

Prenatal SSRI Use and Offspring With Autism Spectrum Disorder or Developmental Delay

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KEY WORDS

selective serotonin reuptake inhibitors, autism, developmental delay, pregnancy, epidemiology

ABBREVIATIONS

ADI-R—Autism Diagnostic Interview—Revised
 ADOS—Autism Diagnostic Observation Schedule
 ASD—autism spectrum disorder
 CHARGE—Childhood Autism Risks from Genetics and the Environment
 CI—confidence interval
 DD—developmental delay
 OR—odds ratio
 SCQ—Social Communication Questionnaire
 SSRI—selective serotonin reuptake inhibitor
 TD—typical development

Dr Harrington conceptualized and designed the selective serotonin reuptake inhibitor (SSRI) study, acquired data, carried out the initial analyses, interpreted data, and drafted and revised the initial manuscript; Dr Lee conceptualized and designed the SSRI study, interpreted data, and reviewed and revised the manuscript; Drs Crum and Zimmerman interpreted data and reviewed and revised the manuscript; Dr Hertz-Picciotto conceptualized, designed, and obtained funding for the Childhood Autism Risks from Genetics and the Environment (CHARGE) Study, acquired and interpreted data, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Serotonin is critical in early brain development, creating concerns regarding prenatal exposure to factors influencing serotonin levels, like selective serotonin reuptake inhibitors (SSRIs). Prenatal SSRI use was recently associated with autism; however, its association with other developmental delays is unclear.



WHAT THIS STUDY ADDS: This population-based case-control study in young children provides evidence that prenatal SSRI use may be a risk factor for autism and other developmental delays. However, underlying depression and its genetic underpinnings may be a confounder.

abstract



OBJECTIVE: To examine associations between prenatal use of selective serotonin reuptake inhibitors (SSRIs) and the odds of autism spectrum disorders (ASDs) and other developmental delays (DDs).

METHODS: A total of 966 mother-child pairs were evaluated (492 ASD, 154 DD, 320 typical development [TD]) from the Childhood Autism Risks from Genetics and the Environment (CHARGE) Study, a population-based case-control study. Standardized measures confirmed developmental status. Interviews with biological mothers ascertained prenatal SSRI use, maternal mental health history, and sociodemographic information.

RESULTS: Overall, prevalence of prenatal SSRI exposure was lowest in TD children (3.4%) but did not differ significantly from ASD (5.9%) or DD (5.2%) children. Among boys, prenatal SSRI exposure was nearly 3 times as likely in children with ASD relative to TD (adjusted odds ratio [OR]: 2.91; 95% confidence interval [CI]: 1.07–7.93); the strongest association occurred with first-trimester exposure (OR: 3.22; 95% CI: 1.17–8.84). Exposure was also elevated among boys with DD (OR: 3.39; 95% CI: 0.98–11.75) and was strongest in the third trimester (OR: 4.98; 95% CI: 1.20–20.62). Findings were similar among mothers with an anxiety or mood disorder history.

CONCLUSIONS: In boys, prenatal exposure to SSRIs may increase susceptibility to ASD or DD. Findings from published studies on SSRIs and ASD continues to be inconsistent. Potential recall bias and residual confounding by indication are concerns. Larger samples are needed to replicate DD results. Because maternal depression itself carries risks for the fetus, the benefits of prenatal SSRI use should be carefully weighed against potential harms. *Pediatrics* 2014;133:e1241–e1248

Autism spectrum disorders (ASDs) are estimated to affect 1 in 88 children,¹ and the prevalence continues to increase. Hyperserotonemia is found in approximately one-third of children with autism.² Altered serotonin levels during early development are speculated to lead to abnormal brain circuitry and autism symptoms.³ Selective serotonin reuptake inhibitors (SSRIs), which increase extracellular serotonin, are the most common antidepressants prescribed during pregnancy: ~4% of pregnant women use an SSRI, and use has increased over time.⁴ Given the central role of serotonin in brain development through maternal-fetal and placental interactions,^{5,6} potential long-term developmental effects from prenatal SSRI exposure should be assessed.

