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Antidepressant Use During Pregnancy and Childhood Autism Spectrum Disorders

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Context: The prevalence of autism spectrum disorders (ASDs) has increased over recent years. Use of antidepressant medications during pregnancy also shows a secular increase in recent decades, prompting concerns that prenatal exposure may contribute to increased risk of ASD.

Objective: To systematically evaluate whether prenatal exposure to antidepressant medications is associated with increased risk of ASD.

Design: Population-based case-control study. Medical records were used to ascertain case children and control children and to derive prospectively recorded information on mothers' use of antidepressant medications, mental health history of mothers, and demographic and medical covariates.

Setting: The Kaiser Permanente Medical Care Program in Northern California.

Participants: A total of 298 case children with ASD (and their mothers) and 1507 randomly selected control children (and their mothers) drawn from the membership of the Kaiser Permanente Medical Care Program in Northern California.

Main Outcome Measures: ASDs.

Results: Prenatal exposure to antidepressant medications was reported for 20 case children (6.7%) and 50 control children (3.3%). In adjusted logistic regression models, we found a 2-fold increased risk of ASD associated with treatment with selective serotonin reuptake inhibitors by the mother during the year before delivery (adjusted odds ratio, 2.2 [95% confidence interval, 1.2-4.3]), with the strongest effect associated with treatment during the first trimester (adjusted odds ratio, 3.8 [95% confidence interval, 1.8-7.8]). No increase in risk was found for mothers with a history of mental health treatment in the absence of prenatal exposure to selective serotonin reuptake inhibitors.

Conclusion: Although the number of children exposed prenatally to selective serotonin reuptake inhibitors in this population was low, results suggest that exposure, especially during the first trimester, may modestly increase the risk of ASD. The potential risk associated with exposure must be balanced with the risk to the mother or fetus of untreated mental health disorders. Further studies are needed to replicate and extend these findings.

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AUTISM SPECTRUM DISORDERS (ASDs) are neurodevelopmental disorders that are evident in early childhood and characterized by pervasive impairments in social interaction and communication and by restricted and stereotyped patterns of behavior. Data from twin and family studies suggest a strong genetic component in the etiology of autism,[1-4] and results from neuropathology and brain imaging studies provide evidence for dysregulation in normal brain development during the prenatal or early postnatal period.[5,6] Since the first epidemiologic survey was conducted in 1966,[7] the reported prevalence of autism has increased dramatically, from 4 to 5 cases per 10 000 population in 1966 to approximately 100 cases per 10 000 population (1%) today.[8,9] While at least some of this observed increase in prevalence can be attributed to changing diagnostic standards, availability of services, and greater public awareness, there is considerable scientific and public concern about environmental factors that may contribute to autism risk, most likely in interaction with genetic factors.

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Among the numerous secular trends that have occurred during the period of the recognized increase in autism prevalence is an increase in the use of antidepressant medications during pregnancy: from a range of approximately 1% to 6% in the early to mid-1990s to as high as 7% to 13% in more recent years.[10-13] Based on their efficacy and superior safety profile, selective serotonin reuptake inhibitors

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(SSRIs) have become the first-line treatment for depression and other psychiatric conditions, including anxiety and obsessive-compulsive disorders. Selective serotonin reuptake inhibitors and other antidepressant medications cross the placenta[10-12] and are secreted in breast milk,[12,13] thus raising concerns about adverse effects from fetal and infant exposure. Atypical serotonin patterns in blood specimens obtained from individuals diagnosed with ASD and their family members have been consistently reported from multiple studies,[14] but the underlying biologic pathways that may link serotonin in peripheral blood with phenotypic expression of ASD remain to be elucidated. As called for in a recent article by Hadjikhani,[15] systematic study of ASD and prenatal exposure to SSRIs and other antidepressant medications is clearly needed. To our knowledge, no prior studies have addressed this important question.

