ORIGINAL ARTICLE

Use of Selective Serotonin Reuptake Inhibitors during Pregnancy and Risk of Autism

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ABSTRACT

BACKGROUND

Studies have raised concern about an association between the use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy and an increased risk of autism spectrum disorders in the offspring.

METHODS

We conducted a cohort study of all singleton live births in Denmark from 1996 through 2005 (626,875 births), with follow-up through 2009. Using Danish population registries, we linked information on maternal use of SSRIs before and during pregnancy, autism spectrum disorders diagnosed in the offspring, and a range of potential confounders. We used a survival analysis of the time to diagnosis in the offspring with Poisson regression to estimate rate ratios of autism spectrum disorders according to maternal use of SSRIs.

RESULTS

During 5,057,282 person-years of follow-up, we identified 3892 cases of autism spectrum disorder (incidence rate, 77.0 per 100,000 person-years). A total of 52 cases during 42,400 person-years of follow-up involved offspring of women who were exposed to SSRIs during their pregnancy (incidence rate, 122.6 per 100,000 person-years). As compared with no use of SSRIs both before and during pregnancy, use during pregnancy was not associated with a significantly increased risk of autism spectrum disorders (fully adjusted rate ratio, 1.20; 95% confidence interval [CI], 0.90 to 1.61). Among women who received SSRIs before pregnancy but not during pregnancy, the corresponding fully adjusted rate ratio was 1.46 (95% CI, 1.17 to 1.81).

CONCLUSIONS

We did not detect a significant association between maternal use of SSRIs during pregnancy and autism spectrum disorder in the offspring. On the basis of the upper boundary of the confidence interval, our study could not rule out a relative risk up to 1.61, and therefore the association warrants further study. (Funded by the Danish Health and Medicines Authority.)

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Selective serotonin reuptake inhibitors (SSRIs) are increasingly used in the treatment of depression and anxiety disorders. Currently, SSRIs appear to provide the best balance between efficacy and safety and are the preferred first-line treatment. Depression is common during pregnancy, and given the risks of untreated depression to mother and fetus,[1,2] pharmacologic treatment is warranted, often with SSRIs.[3] However, SSRIs cross the placenta, and a number of safety concerns have been raised.[4] These include concerns about birth defects, adverse obstetrical and neonatal outcomes, and effects on cognitive and behavioral development in childhood.

Recently, autism spectrum disorders have been linked to maternal use of SSRIs during pregnancy. In a case–control study involving 298 children with autism spectrum disorders, the use of SSRIs by the mother during pregnancy was shown to be associated with a risk of autism spectrum disorder that was increased by a factor of 2.[5] A causal association is plausible. Increased blood levels of the neurotransmitter serotonin have been observed in persons with autism spectrum disorders.[6] Furthermore, this neurotransmitter appears to play an important role in early brain development, and manipulation of serotonin homeostasis can alter neuroanatomical and neurophysiological development and produce enduring behavioral changes in animal models.[7-9] However, more research — including large observational studies involving humans — is needed to address a potential association. Using data from the Danish health registries, we conducted a nationwide cohort study of SSRI use during pregnancy and the risk of autism spectrum disorders in the offspring.

Methods

Study Cohort

We used the nationwide Medical Birth Registry to construct a cohort of all live births in Denmark during the study period of January 1, 1996, through December 31, 2005.[10] The Medical Birth Registry contains records of all births in Denmark, including information on the personal identification number (a 10-digit number assigned to all Danish residents and used in all nationwide registries[11]) of the parents and the newborn, the date of birth, whether the birth was a single or multiple birth, the gestational age, vital status, and other physical characteristics of the newborn. The study was approved by the Danish Data Protection Agency. Approval by an institutional review board and informed consent are not required for registry-based research in Denmark. The first author vouches for the accuracy and completeness of the data.

We estimated the beginning of pregnancy by subtracting the gestational age from the date of birth. The gestational age recorded in the Medical Birth Registry is based on the self-reported first day of the last menstrual period and in most cases is confirmed by prenatal ultrasonography. An estimated 93% of all pregnant women underwent an obstetrical ultrasound examination in 2000.[12] We included only births with a known gestational age and further restricted the cohort to singleton births.