Animal models of autism using serotonin agonists and medications that increase serotonin^{5,7} support the notion that during early gestation, high circulating serotonin reaches the fetal brain, causing loss of serotonin nerve terminals.³ Conversely, SSRIs and similar-acting medications could be protective by re-regulating maternal serotonin levels. In mice, maternal fluoxetine in early development reversed the effects of prenatal maternal stress on depressive-like behaviors and hippocampal neurogenesis in adolescent offspring.⁸

In humans, SSRIs cross the placenta,⁹ reduce serotonin reuptake in the placenta¹⁰ and fetus,¹¹ and may reduce uterine blood flow, leading to fetal hypoxemia.¹² Fetal hypoxia can adversely affect birth and developmental outcomes; an association with ASD is plausible.¹³ Recently, 2 large case-control studies using medical records/registries reported elevated risk of ASD with prenatal SSRI exposure,^{14,15} whereas a registry-based cohort study reported no association.¹⁶ Building on previous literature, we used a population-based

study in which diagnoses of ASD and other developmental delays (DDs) were confirmed by standardized instruments to investigate prenatal SSRI use.

METHODS

Participants were families enrolled in the Childhood Autism Risks from Genetics and the Environment (CHARGE) Study.¹⁷ This population-based case-control investigation recruited children with ASD, with DDs other than ASD, and from the general population. CHARGE eligibility criteria included being 2 to 5 years old, born in California, having a parent who speaks English or Spanish, and living with at least 1 biological parent and in the study catchment area of specified California Regional Centers, which coordinate services for persons with developmental disabilities.

Children with ASD and DD were identified from those qualifying for services through California's Department of Developmental Services, provider referrals, public outreach, and self-referrals. Population controls were identified by using state birth files and were frequency matched to autism cases by age, gender (targeted 4:1 male:female ratio), and regional center. CHARGE was approved by institutional review boards at the University of California, Davis; the University of California, Los Angeles; and the State of California. Written informed consent was obtained. Clinical assessments and standardized interviews were conducted in English or Spanish by trained staff with reliability on the respective instruments. This analysis includes CHARGE enrollees between April 2003 and August 2010.

To confirm ASD diagnoses, children were assessed with the Autism Diagnostic Interview—Revised (ADI-R)¹⁸ and the Autism Diagnostic Observation Schedule (ADOS).¹⁹ A final autism di-

agnosis required meeting criteria on the communication, social interaction, and repetitive behavior domains of the ADI-R and scoring at or above the social plus communication cutoff for autism on the ADOS. ASD was defined by using the criteria of Risi et al.²⁰ Children with DD diagnosed by regional centers and general population controls were screened for autism by using the Social Communication Questionnaire (SCQ).²¹ The ADI-R and ADOS were administered for children who screened positive (SCQ ≥ 15), and if they met criteria, were reclassified as ASD. The Vineland Adaptive Behavior Scales²² and Mullen Scales of Early Learning²³ were used to define DD (composite score ≤ 70 on either scale). The typical development (TD) group comprised children recruited from the general population scoring >69 on the Mullen Scales of Early Learning and Vineland Adaptive Behavior Scales and <15 on the SCQ. Siblings of probands were excluded, regardless of case status. The final sample included 966 mother-child pairs: 492 ASD, 154 DD, and 320 TD.