Studies evaluating prenatal antidepressant exposure and other pediatric outcomes, such as major congenital malformations[12,16-19] and other adverse obstetric or neonatal outcomes, have shown weak and inconsistent associations.[16,18,20-22] Poor neonatal adaptation has been reported for exposure late in pregnancy.[18,23,24] Directly relevant to concerns about a possible association with ASD, very few studies have evaluated the possible effects of prenatal exposure on longer-term outcomes, such as milestone achievement, cognitive skills, and behavioral outcomes. Although the majority of such studies have found no difference between prenatally exposed and unexposed children, some reports indicate possible subtle effects on motor development and control[25] and differences in reaching milestones.[26] Experimental studies using rodent models indicate that transient inhibition of the serotonin transporter with the SSRI fluoxetine hydrochloride during early brain development has consequences for some measured behaviors later in life.[27,28]

Evaluation of fetal exposure to SSRIs and other antidepressant medications as a potential risk factor for ASD and other neurodevelopmental conditions is complicated by the difficulty in distinguishing the effects of medication exposure from the effects of the underlying condition that led to treatment. Making this distinction is especially important for the study of autism because a prior history of psychiatric disorders, including depression, has been reported to be more common among mothers of infants later diagnosed with autism than among mothers of unaffected children, suggesting an underlying, preexisting genetic risk.[29-32] We conducted a large, population-based case-control study with prospective ascertainment of mothers' prescription drug use and history of mental health disorders to investigate the association between antidepressant use by mothers during pregnancy and subsequent diagnoses of ASDs in children.

METHODS

The study sample was drawn from the Childhood Autism Perinatal Study, a large case-control study of prenatal, perinatal, and neonatal risk factors for ASDs set within the Kaiser Permanente Medical Care Program in Northern California (KPNC), which is a large integrated health care organization that provides care for more than 3.2 million residents and approximately 25% of births in 14 northern California counties. Except for the lowest and highest income earners, the KPNC membership is representative of the total population in the region.[33]

Details of case and control selection have been described previously.[34] Briefly, all infants born at a KPNC facility between January 1995 and June 1999 and who remained health plan members for at least 2 years following birth were eligible for inclusion (n=88 163). On the basis of the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), children with at least 1 diagnosis of autism (*ICD-9-CM* code 299.0), Asperger syndrome (*ICD-9-CM* code 299.8), or pervasive developmental disorder not otherwise specified (*ICD-9-CM* code 299.8) recorded in the KPNC outpatient clinical databases between January 1995 and November 2002 were considered case children (n=420). Previous studies, which we have conducted within the KPNC health care system, indicate a high level of diagnostic validity for these case ascertainment procedures.

Children without an ASD diagnosis were randomly sampled from the remaining cohort of live births at a ratio of 5 control children per 1 case child. Control children (n=2100) were frequency matched to case children by sex, birth year, and hospital of birth.

Because we were interested in examining characteristics of the mother in relation to autism risk in the offspring, we restricted the analysis to 1 child per mother, selecting the case child for women with both a case and a control child in the original study sample and randomly sampling 1 child for inclusion for other women with 2 case or control children (13 case mothers and 5 control mothers). We further restricted the sample to children (73% of initial cases and 72% of initial controls) whose mothers were KPNC members with full pharmacy benefits in the year before delivery (ie, 3 months prior to conception and during each trimester of pregnancy), and we excluded 16 controls whose medical records contained an ASD diagnosis recorded after initial control selection. The final analytic file included all remaining cases and controls from the original study sample.

All inpatient and outpatient prescriptions for antidepressants dispensed at a KPNC pharmacy in the 3 months before the last menstrual period (LMP) through the date of delivery of the study child were identified from the Pharmacy Information Management System. Antidepressants were classified as (1) SSRIs (citalopram hydrobromide, fluoxetine, fluvoxamine maleate, paroxetine hydrochloride, and sertraline hydrochloride); (2) dual-action antidepressants (nefazodone hydrochloride, trazodone hydrochloride, and venlafaxine hydrochloride), including serotonin-noradrenergic-reuptake inhibitors, noradrenergic and specific serotoninergic antidepressants, and noradrenaline-reuptake inhibitors; and (3) tricyclic antidepressants (amitriptyline hydrochloride, desipramine hydrochloride, doxepin hydrochloride, imipramine hydrochloride, nortriptyline hydrochloride, and protriptyline hydrochloride).

In the year before delivery, 4 exposure times were defined: preconception (3 months prior to the estimated LMP), first trimester (first 90 days after the LMP), second trimester (91-180 days after the LMP), and third trimester (181 days after the LMP to date of delivery). The date that the prescription was dispensed and the number of days for which the medication was supplied were used to determine exposure status during each time period. Exposure to antidepressants during a given time period was assumed if a prescription was dispensed during that time period or if the number of days for which the medication was supplied overlapped some portion of the time period. Women were considered "unexposed" if they had no dispensed antidepressant prescriptions and no supply overlap during the entire time period from 3 months prior to the LMP through the date of delivery. The estimated LMP was as re-