From the National Patient Register,[13] we obtained information on a number of genetic conditions (the fragile X syndrome, tuberous sclerosis, Angelman's syndrome, Down's syndrome, DiGeorge's syndrome, neurofibromatosis, and the Prader–Willi syndrome) and on the congenital rubella syndrome. All these conditions are associated with an inherent increased risk of autism, and offspring with any of these conditions were excluded from the cohort.

The unique personal identification numbers for mother and child allowed us to link information on maternal use of SSRIs, diagnoses of autism spectrum disorders among offspring, and potential confounding variables relevant to the births in the cohort.

Exposure to SSRI Drugs

Information on SSRI prescriptions filled by women in the cohort was obtained from the National Prescription Registry.[14] This register contains individual-level information on all prescriptions dispensed at Danish pharmacies since 1995. Each record includes the personal identification number of the patient, the date the prescription was filled, the type of drug according to the Anatomical Therapeutic Chemical (ATC) classification system, the number of daily doses specified in the prescription, and the number of packages obtained. We included prescriptions with the ATC code N06AB (selective serotonin reuptake inhibitors) that were filled during the period from 2 years before the beginning of the pregnancy until delivery. We used the date on which a prescription was filled to indicate initial use of the prescribed drug.

AUTISM SPECTRUM DISORDERS

Information on diagnoses of autism spectrum disorder during the study period was obtained from the Danish Psychiatric Central Register.[15] This register includes diagnoses made and diagnostic codes assigned by child psychiatrists and contains information from psychiatric hospitals and psychiatric units (inpatient and outpatient). The coding classification used during the study period was the *International Classification of Diseases, 10th Revision* (ICD-10). We classified autism spectrum disorders in two groups: autistic disorder (ICD-10 code F84.0) and other autism spectrum disorders (including atypical autism, Asperger's syndrome, and other or unspecified pervasive developmental disorder; ICD-10 codes F84.1, F84.5, F84.8, and F84.9).

POTENTIAL CONFOUNDERS

We selected a priori a number of potential confounders that were plausible risk factors for either autism or SSRI use and for which information was available to us from the nationwide Danish health registries. From the Medical Birth Registry and the Danish Civil Registration System[11] (the key national demographic registry in Denmark) we obtained information on the year of the birth and on maternal parity, age at the onset of pregnancy, country of origin, place of residence at the start of the pregnancy, and smoking status during pregnancy, and we linked this information to the cohort. From the Danish Psychiatric Central Register and the National Prescription Registry we obtained information on maternal psychiatric conditions and selected drugs other than SSRIs that were used during the pregnancy. The Danish Psychiatric Central Register includes diagnoses made in a psychiatric hospital or psychiatric unit (inpatient or outpatient) but does not include diagnoses made by a medical specialist in the primary care setting. Information on employment status and the mother's level of education was obtained from Statistics Denmark.[16]

STATISTICAL ANALYSIS

We performed a survival analysis to follow up children from birth until January 1, 2010, or until the child reached 10 years of age, died or was lost to follow-up, or received a diagnosis of autism spectrum disorder — whichever came first.

The resulting follow-up times and numbers of diagnoses of autism (autism counts) were aggregated according to maternal use or nonuse of SSRIs during pregnancy. We used Poisson regression on the autism counts with the logarithm of the follow-up times as the offset term, assuming a Poisson distribution for the autism counts, to estimate incidence rate ratios and 95% confidence intervals so that we could compare the rates of autism spectrum disorder among the offspring of women who had been exposed to SSRIs during pregnancy with the rates among the offspring of women who had not been exposed to SSRIs during pregnancy.[17] The regression analysis was performed with the use of the PROC GENMOD procedure in SAS software, version 9.1 (SAS Institute).

The date the prescription was filled was considered to be the date of exposure. The use of SSRIs during pregnancy was defined as use during the period 4 weeks before the beginning of the pregnancy until delivery. We further analyzed the use of SSRIs specifically in the first trimester. To evaluate the potential for confounding by indication (i.e., the possibility that women with depression or other indications for SSRI use would be more likely to have children with autism spectrum disorders), we also looked at the use of SSRIs during the period from 2 years until 6 months before the beginning of the pregnancy. This allowed us to identify a group of women who received SSRIs during that period but not during pregnancy and two groups of women who received SSRIs during pregnancy: those who received the drugs both before and during the pregnancy and those who did not receive the drugs before the pregnancy but did receive them during the pregnancy. In all the analyses, unexposed pregnancies were considered to be pregnancies in women who had no exposure to SSRIs from 2 years before the beginning of pregnancy through the end of the pregnancy.

