In utero Exposure to β-2-Adrenergic Receptor Agonist Drugs and Risk for Autism Spectrum Disorders

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abstract

OBJECTIVES: The purpose of this study was to investigate associations between use of β-2-adrenergic receptor (B2AR) agonist drugs during pregnancy and risk for autism spectrum disorders (ASD).

METHODS: A case-control study was conducted by using Denmark's health and population registers. Among children born between 1997 and 2006, 5200 cases with ASD admission diagnoses and 52 000 controls without ASD were identified and individually matched on month and year of birth. Conditional logistic regression models were used to estimate odds ratios (OR) and confidence intervals (CI) for any B2AR agonist exposure during pregnancy, preconception, and by trimester.

RESULTS: In total, 3.7% of cases and 2.9% of controls were exposed to B2ARs during pregnancy. Use of B2ARs during pregnancy was associated with increased risk of ASD, even after adjustment for maternal asthma and other covariates (OR: 1.3, 95% CI: 1.1–1.5). The elevated risk was observed with use of B2AR during preconception (OR: 1.3, 95% CI: 1.0–1.6), first trimester (OR: 1.3, 95% CI: 1.1–1.5), second trimester (OR: 1.5, 95% CI: 1.1–1.7), and the third trimester (OR: 1.4, 95% CI: 1.1–1.7). There was some evidence that longer B2AR within-pregnancy use was associated with the increased risk.

CONCLUSIONS: B2AR agonist exposure during pregnancy may be associated with an increased risk for ASD. If the effect is real, any intervention must be balanced against benefits of indicated medication use by pregnant women.

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WHAT'S KNOWN ON THIS SUBJECT: Certain medications such as β-2 adrenergic receptor agonist drugs are known to cross the placenta and may affect developing neurons in the fetus. Only 1 epidemiologic study thus far has investigated this association.

WHAT THIS STUDY ADDS: β-2 adrenergic receptor agonist drug exposure during pregnancy may be associated with an increased risk for autism spectrum disorders. Results from this study add to the limited knowledge on prenatal pharmacological exposures as potential autism spectrum disorders risk factors.

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Prenatal pharmacologic exposures have been implicated as potential risk factors for autism spectrum disorders (ASD).[1–3] In particular, concerns have been expressed that exposure to terbutaline, a β-2 adrenergic receptor (B2AR) agonist drug, used as indicated as an antiasthmatic[4] and used off-label later in pregnancy as a tocolytic agent,[5] may increase the risk for neurodevelopmental disorders in offspring.[6–8] The prevalence of B2AR agonist drug exposure during pregnancy range from 1.0% to 7.5% in Denmark and throughout Europe.[9–11] A study of in utero B2AR agonist drug exposure in a small series of dizygotic twin pairs suggested an increased risk associated with ASD.[12] A case-control study of 291 cases and 284 controls found that exposure for more than 2 days during the third trimester was associated with increased risk for ASD, although estimates were imprecise (adjusted odds ratio [OR] 6.0, 95% confidence interval [CI] 1.1–34.3).[13]

It is unclear if the apparent effects are due to confounding by indication: whether it is the pharmacologic exposure or the indicating condition that increases risk to ASD. Long-acting B2AR agonist drugs such as salmeterol and formoterol are used to reduce asthma exacerbations and provide asthma control in adults.[14] Croen et al observed that maternal diagnosis of asthma or allergies during the second trimester was associated with risk of ASD.[15] However, Lyall et al reported no association of maternal asthma with child ASD.[16]