A standardized telephone interview was conducted with the child's biological mother to collect exposures for an index period covering 3 months before conception to the end of pregnancy or through breastfeeding. Mothers who reported having a medical condition or taking medication, including SSRIs, during the index period were asked to specify timing in monthly intervals. Information was also collected on the following: maternal age, education, and birthplace; maternal use during pregnancy of nicotine, alcohol, illicit substances, non-SSRI medications (eg, tricyclic antidepressants), and supplements that affect serotonin (eg, St John's wort); maternal obesity, diabetes, or hypertension; mother's anxiety/mood disorder history; and child's year of birth and race. Prenatal medical records were used, when

available, to supplement self-reported mental health history and for cross-source comparison of self-reported SSRI use. Preterm birth and low birth weight were analyzed but not included in multivariate models because they were potentially affected by SSRIs, the adjustment for which could introduce bias.²⁴

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by using logistic regression. Inverse probability weights were used in all models to address differential participation and to obtain results generalizable to the study's base population. Two models were constructed with SSRI use in pregnancy as the exposure: ASD versus TD and DD versus TD. We fit separate models for SSRI use during each trimester relative to no use during pregnancy. To address confounding, covariates were included in the models if associated with both SSRI exposure and diagnostic group (OR ≥ 2.0 or $P < .20$) and not an intermediate between exposure and outcome. Final models included child's birth year (1998–2003, 2004–2007), regional center, and mother's birthplace (United States, Mexico, or elsewhere). We also stratified by child gender to examine effect modification. To separate effects of maternal mental health status from those of SSRI use, we then restricted analyses to mothers who experienced an anxiety or mood disorder at any time before their child's birth.

Prenatal medical record information was compared with self-reported SSRI use during pregnancy to assess reporting bias. Intermethod reliability was calculated (percentage of agreement and κ). Outside limits of agreement were generated by recoding unavailable medical records to either concordant or discordant with self-report. Neither self-report nor medical records represent a gold standard.

Self-report depends on recall, whereas prenatal medical records may under- or overreport: prenatal records may not capture SSRI prescriptions from other providers, and not all prescriptions are filled and taken. These statistics therefore measure reliability, not validity. Analyses were conducted by using Stata/SE 11.2 (StataCorp LP, College Station, TX).

RESULTS

Table 1 presents study population characteristics. The mean age of enrolled children was 3.7 (SD: 0.81) years. TD children were slightly younger (3.6 years) than children with ASD (3.8 years; $P < .001$) or DD (3.8 years; $P < .001$). ASD and TD children had similar birth weight and preterm delivery and maternal socioeconomic characteristics. DD children were more likely to be female (because they were not matched), Hispanic, to have low birth weight, to have mothers born in Mexico, to have a lower education, and use public health insurance. Two-thirds of the sample was born between 1998 and 2003, before the Food and Drug Administration began changes to SSRI labeling, calling into question the safety of prenatal SSRI use. A greater proportion of ASD children were born before 2004 compared with DD ($P = .001$) and TD children ($P < .001$). No mothers born outside the United States reported SSRI use during pregnancy.

Forty-eight women (5%) reported prenatal SSRI use. Of these, 44% took fluoxetine, 21% sertraline, 19% paroxetine, 8% citalopram, and 8% escitalopram. Among SSRI users, 5 also reported using a non-SSRI antidepressant, 2 an anxiolytic, and 1 an antipsychotic. In unadjusted analyses (Table 2), prenatal SSRI use was lowest among TD mothers, but not significantly so in boys and girls combined. Among boys, prenatal SSRI use was higher in ASD compared with TD mothers ($P = .04$), and use

during the third trimester was higher among both ASD and DD compared with TD mothers ($P = .03$ for both). For girls, small cell sizes precluded analysis. Among mothers whose mental health history was available (440 ASD, 140 DD, 300 TD), more than one-quarter whose child had ASD (28%) or DD (29%) had a lifetime history of anxiety or mood disorder before the child's birth, as compared with 22% in the TD group ($P = .19$) (data not shown). Of mothers with a history of anxiety or mood disorder, 20% reported SSRI use during pregnancy. Two with SSRI use during pregnancy had no anxiety or mood disorder history. Within the anxiety/mood disorder subset, prenatal SSRI use did not differ significantly by child's diagnosis, overall or in boys.