We explored whether the association between the use of SSRIs during pregnancy and autism spectrum disorder differed in subgroups defined according to the child's age at the time of the follow-up assessment, the calendar period during which the follow-up assessment was performed, the type of SSRI used, previous psychiatric diagnoses in the mother, other drugs used during pregnancy, and the type of autism spectrum disorder in the offspring. We estimated crude rate ratios, rate ratios adjusted for age and calendar period, and fully adjusted rate ratios that included, in addition to age and calendar period, all the potential confounders listed

above. No more than 5% of the values were missing for any of the potential confounders, and we therefore used simple imputation, in which missing values were replaced with the most common value.[18] The implications of this strategy were explored in sensitivity analyses.

RESULTS

STUDY COHORT

We identified 658,755 live births in Denmark during the period from January 1, 1996, through December 31, 2005. We then excluded births without a known gestational age (4016), multiple births (26,526), and births resulting in offspring with the congenital rubella syndrome or with genetic conditions that are associated with an inherent risk of autism (1338). This resulted in a final study cohort of 626,875 children (51.3% were boys). A total of 6068 mothers (1.0%) of the children in the cohort used SSRIs during pregnancy. Table 1 shows the characteristics of the mothers according to their status with respect to SSRI use during pregnancy. Parity and maternal age at the beginning of the pregnancy were similar in the group of women who received SSRIs and the group of women who did not receive SSRIs. As compared with women who did not use SSRIs during pregnancy, those who did were slightly more likely to have been born in Denmark and to be residing in Jutland or Funen; had a lower level of education and lower socioeconomic status; and were more likely to have psychiatric diagnoses, to use other drugs during pregnancy, and to smoke during pregnancy. Furthermore, the use of SSRIs during pregnancy became more prevalent over the course of the study period.

AUTISM SPECTRUM DISORDER

During 5,057,282 person-years of follow-up, we identified 3892 cases of autism spectrum disorder (1603 cases of autistic disorder and 2289 cases of other autism spectrum disorders), yielding an incidence rate of 77.0 per 100,000 person-years. The median age at the diagnosis of autism spectrum disorder was 5.6 years (interquartile range, 4.1 to 7.5). During the follow-up period, 15,585 children emigrated from Denmark, 3157 died, and 387 were lost to follow-up (i.e., their personal identification numbers could no longer be found in the national registries). Table 2 shows some of the risk factors for autism spectrum disorder among the offspring in this study. (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org, shows the association of autism spectrum disorder with other risk factors, including the age of the child, the calendar period, and maternal age at the time of delivery.) Strong associations were seen between autism spectrum disorder and maternal psychiatric diagnoses and the use of drugs other than SSRIs during pregnancy. These associations suggest possible confounding by indication, especially given that mothers with these characteristics were also more likely to use SSRIs during pregnancy (Table 1).

SSRI USE DURING PREGNANCY AND RISK OF AUTISM SPECTRUM DISORDER

Table 3 shows the association between maternal use of SSRIs during pregnancy and the risk of autism spectrum disorder in the offspring. During 42,400 person-years of follow-up, we identified 52 cases of autism spectrum disorder among the offspring of women who were exposed to SSRIs during pregnancy (incidence rate, 122.6 per 100,000 person-years). For the comparison with no use of SSRIs before or during pregnancy, this rate corresponded to a crude rate ratio of 1.62 (95% confidence interval [CI], 1.23 to 2.13). However, in a fully adjusted analysis, the use of SSRIs during pregnancy (including use both before and during pregnancy and use only during pregnancy) was not associated with a significantly increased risk of autism spectrum disorder in the offspring (rate ratio 1.20; 95% CI, 0.90 to 1.61). Table S2 in the Supplementary Appendix shows the extent to which each potential confounder included in the fully adjusted models influenced the estimate. The fully adjusted rate ratio associated with the use of SSRIs in the first trimester was 1.35 (95% CI, 0.97 to 1.87), whereas the fully adjusted rate ratio in the subgroup of women who received SSRIs during pregnancy but not before pregnancy was 1.40 (95% CI, 0.92 to 2.13). These estimates should be compared with the fully adjusted rate ratio of 1.46 (95% CI, 1.17 to 1.81) in the subgroup of women who had used SSRIs before pregnancy but did not use these drugs during pregnancy.