There is some mechanistic evidence to support the role of B2AR in development of ASD. β-2 adrenergic receptors within the catecholamine system are involved in normal nervous system development and the function of both neural and nonneural tissues in adults.[17] The most common approach to treatment of asthma in Denmark is inhalation of B2AR agonist drugs[18] and placental transfer of B2AR agonists has been demonstrated in vitro[19] and indicated in vivo even at inhaled concentrations.[20] B2AR agonist drugs used during pregnancy can affect the fetal brain by crossing the placenta, resulting in the disruption of either replication or differentiation of the developing neurons.[21] The mechanisms within the mature β-2-adrenergic receptors protect against overstimulation; however, fetal receptors do not have the ability to regulate any imbalance and may in fact become sensitized.[22] Early research has shown that B2AR agonist drugs administered to pregnant rats during gestation alters neural cell replication and differentiation, synaptogenesis, and expression of synaptic proteins involved in neurotransmission.[23–25] Although animal studies support the biological plausibility of adverse effects associated with prenatal B2AR agonists drug exposure, the findings are not trimester specific and suggest that there may be multiple critical periods throughout early development.[22,25,26] However, because uncontrolled asthma has been associated with poor birth outcomes, pregnant women are generally recommended to continue asthma medication.[27,28] Given the biological plausibility and limited knowledge regarding risks of prenatal pharmacologic exposures, we conducted a population-based case-control study to estimate the associations of maternal exposure to B2AR agonist drugs used during preconception and pregnancy with the risk of delivering a child who goes on to develop ASD.

METHODS

The Institutional Review Board of Drexel University and the Danish Data Protection Agency (Record No. 2010-41-4861) approved this study.

Participants

All children (n = 749 755) born in Denmark between January 1, 1997, and December 31, 2006, were identified through the Civil Registration System.[29] Children were excluded if they could not be linked to their biological mother (n = 1139), if the biological mother did not live in Denmark a year before delivery (n = 10 806), or if the child was of gestational age <23 weeks or >43 weeks (n = 1774). Therefore, the study population (n = 628 408) was then drawn from all biological singletons; for women with multiple births, 1 child was randomly selected for inclusion in the study.

Cases were identified from the National Hospital Register and the Danish Psychiatric Central Register that includes information on all inpatient and outpatient care from psychiatric hospitals and psychiatric wards in general hospitals in Denmark.[30] The quality of the diagnosis of childhood autism in the Denmark registers was evaluated through medical records review: register-based diagnosis of childhood autism was confirmed 94% of the time with an additional 3% falling within ASD.[31] However, there is also a possibility for unregistered cases of ASD. Subjects' records from January 1, 1999, to March 31, 2011, were searched for *International Classification of Diseases, 10th Revision*, codes (*ICD-10*) of F840, F841, F845, and F848/F849 (childhood autism, atypical autism, Asperger syndrome, and pervasive developmental disorder-unspecified, respectively). Subjects were considered a case if any of these codes were present.

Controls were defined as individuals without ASD admission diagnoses. Ten controls per case were individually matched on month and year of birth, assuring the same follow-up period for cases and controls, and thus the same opportunity to be diagnosed.

Exposure

Pharmacologic exposure information was drawn from the Drug Prescription Register, which records all dispensed prescribed medication from any pharmacy, except hospital dispensaries in Denmark. Therefore, we were unable to capture B2AR agonist use as a tocolytic in the third trimester. The drug codes included in the exposure definition are R03AC02, R03AC03, R03AC04, R03AC05, R03AC12, R03AC13, R03CC02, R03CC03, and R03CC12. We extracted information regarding personal identification number, dispense date, drug code (the World Health Organization Anatomic Therapeutic Chemical classification system), name of drug, number of packaged dispensed, and the number of defined daily dosage per package.[32] The exposure windows were defined as preconception (90 days before the estimated CD), first trimester (within 90 days after the estimated CD), second trimester (within 90–180 days after estimated CD), and third trimester (180 days after the estimated CD to delivery date). A child was considered exposed if the dispense date fell within the specified exposure period or the days supplied overlapped any portion of the exposure period or interest. Children born to women who did not fill a prescription for B2AR agonist drugs for the entire period from 90 days before estimated CD through the date of delivery were considered unexposed. To calculate duration of use, the number of defined daily dosages in each dispensed package for the period falling within a given exposure window, based on dispensed date, were summed. Duration was dichotomized into 2 categories representing use for more or less than half a trimester (1–45 days and ≥45 days) in each exposure window.