In multivariate analyses (Table 3) involving the total sample or the subset of mothers with anxiety/mood disorder history, children exposed to SSRIs during pregnancy were no more likely to have an ASD or DD than were unexposed children. However, among boys, prenatal exposure to SSRIs nearly tripled the association with ASD (OR: 2.92; 95% CI: 1.07–7.93), and more than tripled it for DD (OR: 3.39; 95% CI: 0.98–11.75). The highest association for ASD was with first-trimester exposure, whereas the association with DD was elevated in the second and third trimesters, although few DD children were exposed. The pattern was similar among boys in the anxiety/mood disorder subset, but with low precision (102 ASD, 29 DD, 50 TD). Adjusting, rather than restricting, for maternal mental health yielded similar findings. Possible exposure misclassification of first-trimester use was examined by considering women who reported stopping SSRI use the month before conception as exposed during the first trimester. Results were similar, although attenuated. We also examined breastfeeding as a potential

confounder; however, it was not associated with prenatal SSRI exposure, and therefore was unlikely to confound study results.

Overall percentage agreement between self-reported and prenatal medical record report of SSRI use during pregnancy was 96.7%, with $\kappa = 0.66$. These statistics were highest for the DD group (98.2% agreement, $\kappa = 0.85$) compared with ASD and TD groups (95.8% and 97.4% agreement, respectively; both $\kappa = 0.61$) (Table 4). A standard interpretation of κ is that 0.61 to 0.80 reflects substantial agreement, whereas 0.81 to 1.00 is almost perfect.²⁵

DISCUSSION

In this population-based case-control study, mothers' reported use of SSRIs during pregnancy was associated with increased risk of ASD and DD in boys. Too few girls were exposed for analysis. Results were robust to sensitivity analyses and adjustment for confounders. Trimester-specific analyses in boys showed the greatest association with ASD during first-trimester SSRI exposure. Among the subset whose mothers previously had an anxiety or mood disorder, the association was also elevated among boys, although not significantly. Third-trimester exposure conveyed a 5-fold higher association with DD. The small numbers of exposed DD cases and exposed TD controls resulted in low precision.

Although we had few girls, the substantially stronger effect in boys alone compared with the combined analysis suggests possible effect modification by gender. Serotonergic function is influenced by sex hormones,^{26,27} and serotonin system biological variations by gender have been reported.²⁸ Mice pups prenatally exposed to agents that can alter serotonergic function, including an SSRI,^{29,30} showed perma-

nent sex-specific changes in behavior. Moreover, in children exposed prenatally to antidepressants, delays in motor milestones were greater in boys.³¹

An obstacle to drawing inferences about prenatal SSRI exposure is the difficulty in isolating SSRIs' effects from those of their indications for use. This problem is underscored by aggregation of psychiatric conditions in relatives of children with autism.³² Reliance on medical records to assess mental health history^{14,15} is problematic because mothers who do not seek services are missed, and mental health conditions may be underreported in medical records.³³ However, underreporting of depression may also occur with maternal recall.³⁴ Studies adjusting for maternal mental health ascertained from either source may

therefore overestimate psychotropic medication effects.

Studies of prenatal SSRI exposure with infant and child development generally indicate no adverse effects,³⁵ except for a few reports of gross motor development deficits.^{31,36,37} Limitations in this literature include small samples and insufficient control for maternal mental health. Furthermore, whether observed differences predict persistent impairment is unknown. Recent ASD studies^{14–16} using electronic medical records and registries included large samples of pregnant women with prospectively collected medication use. However, ASD diagnoses were not validated. Furthermore, studies by Croen et al¹⁴ using Kaiser patients and by Hviid et al¹⁶ using Danish registries were unable to confirm whether dispensed SSRIs were actually taken by

