Gestational Exposure to Selective Serotonin Reuptake Inhibitors and Offspring Psychiatric Disorders: A National Register-Based Study

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Objective: To investigate the impact of gestational exposure to selective serotonin reuptake inhibitors (SSRIs) on offspring neurodevelopment.

Method: This is a cohort study using national register data in Finland between the years 1996 and 2010. Pregnant women and their offspring were categorized into 4 groups: SSRI exposed (n = 15,729); exposed to psychiatric disorder, no antidepressants (n = 9,651); exposed to SSRIs only before pregnancy (n = 7,980); and unexposed to antidepressants and psychiatric disorders (n = 31,394). We investigated the cumulative incidence of offspring diagnoses of depression, anxiety, autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD) for the 4 groups from birth to 14 years, adjusting for confounders.

Results: The cumulative incidence of depression among offspring exposed prenatally to SSRIs was 8.2% (95% CI = 3.1–13.3%) by age 14.9 years, compared with 1.9% (95% CI = 0.9–2.9%) in the psychiatric disorder, no medication group (adjusted hazard ratio [HR] = 1.78; 95% CI = 1.12–2.82; $p = .02$) and to 2.8% (95% CI = 1.4–4.3%) in the SSRI discontinued group (HR = 1.84; 95% CI = 1.14–2.97; $p = .01$). Rates of anxiety, ASD, and ADHD diagnoses were comparable to rates in offspring of mothers with a psychiatric disorder but no medication during pregnancy. Comparing SSRI exposed to unexposed individuals, the HRs were significantly elevated for each outcome.

Conclusion: Prenatal SSRI exposure was associated with increased rates of depression diagnoses in early adolescence but not with ASD or ADHD. Until confirmed, these findings must be balanced against the substantial adverse consequences of untreated maternal depression.

Key words: SSRI, pregnancy, offspring depression, ASD, ADHD

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Exposure to selective serotonin reuptake inhibitors (SSRIs) during sensitive developmental periods in rodents produces long-lasting effects on behavior, neural circuitry, morphology, and physiology.[1-3] Importantly, the developmental period during which rodents are sensitive to the effects of SSRI exposure overlaps extensively with human brain development during the fetal period. Because the serotonin (5HT) system is highly conserved across phylogeny, we suspected that similar effects might be seen in humans, as SSRIs pass readily through the placenta and enter the fetal circulation.[4] SSRIs have been prescribed increasingly to pregnant women since their introduction 30 years ago.[5,6] However, no studies have been undertaken that followed up children beyond 6 years of age for depressive disorders, which typically emerge after the onset of puberty.[7,8] Research on associations between SSRI exposure and other neurodevelopmental disorders, including autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), has shown inconsistent results.[9-14]

The potential effect of prenatal SSRI exposure on vulnerability to later life disorders is confounded by maternal and paternal mental illness that would increase the risk of neuropsychiatric diagnoses in these children. To address these potential confounds and to better address the long-term safety of SSRI use during pregnancy for the offspring, we performed a large population-based study to investigate the effect of prenatal exposure to SSRIs, or maternal depression–related psychiatric disorders without medication, on offspring neurodevelopment through 14 years of age. Because of the steadily increasing use of SSRIs during pregnancy and the potential long-term burden of offspring depression and anxiety, this question carries substantial public health importance.

This article is discussed in an editorial by Drs. Tim F. Oberlander and Simone N. Vigod on page 351.

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METHOD

Data Sources and Study Population

We used a population-based, prospective cohort study design. All data were collected from

national registers linked by the unique personal identification number assigned to all citizens and permanent residents of Finland. In Finland, all children regularly attend child welfare clinics where trained public health nurses or physicians perform medical examinations; this is offered to all and is free of charge. These services are particularly designed to identify psychiatric and neurodevelopmental disorders. Annual examinations are performed for all school children, and, when indicated, a referral is made to specialized health care; these conditions are then recorded in the inpatient and outpatient registries. Specialized care includes hospital outpatient clinics and inpatient hospital units that are run by specialists. Psychiatric services are run by psychiatrists, who are required to have a 6-year postdoctoral specialist education. A detailed description of the registers and the study design has been published previously.[5]

The total sampling frame includes 845,345 singleton live births in Finland between January 1, 1996, and December 31, 2010. Accordingly, the age range of children in the study cohort is from birth to age 14 years. The mother–child dyads were identified from the national Medical Birth Register (MBR). The register collects data on maternal demographics, reproductive and medical history, health-related behaviors, diagnoses during pregnancy and delivery, and neonatal outcome since 1987, using the *International Classification of Diseases, 10th Revision (ICD-10)* coding since 1996.

The Drug Reimbursement Register, maintained since 1995, collects data on prescription drug purchases and was used to identify the study groups. Drug purchases are recorded concomitantly with the purchase at pharmacies using the International Anatomic-Therapeutic-Chemical (ATC) classification, and drugs are supplied for a maximum of 3 months at a time. The Special Reimbursement Register contains data on chronic illnesses requiring continuous medication since 1964.

