METHODS

Using Denmark's health population registers, 5200 children with ASD born between 1997 and 2006 were identified. Children without ASD (n = 52,000) matched on month and year of birth were used as controls. Children whose biological mother did not live

in Denmark a year before the delivery, and those born at gestational age of <23 weeks were excluded. For multiple births, one child was randomly selected. Exposure to inhaled B2AR agonists was ascertained through Drug Prescription Register. The exposure windows were defined as preconception, first trimester, second trimester, and third trimester. The children born to mothers who had no prescription records of B2AR were considered unexposed. Other variables collected include parental age, psychiatric history, mother's number of live births, child's gestational age, birth weight, obstetric complications, and socioeconomic status.

RESULTS

B2AR agonist drug exposure in pregnancy was noted in 3.7% (190) of cases and 2.9% (1489) of controls. Children with ASD were more likely than controls to be male, have a higher parental age, and have a mother with an asthma diagnosis before the birth of the child. Use of B2AR agonists during pregnancy was associated with increased risk of ASD, after controlling for the child's birth year and month, gender of the child, and parental age (odds ratio [OR]: 1.3; 95% confidence interval [CI]: 1.1-1.5). The elevated risk was observed with the use of B2AR agonists during preconception (OR: 1.3; 95% CI: 1.0-1.6), first trimester (OR: 1.3; 95% CI: 1.5-1.5), second trimester (OR: 1.5; 95% CI: 1.1-1.7), and third trimester (OR: 1.4; 95% CI: 1.1-1.7). The authors also found some evidence that longer B2AR use in pregnancy was associated with increased risk.

CRITICAL APPRAISAL

This population study reports a 1.3-fold increase in ASD in children born to mothers who presumably used B2AR agonists during pregnancy. B2AR agonists are known to cross the placenta, and some animal studies indicate that this may affect developing neurons in the fetus.⁷⁻⁹ Beta adrenergic drugs are widely used in the treatment of asthma. Although associations with congenital malformations have been reported, methodological limitations prevent firm conclusions regarding an increased risk of adverse perinatal outcomes associated with gestational use of beta agonists.¹⁰ Hence, a closer look at the strength of association in the study of Gidaya et al is needed.

This study has some strengths and significant weaknesses: it is population based including almost all children born over a 6-year period with follow-up to at least 5 years of age. This provided a large group of 5200 cases of ASD. When assessing the hazard risk, they used conditional logistic regression analysis and adjusted the risk for gender, parental age, and maternal diagnosis

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of asthma. However, although asthma was a covariate, asthma severity, control, and oral steroid use were not captured.

In a case-control study, the impact of potentially important confounders should always be considered. In this study, cases (children with ASD) were more likely to be male, have higher parental age, and have a mother with diagnosis of asthma. Boys are at higher risk for ASD, and in this study, 82% of cases were male, whereas only 50.7% of controls were male. However, the authors report a significant increase in ASD risk despite controlling for the gender differences between cases and controls. Of greater concern, though, is the possible impact of *unmeasured* confounders. For example, other previously reported risk factors for ASD, such as premature birth, low birth weight, siblings, and family history of ASD, were not analyzed.¹¹ The authors reported collecting data on gestational age at birth, but the results were not shown. Exposure to other drugs known to cause ASD was not studied, and the potential contribution of uncontrolled asthma to ASD development cannot be ascertained.

The methods used to measure exposure also have several drawbacks. Exposure data were restricted to outpatient prescriptions that were equated to exposure. However, the actual dose and duration of exposure were unknown. Most patients with asthma have a B2AR inhaler at home, but that does not equate to use. As exposure data relied on outpatient prescriptions, true exposure in hospitalized patients with severe asthma and exposure to intravenous terbutaline (a B2AR agonist, used to prevent preterm labor) were not measured.

RECOMMENDATION

The data from this study should be interpreted with caution. Limitations of “exposure” ascertainment and the many potential confounding variables that were not analyzed make it hard to know if there is a true link between B2AR use and ASD. Further prospective population-based studies better accounting for known risk factors of autism and parameters of asthma severity and/or control may serve to confirm or refute the observations of this study and address their potential causal relationships.

Even if there is a true increased relative risk, this study would suggest that the absolute risk of ASD related to B2AR agonists is “less than 1%” according to the authors. Making the correct diagnosis and using asthma controller therapies to minimize asthma symptoms should be our goal with every patient. In our opinion, the benefits and risks of any treatment option should be balanced, and B2AR agonists should not be withheld for appropriate indications in pregnant women with acute asthma.

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