TABLE 1 Demographic and Perinatal Characteristics of Children With ASD, DD, and TD

| Characteristic | ASD (n = 492) | DD (n = 154) | TD (n = 320) | P |
|---|---------------|--------------|--------------|----------|
| Children | | | | |
| Age | | | | .002*§ |
| 2 years | 104 (21.1) | 25 (16.2) | 98 (30.6) | |
| 3 years | 178 (36.2) | 61 (39.6) | 114 (35.6) | |
| 4–5 years | 210 (42.7) | 68 (44.2) | 108 (33.8) | |
| Male gender | 421 (82.5) | 101 (65.6) | 264 (85.6) | <.001*†§ |
| Race/ethnicity | | | | .20 |
| Non-Hispanic white | 247 (50.2) | 64 (41.6) | 165 (51.6) | |
| Non-Hispanic black, Asian, or multiracial | 90 (18.3) | 28 (18.2) | 60 (18.8) | |
| Hispanic | 155 (31.5) | 62 (40.3) | 95 (29.7) | |
| Year of birth | | | | <.001*† |
| 1998–2003 | 352 (71.5) | 84 (54.6) | 193 (60.3) | |
| 2004–2007 | 140 (28.5) | 70 (45.5) | 127 (39.7) | |
| Low birth weight (<2500 g) | 36 (7.3) | 21 (13.6) | 20 (6.3) | .03†§ |
| Preterm birth (<37 weeks) | 51 (10.4) | 20 (13.0) | 33 (10.3) | .64 |
| Mothers | | | | |
| Age | | | | .13 |
| <25 years | 70 (14.2) | 33 (21.4) | 56 (17.5) | |
| 25–34 years | 287 (58.3) | 79 (51.3) | 191 (59.7) | |
| ≥35 years | 135 (27.4) | 42 (27.3) | 73 (22.8) | |
| Education | | | | <.001*†§ |
| ≤High school | 68 (13.8) | 43 (27.9) | 51 (15.9) | |
| Some college | 200 (40.7) | 65 (42.2) | 101 (31.6) | |
| ≥College degree | 224 (45.5) | 46 (29.9) | 168 (52.5) | |
| Birthplace | | | | .001†§ |
| United States | 370 (75.2) | 118 (76.6) | 258 (80.6) | |
| Mexico | 41 (8.3) | 25 (16.2) | 22 (6.9) | |
| Other | 81 (16.5) | 11 (7.1) | 40 (12.5) | |
| Private insurance | 400 (81.3) | 108 (70.1) | 276 (86.5) | <.001*†§ |

Data are presented as n (%) unless otherwise indicated. Percentages may not total 100 because of rounding. P values were calculated by using likelihood ratio χ^2 tests for overall associations across the 3 diagnostic groups. Significant pairwise group differences ($P \leq .05$) calculated by using likelihood ratio χ^2 tests are designated as follows: *ASD versus TD, †ASD versus DD, §DD versus TD.

mothers, whereas the Rai et al¹⁵ study from Stockholm, Sweden, only included self-reported use at the first antenatal visit (median of 10 weeks' gestation). The Kaiser and Swedish studies reported modestly increased ASD risk among children prenatally exposed to SSRIs, independent of maternal mental health, whereas no significant differences were observed in the Danish cohort. Similar to our results, the Kaiser study found the highest risk with first-trimester use. The Swedish study could not assess timing of use. Neither assessed differences in SSRI effects by child gender.

Similar to the Danish cohort results, we found no association when boys and girls were combined. SSRI use by CHARGE study participants during pregnancy only revealed significant associations with ASD among boys. Hviid et al¹⁶ reported no data on gender, nor gender-stratified analyses. The authors also did not assess effect modification by indication; their larger number of exposed cases might have permitted an informative analysis among mothers with depression and provided evidence on the replicability of results from Sweden.¹⁵ Despite the large Danish cohort, the prevalence of prenatal SSRI use was much lower

than in our study, as was the prevalence in Sweden, raising questions about generalizability and whether prenatal SSRI users in Scandinavia are a more select group than in the United States.