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Table 1. Characteristics of the Study Population From the Kaiser Permanente Medical Care Program in Northern California

Characteristic	No. (%) ASD Cases (n=298)	No. (%) Controls (n=1507)	*P* Value
Mothers			
Age, mean (SD), y	31.60 (5.19)	30.19 (5.74)	<.001
Race/ethnicity			
White, non-Hispanic	163 (54.7)	700 (46.4)	.04
White, Hispanic	40 (13.4)	307 (20.4)	
Black	27 (9.1)	151 (10.0)	
Asian	28 (9.4)	149 (9.9)	
Other	40 (13.4)	200 (13.3)	
Education			
<High school[a]	10 (3.4)	115 (7.6)	<.001
High school[b]	51 (17.1)	407 (27.0)	
College	166 (55.7)	755 (50.1)	
Postgraduate	70 (23.5)	209 (13.9)	
Unknown	1 (0.3)	21 (1.4)	
Parity			
Primiparous	124 (41.6)	636 (42.2)	.59
Multiparous	174 (58.4)	866 (57.5)	
Unknown	0 (0)	5 (0.3)	
Children			
Male sex	247 (82.9)	1214 (80.6)	.35
Birth weight <2500 g	25 (8.4)	79 (5.2)	.03
Gestational age <37 wk	34 (11.4)	110 (7.3)	.02
Birth year			
1995	86 (28.9)	411 (27.3)	.69
1996	66 (22.1)	384 (25.5)	
1997	63 (21.1)	286 (19.0)	
1998	60 (20.1)	320 (21.2)	
1999	23 (7.7)	106 (7.0)	

Abbreviation: ASD, autism spectrum disorder.
[a] Includes elementary and middle school and some high school.
[b] High school graduate.

Table 2. Type of Antidepressant Prescribed in the Year Prior to Delivery of Study Children From the Kaiser Permanente Medical Care Program in Northern California, 1995-1999

Type of Antidepressant	No./Total No. (%) ASD Cases	No./Total No. (%) Controls
Any	20/298 (6.7)	50/1507 (3.3)
SSRIs	15/298 (5.0)	34/1507 (2.3)
Fluoxetine hydrochloride	10/298 (3.4)	17/1507 (1.1)
Paroxetine hydrochloride	13/298 (4.4)	25/1507 (1.7)
Sertraline hydrochloride	15/298 (5.0)	34/1507 (2.3)
Fluvoxamine maleate	10/298 (3.4)	17/1507 (1.1)
TCAs	5/298 (1.7)	17/1507 (1.1)
DAAs	2/298 (0.7)	8/1507 (0.5)
SSRIs only	13/20 (65.0)	25/50 (50.0)
SSRIs plus TCAs and/or DAAs	2/20 (10.0)	9/50 (18.0)
TCAs and/or DAAs	5/20 (25.0)	16/50 (32.0)

Abbreviations: ASD, autism spectrum disorder; DAAs, dual-action antidepressants; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclics.

corded in the medical records for women with regular menstrual periods and if in 7-day agreement with a first trimester ultrasonography; for other women, the estimated LMP was derived from a first trimester ultrasonography.

To address the analytic concern about treatment vs underlying condition for which the treatment was prescribed, the mothers' psychiatric conditions diagnosed at any time preceding delivery were identified from inpatient and outpatient databases. These included major depressive disorder (*ICD-9-CM* codes 296.2, 296.3, and 311), anxiety or phobia (*ICD-9-CM* codes 300.0 and 300.2), bipolar disorder (*ICD-9-CM* codes 296.4-296.8), obsessive-compulsive disorder (*ICD-9-CM* code 300.3), adjustment disorder (*ICD-9-CM* code 309), and schizophrenic disorders (*ICD-9-CM* code 295). Mental health diagnoses were typically made by psychiatric or internal medical specialists before the index pregnancies and by psychiatric or women's health specialists during pregnancy. Other relevant medical and utilization history data were obtained from health plan files; data on the mothers' demographic characteristics (self-reported age at delivery, race/ethnicity, educational attainment, and parity) and data on infants' characteristics (birth year, sex, birth weight, and gestational age) were obtained from birth certificates.