Table S3 in the Supplementary Appendix shows the association between the use of SSRIs during pregnancy and the risk of autism spectrum disorder in offspring according to several prespecified characteristics. Although the point estimates suggested that in some subgroups of women the association differed from the fully adjusted rate ra-

tio of 1.20, tests of homogeneity were consistent, with no significant differences.

Since we used a simple form of imputation for missing data, we tested the validity of this approach by assessing the association between SSRIs use during pregnancy and the risk of autism spectrum disorder in offspring in an analysis that was restricted to pregnancies for which complete information was available (574,020 pregnancies). This analysis yielded a fully adjusted rate ratio of

Table 1. Characteristics of Mothers in a Cohort of 626,875 Live Births in Denmark, According to Status with Respect to SSRI Use during Pregnancy.*

Characteristic	SSRI Use during Pregnancy (N=6068)	No SSRI Use during Pregnancy (N=620,807)
Age at beginning of pregnancy — yr	30.7±5.1	30.0±4.8
SSRI — no. (%)		
Citalopram	1751 (28.9)	—
Fluoxetine	160 (2.6)	—
Sertraline	1576 (26.0)	—
Paroxetine	871 (14.4)	—
Escitalopram or fluvoxamine	1047 (17.3)	—
More than one type	663 (10.9)	—
Year of birth — no. (%)		
1996–1997	478 (7.9)	128,257 (20.7)
1998–1999	671 (11.1)	125,688 (20.2)
2000–2001	1011 (16.7)	125,393 (20.2)
2002–2003	1666 (27.5)	120,882 (19.5)
2004–2005	2242 (36.9)	120,587 (19.4)
Country or region of origin — no. (%)		
Denmark	5348 (88.1)	531,657 (85.6)
Europe or North America	332 (5.5)	30,299 (4.9)
Other	367 (6.0)	56,796 (9.1)
Highest level of completed education at beginning of pregnancy — no. (%)		
Primary or secondary school	2849 (47.0)	220,342 (35.5)
Vocational school or college	1900 (31.3)	223,810 (36.1)
Graduate school	1177 (19.4)	151,367 (24.4)
Employment status at beginning of pregnancy — no. (%)		
Outside labor market	2643 (43.6)	160,920 (25.9)
Employed with basic, no, or unknown qualifications	2055 (33.9)	257,488 (41.5)
Employed with medium-level qualifications	775 (12.8)	117,276 (18.9)
Self-employed or working with spouse	128 (2.1)	15,441 (2.5)
Top manager	466 (7.7)	67,756 (10.9)
Place of residence at beginning of pregnancy — no. (%)		
Copenhagen or suburbs	1337 (22.0)	148,519 (23.9)
Sealand or Bornholm	1197 (19.7)	133,154 (21.4)
Jutland or Funen	3527 (58.1)	338,422 (54.5)
Parity — no. (%)		
0	2636 (43.4)	269,727 (43.4)
≥1	3428 (56.5)	350,474 (56.5)

Table 1. (Continued.)

Characteristic	SSRI Use during Pregnancy (N=6068)	No SSRI Use during Pregnancy (N=620,807)
Self-reported smoking during pregnancy — no. (%)	2265 (37.3)	128,491 (20.7)
Diagnoses before delivery — no. (%)†		
Schizophrenia	100 (1.6)	612 (0.1)
Other nonaffective psychotic disorder	71 (1.2)	575 (0.1)
Depression	835 (13.8)	2,647 (0.4)
Other affective disorder	101 (1.7)	476 (0.1)
Neurotic, stress-related, or somatoform disorder	1198 (19.7)	9,180 (1.5)
Autism spectrum disorder	3 (<0.1)	8 (<0.1)
Adult personality or behavior disorder	716 (11.8)	4,329 (0.7)
Eating disorder	195 (3.2)	1,864 (0.3)
Postpartum depression or psychosis	9 (0.1)	90 (<0.1)
Substance abuse	182 (3.0)	1,169 (0.2)
Use of drugs other than SSRIs during pregnancy — no. (%)		
Other antidepressant	434 (7.2)	1,111 (0.2)
Antipsychotic agent	342 (5.6)	854 (0.1)
Mood stabilizer	88 (1.5)	1,605 (0.3)
Category D drug‡	61 (1.0)	1,420 (0.2)
Category X drug‡	950 (15.7)	11,945 (1.9)