Strengths of our study include its relatively large sample of cases, population-based controls, and a uniform protocol to confirm ASD and DD diagnoses by trained clinicians using validated standardized instruments. Different from the 3 previous reports, ours is the first to examine a DD group. We adjusted for selection bias and systematically assessed and controlled for confounders, including maternal mental health. The collection of exposure data via maternal recall has both strengths and weaknesses. A strength is that one can capture whether SSRIs were actually taken by the mother, rather than simply dispensed. A limitation is potential recall bias. Some evidence supports accurate recall for psychotropic medication use during pregnancy in women with a history of mental health problems.³⁴ One study found that, compared with antenatal medical records, maternal recall 4 to 9 years after childbirth was very good for the majority of outcomes examined and generally did not vary by maternal

characteristics or child behavior problems.³⁸ We found cases and controls were similar in the level of discrepancy between self-reported and prenatal medical record SSRI use, suggesting very little recall bias. Moreover, some discrepancies between self-report and medical records in our sample could be due to use of prenatal records for comparison. Had other maternal medical records been available (eg, primary care and mental health), more of the positive self-reports might have been confirmed. However, the impact of additional medical record information on measures of agreement would be unlikely to vary by case status.

Other potential limitations are of note. First, residual confounding by indication for SSRI use remains possible because we were unable to assess the severity of mental health symptoms. Second, lack of data on SSRI dosage precluded dose-response analyses. However, dosage may not correlate well with circulating SSRI levels, given differences in metabolism arising from, for example, metabolic gene polymorphisms.³⁹ Furthermore, the usually effective minimum dose of each SSRI produces comparable effects on the degree of serotonin reuptake inhibition, a surrogate for efficacy.⁴⁰ Third, assessment of individual SSRI formulations was unfeasible, because few women used SSRIs during pregnancy. Fourth, the relatively small sample of DD children resulted in imprecise estimates of association, which should be viewed with caution. The interpretation of findings in the DD group also should be tempered because this heterogeneous group included known genetic or chromosomal syndromes. Because of prenatal and neonatal screening tests, some mothers were likely aware of their child's genetic make-up, which might have led some to use SSRIs. Finally, with regard to possible chance associations, in our

TABLE 2 Unadjusted Prevalence of SSRI Use During Pregnancy

| SSRI Use | Boys and Girls | | | Boys Only | | |
|---|----------------|---------|----------|-----------|----------------------|-----------------------|
| | ASD | DD | TD | ASD | DD | TD |
| Total sample | | | | | | |
| <i>n</i> | 492 | 154 | 320 | 421 | 101 | 264 |
| Pregnancy, <i>n</i> (%) | 29 (5.9) | 8 (5.2) | 11 (3.4) | 25 (5.9)* | 6 (5.9) | 7 (2.7)* |
| Trimester 1 | 21 (4.3) | 4 (2.6) | 10 (3.1) | 18 (4.3) | 4 (4.0) | 6 (2.8) |
| Trimester 2 | 16 (3.3) | 7 (4.6) | 7 (2.2) | 14 (3.3) | 5 (5.0) | 4 (1.5) |
| Trimester 3 ^a | 20 (4.1) | 8 (5.3) | 7 (2.2) | 18 (4.3)* | 6 (6.0) [§] | 4 (1.5)* [§] |
| Anxiety/mood disorder history subset ^b | | | | | | |
| <i>n</i> | 122 | 40 | 67 | 102 | 29 | 50 |
| Pregnancy, <i>n</i> (%) | 28 (23) | 8 (20) | 10 (15) | 24 (24) | 6 (21) | 6 (12) |
| Trimester 1 | 21 (17) | 4 (10) | 9 (13) | 18 (18) | 4 (14) | 5 (10) |
| Trimester 2 | 16 (13) | 7 (18) | 7 (11) | 14 (14) | 5 (17) | 4 (8) |
| Trimester 3 ^a | 19 (16) | 8 (20) | 7 (11) | 17 (17) | 6 (21) | 4 (8) |

P values were calculated by using likelihood ratio χ^2 tests. Significant pairwise group differences ($P \leq .05$): *ASD versus TD, [§]DD versus TD. ASD versus DD did not differ for any comparison.