Covariates

Covariates were derived from available health registers and the social registers of Statistics Denmark. They included parental age, psychiatric history, mother's number of live births, child's gestational age, birth weight, obstetric complications, and family socioeconomic status (a combination of parental income and the highest level of education attained). Gestational age was given in days from self-reported last menstrual period and corrected using an ultrasound if the last menstrual period was uncertain. The variable for psychiatric history included schizophrenia-like psychosis (*ICD, Eighth Revision* [*ICD-8*]: 295, 297, 298.39, 301.83; *ICD-10*: F20–F25, F28–F29), affective disorder (*ICD-8*: 296, 298.09, 298.19, 300.4; *ICD-10*: F30–F39), substance abuse (*ICD-8*: 303, 304; *ICD-10*: F10–F19.9 excluding F1×0.0) and any other psychiatric disorders. These covariates were chosen a priori based on literature suggesting their role as risk factors for ASD.[33–40] Inpatient and outpatient maternal asthma was identified using *ICD-8* codes (493.00 [Asthma bronchiale], 493.01 [Status asthmaticus], 493.02 [Asthma bronchila cum rhinitide allergica], 493.08 [Asthma aliud definitum], and 493.09 [Asthma]) and *ICD-10* codes (J45 [Asthma], J45.0 [Asthma bronchilae allergicum], J45.1 [Asthma bronchiale non allergicum], J45.8 [Mixed asthma], J45.9 [Asthma without specification], J46 [Status asthmaticus], and J46.9 [Status asthmaticus]) present in the register at any time before the delivery of the child.

Analytic Method

Conditional logistic regression analysis estimated associations of maternal B2AR agonist drug exposure variables with the children's ASD diagnoses. Because none of the covariates resulted in a ≥10% change in unadjusted log ORs when added individually, both parental age and gender of the child were forced in all adjusted models as covariates. Parental age and gender have been associated with ASD in other studies and provided a reasonable alternative to the unadjusted model. To address confounding by indication, we included maternal asthma as a covariate and additionally restricted sample to mothers with a history of asthma.

We performed a sensitivity analysis to explore the potential impact of underreporting of B2AR use and maternal asthma in the register.[41] Following previous analyses,[41,42] we reestimated effect estimates under plausible sensitivity and specificity for both B2AR use and maternal asthma diagnosis. Specifically, for B2AR use we simulated B2AR use at 4%, a rate observed in other Nordic countries.[43] Because we hypothesized that possible misclassification was nondifferential by outcome, we assumed equal exposure measurement sensitivity and specificity among cases and controls at 0.73 and 1.0, respectively. We simulated an increase in asthma prevalence from the observed prevalence of 1.3% to a prevalence of 2%, the prevalence estimate suggested by a previous study[9] of hospital data from the County of North Jutland in Denmark, also assuming that misclassification was nondifferential with respect to outcome. Specificity was assumed to be 1.0, and sensitivity was set to 0.66 to reflect the level of underreporting needed consistent with the assumed true asthma prevalence of 2%.

RESULTS

Children with ASD (n = 5200) were more likely than controls (n = 52 000) to be male, have a higher parental age, and have a mother with an asthma diagnosis before the birth of the child (Table 1). The frequency of B2AR agonist drug exposure in the pregnancy period was 3.7% (190) for cases and 2.9% (1489) in

controls. In addition, there were 83 cases (1.6%) and 673 controls (1.3%) with mothers who had a diagnosis for asthma during the pregnancy period.