The characteristics of cases and controls were compared using the χ^2 test (for categorical variables), the Fisher exact test (for proportions), or the 2-sample *t* test (for continuous variables). Unconditional logistic regression analysis was conducted to estimate unadjusted and adjusted relative risks of ASD associated with antidepressant use by the mother during the year before delivery of the study child. Analyses by specific time periods during this 1-year interval compared women with prescriptions for antidepressants during a particular time period with women who were unexposed during the full 1-year interval before delivery of the study child. We considered a covariate to be a possible confounder of the association between antidepressant exposure and autism if it was associated either with the case or control status or with exposure status in this data set ($P<.05$), if it is a covariate for which we have a priori knowledge of associations with case or control status or with exposure status in the general population, or if it was a matching variable for control selection. With the exception of gestational age (which is highly correlated with birth weight but less reliably recorded in available medical records), all covariates that met 1 or more of these criteria were included as confounders in adjusted models. All variables were entered simultaneously, and all statistical tests were 2-tailed, with $P<.05$ considered to represent statistical significance. Further models were adjusted only for those covariates associated both with case or control status and with exposure status among control children. Models were also run with the exclusion of observations with missing data for covariates and for term births only.

To evaluate treatment with antidepressant medications independent of potential effects of the underlying condition for which treatment was prescribed, we included mental health history of the mother as a variable in selected logistic models. In addition, within the stratum of mothers with a mental health history (based on the *ICD-9-CM* codes cited), we evaluated whether antidepressant exposure in the year before delivery was associated with ASD risk in the children. All study procedures were approved by the institutional review board of KPNC and the California State Committee for the Protection of Human Subjects.

RESULTS

The final study population included 298 children with ASD and 1507 control children. The characteristics of the final study population (73% of initial cases and 72% of initial controls) are shown in **Table 1**. Mothers of children with ASD were slightly older, more often White non-Hispanic, and more highly educated. A higher propor-

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Table 3. Risk of Autism Spectrum Disorder Associated With Prescription for Antidepressants for Mothers in the Year Prior to Delivery of Study Children in the Kaiser Permanente Medical Care Program in Northern California, 1995-1999

Type of Antidepressant	No. (%)		OR (95% CI)	
	ASD Cases (n=298)	Controls (n=1507)	Crude	Adjusted[a]
Unexposed in year before delivery	278 (93.3)	1457 (96.7)	1.0 [Reference]	1.0 [Reference]
Any antidepressant	20 (6.7)	50 (3.3)	2.1 (1.2-3.6)	2.0 (1.2-3.6)
Any SSRI	15 (5.1)	34 (2.3)	2.3 (1.2-4.3)	2.2 (1.2-4.3)
SSRIs only	13 (4.5)	25 (1.7)	2.7 (1.4-5.4)	2.6 (1.3-5.4)
TCAs and/or DAAs	5 (1.8)	16 (1.1)	1.6 (0.6-4.5)	1.6 (0.5-4.5)

Abbreviations: CI, confidence interval; DAAs, dual-action antidepressants; OR, odds ratio; SSRI, selective serotonin reuptake inhibitors; TCAs, tricyclics.
[a] Adjusted for age (continuous), race/ethnicity, and education of mother; birth weight (continuous), sex, and birth year of child; and birth facility.

tion of case children had a birth weight of less than 2500 g, and more were delivered before 37 weeks of gestation. The proportion of male children, the proportion of children born in each study year, and the distribution of birth facilities were all similar between case children and control children owing to matching on these variables (data not shown).

Twenty case mothers (6.7%) and 50 control mothers (3.3%) had at least 1 prescription for an antidepressant in the year prior to the birth of the study child (**Table 2**). The majority of these case and control mothers were prescribed SSRIs (Table 2). Of the 20 case mothers who were prescribed an antidepressant medication, 13 (65%) were prescribed SSRIs only, 2 (10%) were prescribed an SSRI in combination with another antidepressant, and 5 (25%) were prescribed 1 or more non-SSRI antidepressants only. Of the 50 control mothers who were prescribed an antidepressant medication, 25 (50%) were prescribed SSRIs only, 9 (18%) were prescribed an SSRI in combination with another antidepressant, and 16 (32%) were prescribed 1 or more non-SSRI antidepressants only.

Among the children with ASD, the median age at ASD diagnosis for those with prenatal SSRI exposure was similar to that for those without prenatal SSRI exposure (3.6 vs 3.8 years of age; $P=.61$). The median number of ASD diagnoses recorded in electronic medical records was also similar between the 2 groups (5.0 vs 5.0; $P=.63$). After adjusting for maternal age, race/ethnicity, education, and child's birth weight, sex, birth year, and facility of birth, mothers of children subsequently diagnosed with ASD were twice as likely to have at least 1 antidepressant prescription in the year prior to delivery of the study child (**Table 3**). When compared with women with no antidepressant prescription during this period, women with a prescription for an SSRI were more than twice as likely to have a child later diagnosed with ASD (any SSRI: adjusted odds ratio [AOR], 2.2 [95% confidence interval {CI}, 1.2-4.3]; SSRI only: AOR, 2.6 [95% CI, 1.3-5.4]); no association was seen for the small group of women who were prescribed a non-SSRI antidepressant only (Table 3).