The Hospital Discharge Register (HDR) includes inpatient diagnoses covering all somatic and psychiatric hospitals in Finland since 1969, and outpatient diagnoses in public hospitals since 1998. The diagnoses are coded using the *ICD-8* (1969–1986), *ICD-9* (1987–1995), and *ICD-10* since 1996. Information on parental psychiatric diagnoses (*ICD-8*, *ICD-9*, and *ICD-10*), and diagnoses of neuropsychiatric disorders in offspring (*ICD-10*) were derived from this register. Patients treated solely in public primary or in private care are not included in this register.

The national population register contains basic information, including country of birth, marital status, marriages and divorces, and deaths of all Finnish citizens and other citizens residing permanently in Finland.

The register administrators and the data protection authority approved the use of sensitive health registry data for scientific research and the data linkages. The Institutional Ethical Review Board at the National Institute for Health and Welfare, the Social Insurance Institution in Finland, and the institutional review board of the New York State Psychiatric Institute approved the study protocol. All data were anonymized and de-identified before analysis. The study participants were not contacted, and, according to Finnish legislation, informed consent was therefore not required.

Exposure Groups, Mother–Child Dyads

SSRI Exposed Group. Mothers in the SSRI exposed group (n = 15,729) had 1 or more purchases of SSRIs (fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram) during the period from 30 days before pregnancy until the end of pregnancy; the date of purchase indicated the beginning date for each exposure. The beginning of gestation corresponding to the last menstrual period was calculated from the best clinical estimation of gestational age at birth, primarily based on ultrasound and MBR registration. Information on diagnosis of depression or depression-related diagnoses was available for 4,811 (30.6%) mothers in this group; that is mothers, who had been treated in inpatient care or outpatient specialized care, and accordingly had a diagnosis in the HDR. Among the mothers with diagnoses available in the register, 4,713 (98.0%) had a diagnosis related to affective disorders (depression, anxiety, bipolar disorder), and 265 (5.5%) had a diagnosis of nonaffective or undefined psychosis.

The mutually exclusive comparison cohorts included:

Psychiatric Disorder, No Medication Group (n = 9,651). The psychiatric disorder, no medication group (n = 9,651) was exposed to maternal psychiatric diagnosis but no SSRI during pregnancy. This group included all mothers who had a diagnosis of depression or other psychiatric disorder related to depression or SSRI use, obtained from the HDR (*ICD-10* F20–F48; *ICD-9* 295–298, 300) from 1 year before pregnancy until discharge (≤3 weeks) from hospital after delivery, and no purchases of antidepressants (ATC codes N06A, N06CA) or antipsychotics (N05A) from 3 months before until the end of pregnancy. In all, 9,407 mothers (97.5%) had a diagnosis related to affective disorders, and 424 (4.4%) had a diagnosis of nonaffective or undefined psychosis.

SSRI Discontinued Group. The SSRI discontinued group (n = 7,980) was exposed to SSRIs only before pregnancy. Mothers had 1 or more purchases of SSRIs during 1 year before pregnancy until 3 months before pregnancy but no purchases of antidepressant or antipsychotic drugs during 3 months before pregnancy until delivery.

Unexposed Group (n = 31,394). The unexposed group (n = 31,394) was not exposed to SSRIs and had no diagnosis of depression or other psychiatric disorder related to depression or SSRI use. This group included mothers with no purchases of antidepressants or antipsychotics, and no depression or related psychiatric disorder at any time before or during pregnancy. Two unexposed per 1 participant exposed to SSRI were matched for offspring date of birth within ±6 months.

Outcome Variables

The outcome variables included the following: depression, including depressive disorders and unspecified affective disorders (*ICD-10* F32–F39); anxiety, including anxiety disorder (F40–F41); autism spectrum disorder (ASD; F84, but excluding Rett syndrome, F84.2); and attention-deficit/hyperactivity disorder (ADHD; F90). Only *ICD* codes used after the diagnosis was established (*ICD-10* F-codes for psychiatric disorders) were included; codes used in the evaluation process (*ICD-10* Z-codes) were excluded. We excluded individuals with a depression diagnosis only during the first 2 years of life if the diagnosis was not recorded at later stages.

Covariates

Data on covariates were derived from the registers described above and are delineated in Table 1. Although the register data have high coverage for most covariates, data on socioeconomic status (SES) are recorded less accurately. The SES classification is based on maternal occupation, and nearly one-third of participants were classified as "others," including students, housewives, entrepreneurs, and those who were unemployed.

Statistical Analyses

Clinically relevant and plausible covariates were first tested (Table 1). Sex was included in all adjusted models. Because SES and maternal psychiatric disorders are associated with psychiatric drug use and child neurodevelopment, SES and maternal history of other