We found an increased risk with exposure to B2AR agonist drugs during pregnancy (OR 1.3; 95% CI: 1.1–1.5), after controlling for child birth year and month, gender of the child, and parental age (Table 2). Trimester-specific effect estimates were similar to each other. While attempting to account for confounding by indication, adjustment for maternal asthma did not substantively change effect estimates, as seen by comparing models 1 and 2 in Tables 2, 3, and 4. Analyses restricting to only 863 mothers who had a diagnosis of asthma (Table 4) suggested an increased risk on average, although the 95% CI around the odds ratio included the null (1.3; 95% CI: 0.8–2.1). Sensitivity analyses suggested that misclassification of B2AR exposure and asthma diagnosis did not greatly influence B2AR effect estimates, for example, upon simulating an increase in maternal asthma prevalence from the observed 1.3% to the posited 2%, the B2AR effect estimate became 1.2 (95% CI: 1.1–1.5; see Supplemental Appendix).

The duration of use was similar between cases and controls within each period (Table 1). In conditional logistic regression results (Table 3), the point estimates for the longer duration exposure category (>45 days) tended to be larger than that for the shorter duration exposure category (1–45 days) during the preconception and first and second trimesters periods. However, the confidence limits for longer duration exposure effects overlapped substantively with those for shorter duration exposure.

TABLE 1 Demographics and Characteristics of Matched Study Population Exposed to B2AR Agonist During Pregnancy

	ASD Cases	Controls
Number (%)	5200 (9.1)	52 000 (90.9)
Maternal age, y		
≤25	814 (15.7)	7461 (14.4)
26–30	1747 (33.6)	18 763 (36.1)
31–35	1738 (33.4)	17 886 (34.4)
≥36	901 (17.3)	7790 (15.2)
Paternal age		
≤29 y	1269 (24.4)	13 089 (25.2)
29–39	2666 (51.3)	27 925 (53.8)
40–49	532 (10.2)	4276 (8.2)
50–54	36 (0.7)	284 (0.6)
≥55	20 (0.4)	118 (0.2)
Missing	677 (13.0)	6308 (12.2)
Child gender, male	4267 (82.1)	26 406 (50.7)
Maternal asthma, yes	83 (1.6)	673 (1.3)
Family socioeconomic status		
Low	831 (16.0)	6624 (12.7)
Medium	2712 (52.2)	26 298 (51.0)
High	1657 (31.9)	19 066 (36.3)
Missing	0 (0.0)	12 (0.0)
Duration of B2AR use, d		
Minimum	2.0	1.0
25th percentile	15.0	15.0
Median	50.0	50.0
75th percentile	72.0	65.0
Maximum	296.0	301.0

DISCUSSION

Our results suggest that exposure to B2AR agonist during the prenatal period was associated with increase in risk for ASD compared with those who were unexposed. These findings are consistent with other epidemiologic evidence regarding in utero exposure to B2AR agonist drugs and risk for ASD.[12,13] Our analyses using sample restriction and adjustment for maternal asthma suggest that maternal B2AR agonist drug use, independent of indication, was associated with increased risk of ASD. Findings here also did not offer strong evidence for a particular exposure vulnerability window. Similar elevated risk was observed across the first, second, and third

TABLE 2 Effect Estimates for Prenatal B2AR Agonist Drug Exposure and Risk for ASD

No. of Cases	Exposure Period	Exposed Counts (%)		Unadjusted OR[a] (95% CI)	Adjusted Model 1 OR[b] (95% CI)	Adjusted Model 2 OR[c] (95% CI)
		Cases	Controls			
5112	Preconception	102 (2.0)	816 (1.6)	1.3 (1.0–1.5)*	1.3 (1.0–1.6)*	1.3 (1.0–1.6)*
5200	Pregnancy	190 (3.7)	1489 (2.9)	1.3 (1.1–1.5)*	1.3 (1.1–1.5)*	1.3 (1.1–1.5)*
5096	First trimester	86 (1.7)	756 (1.5)	1.1 (0.9–1.4)	1.2 (0.9–1.5)	1.1 (0.9–1.4)
5116	Second trimester	106 (2.1)	765 (1.5)	1.4 (1.1–1.7)*	1.4 (1.1–1.7)*	1.5 (1.1–1.7)*
5117	Third trimester	107 (2.1)	805 (1.6)	1.3 (1.1–1.6)*	1.4 (1.2–1.8)*	1.4 (1.1–1.7)*

Reference: no exposure during any exposure period. *$P < .05$.