Owing to the small number of women prescribed antidepressants other than SSRIs and the lack of an association of other antidepressants with ASD risk, all remaining analyses were restricted to the presence or absence of treatment with SSRIs (with or without other antidepressants). Unless otherwise noted, women were considered to be "unexposed" if they had no dispensed SSRI and no supply overlap during the year before delivery. In adjusted models with women not exposed to SSRIs as the reference group (**Table 4**, model 1), risk of ASD was significantly associated with an SSRI prescription during the preconception period, during the first trimester of pregnancy, and anytime during the year. For the second and third trimesters, during which fewer numbers of women were prescribed an SSRI, point estimates were also elevated but did not reach statistical significance (Table 4, model 1). Results were similar when models were adjusted only for maternal race/ethnicity, the only covariate associated with both case or control status and exposure status (data not shown).

TREATMENT VS INDICATION

Of the 298 case mothers, 10 (3.4%) had a diagnosis of depression, and 25 (8.4%) had a history of a mental health disorder in the year prior to delivery (for 11 of these 25 women [44%], the first mental health diagnosis occurred during the index pregnancy). Of the 1507 control mothers, 41 (2.7%) had a diagnosis of depression, and 99 (6.6%) had a diagnosis of a mental health disorder (for 49 of these 99 women [49%], the first mental health diagnosis occurred during the index pregnancy). When logistic models were adjusted for a history of depression during the year prior to delivery (Table 4, model 2) or, more generally, a history of any mental health disorder during the year prior to delivery (Table 4, model 3), SSRI exposure during the first trimester remained significantly associated with risk of ASD, as was a history of SSRI exposure anytime during the year before delivery. In contrast, no association was seen between risk of ASD and the indication for treatment (ie, the mother having a history of depression [model 2] or a history of any mental health disorder [model 3]) for any time period in the year before delivery (Table 4). Results were similar when history of depression or any mental health disorder was expanded to include diagnoses recorded at any time preceding pregnancy (data not shown).

To further evaluate whether the observed association between prenatal SSRI exposure and ASD risk could be attributed to SSRI treatment rather than the indication for treatment, we conducted an analysis restricted to the subgroup of women with a history of a mental health

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Table 4. Risk of Autism Spectrum Disorder Associated with Prescription for Selective Serotonin Reuptake Inhibitors for Mothers in the Year Prior to Delivery of Study Children in the Kaiser Permanente Medical Care Program in Northern California, 1995-1999

	ASD Cases, No.	Controls, No.	AOR (95% CI)		
			Model 1[a]	Model 2[b]	Model 3[c]
No SSRI in year before delivery	283	1473	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Preconception period	13	31			
SSRI use			2.1 (1.1-4.2)	2.3 (1.0-5.2)	1.9 (0.9-4.2)
Maternal illness[d]				0.9 (0.3-2.2)	1.1 (0.7-2.0)
First trimester	14	19			
SSRI use			3.8 (1.8-7.8)	4.1 (1.7-9.8)	3.5 (1.5-7.9)
Maternal illness[d]				0.9 (0.3-2.2)	1.1 (0.6-2.0)
Second trimester	5	13			
SSRI use			1.9 (0.7-5.6)	1.8 (0.5-6.3)	1.5 (0.5-5.0)
Maternal illness[d]				1.1 (0.4-3.2)	1.3 (0.7-2.3)
Third trimester	6	11			
SSRI use			2.9 (1.0-8.0)	2.4 (0.7-8.0)	2.2 (0.7-6.9)
Maternal illness[d]				1.3 (0.5-3.5)	1.4 (0.8-2.4)
Year before delivery	15	34			
SSRI use			2.2 (1.2-4.2)	2.5 (1.1-5.5)	2.1 (1.0-4.4)
Maternal illness[d]				0.8 (0.3-2.0)	1.1 (0.6-1.9)

Abbreviations: AOR, adjusted odds ratio; ASD, autism spectrum disorder; CI, confidence interval; SSRI, selective serotonin reuptake inhibitor.
[a] Adjusted for age (continuous), race/ethnicity, and education of mother; birth weight (continuous), sex, and birth year of child; and birth facility.
[b] Adjusted for all variables in model 1 and mother's history of depression in year before delivery.
[c] Adjusted for all variables in model 1 and mother's history of any mental health disorders in year before delivery.
[d] History of depression in year before delivery for model 2 and history of any mental health disorder in year before delivery for model 3.