^a Preterm delivery led to there being no third trimester for 3 participants in the ASD group (all boys), 2 participants in the DD group (1 boy, 1 girl) in the total sample, and for 1 participant in the ASD group (boy) in the subset.

^b Due to limited precision in the subgroup, percentages are reported without decimals.

TABLE 3 Estimated Risk for ASD and DD Associated With Maternal Reported SSRI Use During Pregnancy

| | Boys and Girls | | Boys Only | |
|--|------------------|-----------------------|---------------------|-----------------------|
| | Unadjusted | Adjusted ^a | Unadjusted | Adjusted ^a |
| Total sample (N = 966) | | | | |
| ASD versus TD | | | | |
| Pregnancy | 1.52 (0.65–3.53) | 1.55 (0.59–4.08) | 2.68 (1.07–6.73)* | 2.92 (1.07–7.93)* |
| Trimester 1 | 1.32 (0.53–3.34) | 1.38 (0.48–4.01) | 2.76 (1.04–7.32)* | 3.22 (1.17–8.84)* |
| Trimester 2 | 0.85 (0.30–2.42) | 0.89 (0.24–3.24) | 1.73 (0.53–5.67) | 2.25 (0.54–9.42) |
| Trimester 3 | 1.15 (0.41–3.19) | 1.18 (0.35–4.02) | 2.40 (0.75–7.65) | 2.91 (0.76–11.10) |
| DD versus TD | | | | |
| Pregnancy | 2.03 (0.68–6.07) | 1.62 (0.59–4.42) | 4.60 (1.37–15.43)* | 3.39 (0.98–11.75) |
| Trimester 1 | 1.21 (0.32–4.61) | 1.05 (0.31–3.54) | 3.69 (0.94–14.46) | 3.26 (0.84–12.71) |
| Trimester 2 | 2.34 (0.67–8.19) | 1.96 (0.64–6.06) | 5.87 (1.40–24.67)* | 4.41 (1.01–19.17)* |
| Trimester 3 | 2.68 (0.80–9.00) | 2.19 (0.74–6.49) | 6.82 (1.71–27.12)** | 4.98 (1.20–20.62)* |
| Anxiety/mood disorder history subset (N = 229) | | | | |
| ASD versus TD | | | | |
| Pregnancy | 1.51 (0.59–3.86) | 1.86 (0.76–4.58) | 2.85 (0.99–8.19) | 3.17 (0.91–11.00) |
| Trimester 1 | 1.39 (0.50–3.84) | 1.70 (0.66–4.37) | 3.25 (1.07–9.85)* | 3.52 (0.93–13.34) |
| Trimester 2 | 0.83 (0.28–2.47) | 1.12 (0.40–3.11) | 1.67 (0.48–5.79) | 1.80 (0.39–8.37) |
| Trimester 3 | 1.05 (0.36–3.09) | 1.43 (0.52–3.95) | 2.17 (0.64–7.41) | 2.45 (0.54–11.22) |
| DD versus TD | | | | |
| Pregnancy | 1.79 (0.54–5.93) | 1.44 (0.44–4.75) | 3.86 (0.99–14.99) | 2.30 (0.55–9.62) |
| Trimester 1 | 1.07 (0.26–4.51) | 0.99 (0.26–3.83) | 3.27 (0.73–14.76) | 2.21 (0.52–9.39) |
| Trimester 2 | 1.92 (0.51–7.25) | 1.76 (0.47–6.60) | 4.28 (0.93–19.61) | 2.62 (0.54–12.80) |
| Trimester 3 | 2.17 (0.60–7.86) | 1.88 (0.51–6.88) | 4.91 (1.13–21.37)* | 2.83 (0.60–13.43) |

Data are presented as ORs (95% CIs) and were weighted to adjust for selection bias. * $P \leq .05$, ** $P \leq .01$.