* The cohort included mothers and children for all singleton live births in Denmark during the period from January 1, 1996, through December 31, 2005. The use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy was defined as use during the period 4 weeks before the beginning of the pregnancy until delivery. Information on the use of SSRIs and other drugs was obtained from the National Prescription Registry.[14]

† Included are diagnoses made in a psychiatric hospital or psychiatric unit (inpatient or outpatient); diagnoses made in primary care settings are excluded.

‡ Category D includes drugs for which there is positive evidence of human fetal risk, but potential benefits may warrant the use of the drug in pregnant women despite potential risks; category X includes drugs for which fetal abnormalities have been shown in studies of animals or humans, there is positive evidence of human fetal risk, or both, and the risks involved in the use of the drug in pregnant women outweigh the potential benefits.

1.15 (95% CI, 0.85 to 1.56), which was similar to the results of our main analysis.

DISCUSSION

In a large population-based study of 626,875 live births, the use of SSRIs during pregnancy was not associated with a significantly increased risk of autism spectrum disorder in the offspring. Our study was prompted by experimental evidence implicating serotonin in autism[6-9] and by recent work from Croen and colleagues, who conducted a case–control study using data from a health maintenance organization in Northern California.[5] The researchers identified 298 children with autism spectrum disorder; the mothers of 20 of those children, had received antidepressants (15 had received SSRIs) during the year before the child's birth. This corresponded to an increase by a factor of 2 in the risk of autism spectrum disorder associated with the use of antidepressants during pregnancy. The risk was increased more with SSRIs than with other antidepressants, and the risk was increased by a factor of more than 3 with the use of SSRIs specifically in the first trimester. A case–control study conducted in Sweden showed an odds ratio of 1.65 (95% CI, 0.90 to 3.03) for the association between SSRI use during pregnancy and the risk of autism spectrum disorder in the offspring, on the basis of 14 exposed pregnancies. The study assessed self-reported SSRI use and could not take confounding by depression directly into account.[19]

Our study has a number of strengths. First,

the Danish registries allowed the linkage between drug use during pregnancy and autism spectrum disorders in the offspring, so that we were able to determine the potential effect of the drugs later in childhood. Second, our study was conducted on a nationwide level, and therefore the cohort was large, with 626,875 live births, including 52 cases of autism spectrum disorder in offspring of women with SSRI exposure during pregnancy — more than three times the number of cases among exposed women in the study by Croen and colleagues or the Swedish study. Third, we used administrative health registry data in a historically prospective study design, with independent ascertainment of exposure and outcome, thus reducing the potential for selection and recall bias. Finally, the National Prescription Registry, from which we obtained data on exposure to SSRIs, is considered to be nearly complete[14]; all Danish pharmacies must report filled prescriptions to this registry for reimbursement purposes.

Our study also has a number of limitations. First, in our cohort, the prevalence of pregnancy-related use of SSRIs was 0.97%. In a survey of the automated databases of seven health plans across the United States during the period from 2001 through 2005, SSRIs were much more

Table 2. Autism Spectrum Disorder in Offspring, According to Maternal Characteristics.*

Maternal Characteristic	Offspring with Autism Spectrum Disorder	Follow-up	Rate Ratio (95% CI)
	no.	*no. of person-yr*	
Country or region of origin			
Denmark	3290	4,392,924	Reference
Europe or North America	203	224,344.92	1.21 (1.05–1.39)
Other	399	440,013.84	1.21 (1.09–1.34)
Highest level of completed education at beginning of pregnancy			
Primary school	1029	1,158,953.71	1.10 (0.99–1.22)
Secondary school	542	671,914.83	Reference
Vocational school or college	1397	2,038,284.04	0.85 (0.77–0.94)
Graduate school	924	1,188,129.71	0.96 (0.87–1.07)
Employment status at beginning of pregnancy			
Outside labor market	1215	1,301,469.89	1.20 (1.07–1.34)
Employed with basic or no qualifications	1350	1,871,460.83	0.93 (0.83–1.04)
Employed with medium-level qualifications	621	942,325.50	0.85 (0.75–0.96)
Self-employed or working with spouse	89	127,390.52	0.90 (0.71–1.13)
Top manager	415	533,475.05	Reference
Employed with unknown qualifications	202	281,160.50	0.92 (0.78–1.09)
Place of residence at beginning of pregnancy			
Copenhagen or suburbs	1432	1,185,227.81	2.05 (1.91–2.21)
Sealand or Bornholm	823	1,088,688.08	1.29 (1.18–1.40)
Jutland and Funen	1637	2,783,366.40	Reference
Parity			
0	1995	2,201,981.54	Reference
1	1276	1,872,589.67	0.75 (0.70–0.81)
2	457	716,727.76	0.70 (0.64–0.78)
≥3	164	265,983.32	0.68 (0.58–0.80)