Table 5. Severity of Mental Health Condition Among Mothers Using Selective Serotonin Reuptake Inhibitors in the Year Before Delivery at the Kaiser Permanente Medical Care Program in Northern California, 1995-1999

	Mean (SD)		
	ASD Cases With Prenatal SSRI Exposure (n=15)	Controls With Prenatal SSRI Exposure (n=34)	*P* Value[a]
Psychiatric hospitalizations,[b] No. (%) of mothers	1 (6.7)	6 (17.6)	.41
Psychiatric hospitalizations[c]	0.07 (0.26)	0.21 (0.48)	.19
SSRI prescriptions[d]	8.2 (7.6)	5.6 (6.0)	.20
Days' supply of SSRI[e]	256.53 (202.86)	222.03 (216.66)	.60

Abbreviations: ASD, autism spectrum disorder; SSRI, selective serotonin reuptake inhibitors.
[a] Using the Fisher exact test.
[b] Ever hospitalized for inpatient psychiatric care before date of delivery.
[c] Number of inpatient psychiatric stays before date of delivery.
[d] Number of SSRI prescriptions between January 1, 1994, and date of delivery.
[e] Days' supply of SSRI prescriptions (no overlap) between January 1, 1994, and date of delivery.

disorder in the year before delivery (25 case mothers and 99 control mothers). Risk of ASD associated with SSRI use anytime during this year was somewhat elevated in this subgroup but did not reach statistical significance (OR, 1.6 [95% CI, 0.6-4.0]) in unadjusted models, perhaps owing to small numbers. The small number of women precluded analyses that were adjusted for covariates or limited to women with a history of depression during this year.

OTHER POSSIBLE CONFOUNDERS

Although we found no association between ASD and a history of depression or a history of any mental health disorder in models that also included a term for SSRI exposure (Table 4, models 2 and 3), it is possible that women who were prescribed SSRIs during the year before delivery had a more severe underlying condition that accounts for our finding of an association between SSRI exposure and risk of ASD. To assess this possibility, we examined selected indicators of severity among case and control mothers who were prescribed an SSRI in the year before delivery (**Table 5**). Among these women, both the proportion of women with previous psychiatric hospitalizations and the mean number of psychiatric hospitalizations were not significantly different for case mothers compared with control mothers, and neither was the mean number of SSRI prescriptions or the mean number of days' supply of SSRIs recorded in their medical records between January 1994 (when the pharmacy database was initiated) and date of delivery (Table 5) significantly different between case and control mothers.

We also performed a sensitivity analysis to examine the possibility that the association between a first tri-

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mester prescription for an SSRI and increased risk of ASD risk was a consequence of exposure misclassification. For this analysis, women whose last dispensed SSRI prescription predated the LMP (4 case mothers and 16 control mothers) were considered unexposed throughout pregnancy, even if the days' supply overlapped with the LMP. Risk of ASD associated with first trimester SSRI exposure remained elevated after adjustment for all demographic factors and for history of depression during the year before delivery (AOR, 4.5; [95% CI, 1.7-12.0]) or any mental health disorder during the year before delivery (AOR, 3.7 [95% CI, 1.5-9.3]).

In further analyses, we restricted the case group to those from simplex families (ie, only 1 child with ASD in the family; N = 279). Results were similar to those for the full study group (data not shown). Results were also similar to those obtained for the full study group when adjusted models excluded observations with missing data on mothers' education and/or parity (data not shown) and when restricted to term births (264 case children and 1397 control children) (data not shown).

COMMENT

In this population-based study with prospectively collected data and an analytic approach that simultaneously considered both SSRI exposure (treatment) and mental health history of mother (indication), we found an approximately 2-fold increased risk of ASD associated with treatment with SSRIs of the mother during the year before delivery and an approximately 3-fold increased risk associated with treatment during the first trimester, independent of indication. Additionally, we observed no increase in ASD risk associated with a history of mental health disorders after controlling for SSRI use during pregnancy. Despite the significant association, the number of women in this population exposed to SSRIs was modest, and the proportion of children with ASD in this population that can be statistically attributed to prenatal SSRI exposure is quite low: 2.1% for exposure during the year before delivery, and 2.3% for exposure during the first trimester.