[a] Controls for matching variables of child year and month of birth through conditioning.

[b] ORs adjusted for parental age and gender of the child (and conditions on matching variables of child birth month and year).

[c] ORs adjusted for parental age, gender of the child, history of maternal asthma (and conditions on matching variables of child birth month and year).

trimester, and all effect estimates had overlapping confidence intervals.

As with a previous study,[13] we observed elevated risk associated with the preconception as well as with prenatal exposure. The reasons, outside of chance, for a preconception association could include the following: misattribution of early prenatal exposure to the preconception window, existence of some mechanism such as cellular reprogramming[6] for persistence of effect into the prenatal period (outside of bioaccumulation because B2AR agonist drugs have half-life of <7 hours[44]), or imperfect confounder control. In addition, epidemiologic studies thus far that have looked at duration of B2AR use report the highest risk with prolonged use (>2 days),[13] which is also consistent with our findings, although our definition of duration differed from that used previously.

There was a possibility for exposure and indication misclassification, although our sensitivity analysis did not suggest this substantively influenced in the B2AR effect estimates. Analyses also assumed that the mothers used all prescribed medication, but we have no information of when the prescribed medication was taken. Therefore, it is possible that portions of prescriptions during the study period were unused (leading to us overestimate of exposure) or that mothers used B2AR agonist drugs prescribed before the preconception period or during a previous trimester (leading to underestimate of exposure). Overestimation of the exposure could lead to an underestimate of effect estimate; however, we would expect this to be consistent throughout each exposure window. The impact of exposure misclassification is not possible to predict a priori in this setting.

Our exposure data were restricted to only outpatient prescriptions. Therefore, we did not have information on in-hospital use of B2AR agonist drugs, which limits our ability to study maternal B2AR agonist drugs used as a tocolytic because inpatient prescription is most common. Although most prescriptions for B2AR agonist drugs including those used for asthma indications are obtained in an outpatient setting, these drugs are also prescribed as a tocolytic for in-hospital use. B2AR agonist drug exposure due to tocolytic use would most likely occur in the third trimester. Therefore, if a B2AR agonist like terbutaline is administered as a tocolytic and this does, as previously reported,[13] increase ASD risk, our estimates of third trimester associations may in fact underestimate the true association. Our findings on outpatient exposure in the third trimester were consistent with those

TABLE 3 Effect Estimates for Any ASD Associated With Duration of Use of Prenatal Exposure to B2AR Agonists

Exposure Period	Models		
	Unadjusted OR[a] (95% CI)	Adjusted Model 1 OR[b] (95% CI)	Adjusted Model 2 OR[c] (95% CI)*
Preconception			
1–45 d	1.2 (0.9–1.5)	1.2 (0.9–1.5)	1.2 (0.9–1.5)
≥45 d	1.4 (1.0–2.0)*	1.5 (1.0–2.1)*	1.5 (1.1–2.1)*
First trimester			
1–45 d	1.0 (0.7–1.4)	1.1 (0.8–1.5)	1.1 (0.8–1.5)
≥45 d	1.4 (1.0–1.1)	1.3 (0.9–1.8)	1.2 (0.8–1.7)
Second trimester			
1–45 d	1.2 (0.9–1.7)	1.2 (0.9–1.7)	1.2 (0.9–1.6)
≥45 d	1.5 (1.2–2.0)*	1.5 (1.2–2.0)*	1.5 (1.1–2.0)*
Third trimester			
1–45 d	1.3 (1.0–1.7)*	1.4 (1.1–1.8)*	1.4 (1.1–1.8)*
≥45 d	1.4 (1.0–1.9)*	1.4 (1.1–2.0)*	1.4 (1.0–2.0)*

The reference group is unexposed. The cutpoint at 45 d was determined because it was median number of days in each 90-d exposure period for preconception and each trimester. *$P < .05$.