Table 2. (Continued.)

Maternal Characteristic	Offspring with Autism Spectrum Disorder	Follow-up	Rate Ratio (95% CI)
	no.	*no. of person-yr*	
Self-reported smoking during pregnancy			
Yes	946	1,092,140.27	1.17 (1.08–1.25)
No	2946	3,965,142.02	Reference
Diagnoses before delivery†			
Schizophrenia	15	5,496.56	3.56 (2.14–5.90)
Other nonaffective psychotic disorder	7	4,848.89	1.88 (0.89–3.94)
Depression	37	26,503.10	1.82 (1.32–2.52)
Other affective disorder	3	4,382.88	0.89 (0.29–2.76)
Neurotic, stress-related, or somatoform disorder	110	81,397.48	1.78 (1.47–2.15)
Autism spectrum disorder	0	68.83	NA
Adult personality or behavior disorder	67	38,005.70	2.31 (1.82–2.95)
Eating disorder	24	14,365.30	2.10 (1.46–3.25)
Postpartum depression or psychosis	0	827.54	NA
Substance abuse	14	10,204.92	1.79 (1.06–3.02)
Use of drugs other than SSRIs during pregnancy‡			
Other antidepressant	13	10,940.29	1.55 (0.90–2.66)
Antipsychotic agent	15	9,424.90	2.07 (1.25–3.44)
Mood stabilizer	23	13,365.97	2.24 (1.49–3.38)
Category D drug	135	105,832.52	1.68 (1.42–2.00)
Category X drug	13	12,141.09	1.39 (0.81–2.40)

* Offspring were followed from birth until January 1, 2010, or until the child reached 10 years of age, died or was lost to follow-up, or received a diagnosis of autism spectrum disorder — whichever came first. NA denotes not applicable.
† Included are diagnoses made in a psychiatric hospital or psychiatric unit (inpatient or outpatient).
‡ Information was obtained from the National Prescription Registry[14] for prescriptions filled by cohort mothers from 4 weeks before the beginning of the pregnancy through delivery.

widely used during pregnancy, with a prevalence of 5.6%.[3] Thus, our findings may not be generalizable to other countries. Second, in our study and similar studies relying on registry data, the date on which the prescription is filled is assumed to be the same as the date of initial use of the prescribed drug. This assumption can overestimate the prevalence of exposure during pregnancy and bias the observed results toward no effect.

Third, we used the Danish Psychiatric Central Register for case ascertainment. A previous study showed that 94% of 499 children registered with autism spectrum disorder diagnoses met the necessary diagnostic criteria in a chart review.[20] The reported prevalence rates in previous Danish epidemiologic studies of autism spectrum disorder that used this register are consistent with rates reported in other, similar countries.[21] The prevalence of autism spectrum disorder in our cohort was 0.62%. The Centers for Disease Control and Prevention recently estimated that the childhood prevalence of autism spectrum disorder in the United States is 1 case per 88 children (1.14%).[22] It is worth noting that not all children in our study have been followed throughout childhood, and it is likely that some will receive a diagnosis of autism spectrum disorder at older ages. However, the date of diagnosis may differ considerably from the date on which symptoms are first noted. This discrepancy can introduce detection bias if autism spectrum disorders are diagnosed earlier in the offspring of women

Table 3. Association between Period of SSRI Use and Autism Spectrum Disorders in Offspring.*