To our knowledge, very few studies have evaluated possible associations between prenatal exposure to SSRIs and outcomes observable beyond the neonatal or early postnatal period, such as milestone achievement, cognitive skills, and behavioral characteristics. In general, studies have been hampered by small numbers of subjects and inadequate control for indication for treatment. Casper et al[25] reported possible subtle effects of in utero SSRI exposure on motor development and motor control in children 6 to 40 months of age. Pedersen et al[26] found some delays in reaching motor milestones with second or third trimester exposure to antidepressants (compared with children born to women with untreated depression), but delays were within the range of normal development and resolved by 19 months of age. In a recent review of studies to date, Gentile and Galbally[35] concluded that, despite the differences in the age of children studied, the measurements used, and the different aspects of neurodevelopment that were assessed, little evidence has emerged indicating differences between exposed and unexposed children.

There are a number of biologically plausible explanations for our finding of an association between prenatal SSRI exposure and ASD. Multiple prior studies have indicated that abnormalities in serotonin levels and serotoninergic pathways may play a role in autism.[36] Brain imaging studies have demonstrated atypical development in brain serotonin synthesis capacity in children with ASD[37,38] and abnormalities in serotonin receptor 2A binding in the cerebral cortex.[39] Other studies have reported elevated levels of serotonin in peripheral blood but low serotonin levels in the brain and decreased serotonin receptor binding in individuals with autism.[40-45] Abnormalities in serotonin-related genes have also been identified in studies of autism, although results are inconsistent across studies.[46,47] Pharmacological interventions with drugs acting on the serotonin receptor 2, including the SSRI fluoxetine, have shown improvements in some autistic behaviors in children[48-52]; other studies have shown that a decreased serotonin level in the central nervous system is associated with increased autistic symptoms.[53] A recent Cochrane review[54] concluded that there is no evidence that SSRIs are effective as a treatment for children with autism and that there is emerging evidence that they may cause harm.

In rodent models, transient inhibition of the serotonin transporter by the SSRI fluoxetine during early brain development produced abnormal emotional behaviors in adult animals, indicating a critical role for serotonin in the maturation of brain systems.[27,28,55,56] The effects of early exposure to SSRIs mimic the behavioral phenotype of mice genetically deficient in serotonin transporter expression.[27] During early fetal development when the blood-brain barrier is still incomplete, the main source of serotonin in rodents is of maternal origin, and maternal serotonin production in these animal models is an important determinant of normal development.[57] Whether there are parallel relationships in humans is not yet known. Collectively, these studies suggest the possibility that prenatal exposure to SSRIs may operate directly on the developing brain, perhaps selectively in fetuses with abnormalities in serotonin-related genes.

Our finding of a link between prenatal SSRI exposure and childhood ASDs is complicated by the difficulty in distinguishing the effects of medication exposure from the effects of the underlying condition that led to treatment. In other words, childhood ASDs could also be associated with a family history of psychiatric disorders; several population-based studies[29-32] have reported an association between family history of schizophrenia or affective disorders and ASD, suggesting a likely link through genetic pathways. However, because these studies[29-32] did not consider maternal treatment with and prenatal exposure to antidepressant medications, caution is warranted in interpreting their findings. In our study, we do not find an association between ASD and a history of depression or other mental health disorders on the part of the mother in the absence of treatment with SSRIs, suggesting that some of the previously reported findings of an association between ASD and family history of psychiatric disorders may be mediated by maternal treatment and fetal exposure.

Finally, physiologic changes related to a mother's stress or depression during pregnancy, in combination with SSRI

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exposure, may contribute to changes in fetal brain development leading to a later diagnosis of ASD. Maternal stress has been shown to decrease serotonin levels and the density of synapses in the hippocampus of offspring, and these changes in brain development have been linked to alterations in spatial learning, memory, and other changes in prenatally stressed rodents.[58,59] A recently reported experimental model demonstrates that the combined effect of maternal serotonin transporter genotype and prenatal stress may contribute to autistic-like behaviors in offspring.[60] Whether the combined effects of prenatal SSRI exposure and prenatal stress is etiologically related to ASD in humans remains to be elucidated.