^a Adjusted for regional center, child's year of birth, and birthplace of mother.

primary analyses (multivariate adjusted, full sample) we presented 8 associations in both genders combined and found none to be significant (<1 would be expected by chance); we additionally presented 8 associations in boys alone, among which 4 were significant, a pattern that did not suggest a random fluctuation.

CONCLUSIONS

Our data suggest that prenatal exposure to SSRIs may be associated with an increased risk of ASD, at least in boys,

with the greatest risk when exposure is during the first trimester. These findings are biologically plausible given that SSRIs interact with the placenta,¹⁰ may raise maternal serotonin to abnormal levels, and act directly on the fetus.⁴¹ Serotonin's integral role in fetal brain development includes modulating early neurodevelopmental processes such as cell division, neurite outgrowth, and neuronal migration,⁵ with the first trimester a period of development especially sensitive to alterations in serotonergic functioning. Recent reviews give a more detailed

discussion relating prenatal SSRI use with ASD and other developmental outcomes.^{42,43}

Whether the risk of DDs other than ASD is also elevated in association with prenatal SSRI exposure requires confirmation with a larger sample size; research might usefully address how maternal SSRI use is affected by the knowledge of predisposing genetic conditions. Also needed are studies in more girls, sufficient sample sizes to address possible differential effects from specific SSRIs, and attention to mechanisms by which SSRIs might influence ASD and other developmental outcomes. The field would benefit from a deeper understanding of the contribution of maternal and fetal genetics in regulating serotonin.

Because of low exposure prevalence and possible cofactors influencing susceptibility to ASD from SSRI exposure, any contribution of these medications to the increase in autism diagnoses over time is likely minimal.⁴⁴ The reported results must be viewed in the context of the disorder they are used to treat and, particularly, with the risks associated with failure to treat the condition. Maternal depression during pregnancy has itself been linked to preterm birth, fetal growth restriction, and preeclampsia,⁴⁵ as well as increased irritability in newborns and reduced activity and attentiveness compared with infants of nondepressed women.⁴⁶ Moreover, gestational depression has been observed to affect DD independent of postpartum depression.⁴⁷ Given these negative consequences, depression during pregnancy and the positive aspects of pharmacologic management present pregnant women and their doctors with complex treatment decisions. The benefits of treating depression with SSRIs during pregnancy should continue to be carefully weighed against any potential risk of harm.

TABLE 4 Intermethod Reliability by Diagnostic Group

| SSRI Exposure During Pregnancy | ASD (n = 492) | DD (n = 154) | TD (n = 320) |
|------------------------------------|------------------|------------------|------------------|
| Self-report/medical records, n (%) | | | |
| Yes/yes | 13 (2.6) | 6 (3.9) | 5 (1.6) |
| Yes/no | 10 (2.0) | 2 (1.3) | 4 (1.3) |
| No/yes | 5 (1.0) | 0 (0.0) | 2 (0.6) |
| No/no | 328 (66.7) | 103 (66.9) | 220 (68.8) |
| No/not available | 130 (26.4) | 43 (27.9) | 87 (27.2) |
| Yes/not available | 6 (1.2) | 0 (0.0) | 2 (0.6) |
| Percentage of agreement (range) | 95.8 (94.3–97.0) | 98.2 (96.8–98.7) | 97.4 (93.7–98.1) |
| κ (range) | 0.61 (0.45–0.70) | 0.85 (0.69–0.85) | 0.61 (0.46–0.69) |

Percentages may not total 100 due to rounding.

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