Period of Maternal SSRI Use	Offspring with Autism Spectrum Disorder	Follow-up	Rate Ratio (95% CI)		
	no.	*no. of person-yr*	*crude*	*age- and period-adjusted*	*fully adjusted*
No use from 2 yr before pregnancy through delivery	3752	4,948,903	Reference	Reference	Reference
Use during pregnancy†	52	42,400	1.62 (1.23–2.13)	1.64 (1.25–2.16)	1.20 (0.90–1.61)
From 2 yr before pregnancy through delivery	29	25,436	1.50 (1.04–2.17)	1.53 (1.06–2.21)	1.08 (0.74–1.58)
Only during pregnancy	23	16,964	1.79 (1.19–2.69)	1.81 (1.20–2.72)	1.40 (0.92–2.13)
During first trimester	40	28,947	1.82 (1.33–2.49)	1.85 (1.36–2.53)	1.35 (0.97–1.87)
Use 2 yr to 6 mo before pregnancy but not during pregnancy	88	65,978	1.76 (1.42–2.27)	1.77 (1.43–2.19)	1.46 (1.17–1.81)

* Offspring were followed from birth until January 1, 2010, or until the child reached 10 years of age, died or was lost to follow-up, or received a diagnosis of autism spectrum disorder — whichever came first. In addition to adjustment for age and calendar period, the rate ratios were adjusted for the mother's age at birth, country of origin, place of residence, parity, psychiatric diagnoses before delivery, other drug use during pregnancy, smoking status during pregnancy, employment status, and level of education. Unless otherwise stated, variables were measured at the beginning of the pregnancy.

† The use of SSRIs during pregnancy was defined as use during the period from 4 weeks before the beginning of the pregnancy until delivery. Included in this category are use of SSRIs both before and during pregnancy and use of SSRIs only during pregnancy.

who were exposed to SSRIs than in the offspring of women who were not, such that the risk with SSRIs would be overestimated if autism spectrum disorders in children whose mothers were not exposed to SSRIs were not detected during the study period.

Finally, the main methodologic challenge of our study and similar studies is confounding by indication.[23] If women with depression or other indications for SSRI use are more likely to have children with autism spectrum disorders, a false association between SSRI use and autism spectrum disorders will be present in an observational study. In unadjusted analyses, we did find a significantly increased risk of autism spectrum disorder in association with the use of SSRIs during pregnancy. In fully adjusted analyses, however, the risk was no longer significant. This result was primarily due to adjustment for a number of psychiatric diagnoses (Table S2 in the Supplementary Appendix), which is consistent with the presence of confounding by indication in the unadjusted analysis. We had access only to maternal psychiatric conditions diagnosed in psychiatric hospitals and psychiatric units (inpatient and outpatient), with no information on cases diagnosed in primary care settings. We introduced a period of SSRI use before pregnancy, which allowed us to evaluate whether maternal use of SSRIs before but not during pregnancy was associated with an increased risk of subsequent autism spectrum disorders in the offspring. The increased risk associated with this pattern of use similarly suggests that any risk associated with SSRI use during pregnancy may be related to the indications for its use rather than a causal effect.

The prevalence of autism spectrum disorders has been increasing in the past couple of decades.[24] The causes of this increase have been hotly debated. Parallel increases in diagnostic practices, the availability of special health care services, public awareness, and suspected environmental risk factors (both intrauterine and postnatal) are often cited. With respect to environmental factors, the use of SSRIs has been increasing. In our study, the risk of autism spectrum disorders was not significantly increased among children whose mothers received SSRIs during pregnancy. The statistical power of the study allows us to rule out an increase in the relative risk of more than 61% with a high degree of certainty, but we cannot exclude the possibility of a smaller increase in risk. However, the increased risk associated with SSRI use before but not during pregnancy suggests that any risk associated with the use of SSRIs during pregnancy may be related to the indications for

their use rather than an effect of these drugs. This highlights the potential effect of confounding by indication in our study and similar studies of SSRIs and the importance of being able to adequately take this confounding into account in the study design. As with all observational studies, the possible presence of residual and unmeasured confounding or ascertainment bias with respect to exposure and outcome adds to the imprecision of our estimates. Interpretation of our results should take this factor into account.

The views and conclusions expressed in this article are those of the authors and should not be understood or cited as being made on behalf of or reflecting the position of the Danish Health and Medicines Authority.

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