To our knowledge, our study is the first to directly examine antidepressant use during pregnancy as a potential risk factor for childhood ASD. A substantial strength of our study is our reliance on data documented in medical records and thus recorded at the time of diagnosis or treatment, avoiding potential biases associated with the mothers' recall after diagnosis of ASD in the children. Mother-child pairs were not self-selected for our study but represent a population-based series of cases and controls from a large health care organization that serves approximately 30% of the population in a 14-county region of northern California. The frequency of in utero exposure to any antidepressant medication or specifically to SSRIs among control children in our study is very similar to that reported for deliveries during 1996 in a large study using automated administrative data from 7 health maintenance organizations in the United States,[61] is somewhat higher than that reported from the Netherlands from this time period,[62] and is lower than that reported from a Tennessee Medicaid population.[63]

Despite these strengths, several limitations need to be considered when interpreting the results of our study. Case or control status for most children in the study sample was not directly validated through clinical evaluations conducted for our study. In a prior study,[64] a subset of 50 children who ended up in our study underwent clinical evaluation with the Autism Diagnostic Interview–Revised[65] and the Autism Diagnostic Observation Schedule–Generic[66]; 94% of these children met criteria for ASD on both instruments, and 100% met criteria on at least one. Furthermore, validation studies conducted by the investigators that included a full review of diagnostic information recorded in KPNC medical records have demonstrated that at least 90% of children with an ASD diagnosis recorded in the KPNC electronic databases meet *DSM-IV*[67] criteria for autism.[34] Any misclassification with regard to case or control status would likely bias results toward the null, diminishing our ability to detect a true association between antidepressant use by the mothers and ASD in children. Another limitation of our reliance on medical records is that we were unable to validate actual use of antidepressants by the mothers during the time period of interest because we relied on documentation of dispensed prescriptions. Of particular concern is that first trimester exposure may be overestimated, although the sensitivity analysis that we conducted to address this concern did not alter our results. The half-lives of fluoxetine and norfluoxetine are relatively short, approximately 1 to 3 days and 7 to 15 days, respectively,[68] but antidepressants may be sequestered in lipophilic fetal tissues such as the brain, prolonging the period of exposure for the developing fetus after ingestion of the medication has been discontinued by the mother. In addition, we were not able to obtain information on any antidepressant medications that may have been obtained through non-KPNC pharmacies or other sources. A recent survey of self-reported behavior among adult members of KPNC indicated that only 2.6% obtained medications from out-of-system pharmacies, 4.5% from friends or family, and 3.3% from free samples. These findings do not represent mutually exclusive outside sources.[69]

Uncontrolled confounding by variables that we could not measure must also be considered. Of particular concern is that mothers of children with ASD in our study may be more likely to have prior children with ASD and also to have been treated with SSRIs to help them manage the challenges of parenting an affected child. Thus, our measure of SSRI exposure, particularly in mothers of children with ASD, may in part represent unmeasured underlying genetic risk. Interestingly, prenatal exposure to SSRIs remained associated with increased risk of ASD in simplex families. A further concern is that we have no data on breastfeeding, and children exposed in utero may also be those most likely to be exposed postnatally through breast milk. However, our finding of a stronger association with first trimester exposure suggests that substantial confounding by postnatal exposure is unlikely. Our findings may also be a result of detection bias, such that women who were prescribed SSRIs as treatment for anxiety may be more concerned about their child's development and more likely to have their child assessed, leading to more diagnoses of ASD.

For a small number of case and control mothers, the pharmacy records documented that SSRI prescriptions were dispensed in the year prior to delivery, but there was no corresponding mental health diagnosis recorded in the mothers' medical records for that time period (3 case mothers and 4 control mothers). This suggests either that some mental health diagnoses were not recorded in the mothers' medical records and/or that SSRIs were being prescribed for conditions other than the mental health diagnoses included in our study. For this reason, our findings with regard to mental health history adjusted for SSRI exposure should be interpreted with caution.

Our results suggest that prenatal exposure to SSRIs, especially during the first trimester, may modestly increase the risk of ASDs. The fraction of cases of ASD that may be attributed to use of antidepressants by the mother during pregnancy is less than 3% in our population, and it is reasonable to conclude that prenatal SSRI exposure is very unlikely to be a major risk factor for ASD. Although these findings indicate that maternal treatment with SSRIs during pregnancy may confer some risk to the fetus with regard to neurodevelopment, this potential risk must be balanced with the risk to the mother or fetus of untreated mental health disorders. We recommend that our findings be considered as preliminary and treated with caution, pending results from further studies designed to address the very complex question of whether prena-

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tal exposure to SSRIs may be etiologically linked to later diagnoses of ASDs in offspring.

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