[a] Controls for matching variables of child year and month of birth through conditioning.

[b] ORs adjusted for parental age and child gender (and conditions on matching variables of child birth month and year).

[c] ORs adjusted for parental age, child gender, history of maternal asthma (and conditions on matching variables of child birth month and year).

TABLE 4 Effect Estimates for Any ASD Associated With Any Prenatal Exposure to B2AR Restricted to Mothers With Asthma

Exposure Period	Exposed: N(%)		Models		
	ASD Cases	Controls	Unadjusted OR (95% CI)	Adjusted Model 1 OR[a] (95% CI)	Adjusted Model 2 OR[b] (95% CI)
Preconception	25 (37.9), *n* = 66	234 (35.5), *n* = 660	1.1 (0.7–1.9)	1.2 (0.7–2.1)	1.2 (0.7–2.1)
Pregnancy	42 (50.6), *n* = 83	363 (43.7), *n* = 830	1.3 (0.8–2.1)	1.4 (0.9–2.3)	1.4 (0.9–2.3)
First Trimester	29 (41.4), *n* = 70	241 (34.4), *n* = 700	1.4 (0.8–2.3)	1.3 (0.8–2.3)	1.3 (0.8–2.2)
Second Trimester	28 (40.6), *n* = 69	228 (33.0), *n* = 690	1.4 (0.8–2.3)	1.6 (0.9–2.7)	1.6 (0.9–2.7)
Third Trimester	32 (43.8), *n* = 73	254 (34.8), *n* = 730	1.5 (0.9–2.5)	1.6 (0.9–2.8)	1.7 (1.0–2.9)

The reference group had no exposure during the exposure period of interest. Maternal asthma: *ICD-10* codes J45, J45.0, J45.1, J45.8, J45.9, J46, J46.9 ; *ICD-8* codes: 493.00, 493.01, 493.02, 493.08, 493.09.

[a] ORs were adjusted for parental age and child gender (matching on child birth month and year).

[b] ORs were adjusted for parental age, child gender, maternal asthma (matching on child birth month and year).

of Croen et al, who considered both inpatient and outpatient exposure and also observed a third trimester association.[13]

As with most observational epidemiology, unmeasured confounding is a potential limitation. We were able to adjust for numerous covariates that were available in the Danish register. However, potential confounders not represented in the register include in-home environmental exposures and pollutants, which may be associated with ASD[45] but are unlikely to be strongly associated with medication use.

Although our results add to the limited knowledge on prenatal pharmacological exposures as potential ASD risk factors and suggest further consideration of other exposures and vulnerabilities that share mechanistic similarities with B2AR agonists, one must be cautious when considering the public health implications of our current work. Under the assumptions that the association we observed is causal and precisely calculated, we estimate that <1% of ASD cases in the population can be attributed to prenatal B2AR agonists drug exposure (the population attributable fraction[46] for any B2AR agonists exposure estimated based on an OR of 1.3 and the 2.9% observed exposure prevalence). Given this, with respect to individual decisions regarding B2AR agonist drug use during pregnancy, because uncontrolled asthma in pregnancy has been associated with poor birth outcomes,[28,47] any potential modestly increased ASD risk needs to be carefully balanced against the established benefits of indicated medication use.

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ABBREVIATIONS

ASD: autism spectrum disorders
B2AR: β-2-adrenergic receptor
CD: conception date
CI: confidence interval
ICD: *International Classification of Diseases*
OR: odds ratio

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