Pregnancy Complications Following Prenatal Exposure to SSRIs or Maternal Psychiatric Disorders: Results From Population-Based National Register Data

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Objective: Using national register data, the authors examined the relationship between prenatal selective serotonin reuptake inhibitor (SSRI) treatment and pregnancy complications, accounting for psychiatric diagnoses related to SSRI use.

Method: This was a population-based prospective birth cohort study using national register data. The sampling frame included 845,345 offspring, representing all singleton live births in Finland between 1996 and 2010. Pregnancies were classified as exposed to SSRIs (N=15,729), unexposed to SSRIs but with psychiatric diagnoses (N=9,652), and unexposed to medications and psychiatric diagnoses (N=31,394). Pregnancy outcomes in SSRI users were compared with those in the unexposed groups.

Results: Offspring of mothers who received SSRI prescriptions during pregnancy had a lower risk for late preterm birth (odds ratio=0.84, 95% CI=0.74–0.96), for very preterm birth (odds ratio=0.52, 95% CI=0.37–0.74), and for cesarean section (odds ratio=0.70, 95% CI=0.66–0.75) compared with offspring of mothers unexposed to medications but with psychiatric disorders. In contrast, in SSRI-treated mothers, the risk was higher for offspring neonatal complications, including low Apgar score (odds ratio=1.68, 95% CI=1.34–2.12) and monitoring in a neonatal care unit (odds ratio=1.24, 95% CI=1.14–1.35). Compared with offspring of unexposed mothers, offspring of SSRI-treated mothers and mothers unexposed to medications but with psychiatric disorders were both at increased risk of many adverse pregnancy outcomes, including cesarean section and need for monitoring in a neonatal care unit.

Conclusions: In a large national birth cohort, treatment of maternal psychiatric disorders with SSRIs during pregnancy was related to a lower risk of preterm birth and cesarean section but a higher risk of neonatal maladaptation. The findings provide novel evidence for a protective role of SSRIs on some deleterious reproductive outcomes, possibly by reducing maternal depressive symptoms. The divergent findings suggest that clinical decisions on SSRI use during pregnancy should be individualized, taking into account the mother's psychiatric and reproductive history.

Am J Psychiatry 2015; 172:1224–1232; doi: 10.1176/appi.ajp.2015.14121575

The selective serotonin reuptake inhibitors (SSRIs) are the most commonly used antidepressants during pregnancy, with 4%–10% of pregnant women in Finland (1) and in the United States (2) receiving prescriptions for SSRIs. While considered relatively safe, SSRI use during pregnancy has been associated with an increased risk for several pregnancy complications, including preterm birth (3–8), small-for-gestational-age offspring (9), and postpartum hemorrhage (10). Other reported adverse outcomes include poor neonatal adaptation (5, 6, 11–13) and persistent pulmonary hypertension of the newborn (14–16). The most common indications for SSRIs are depressive and anxiety disorders (17). Depressive disorders occur in 10% of pregnant women (18), and depression itself has been associated with adverse pregnancy outcomes (19). Underlying maternal depression is therefore a crucial potential confounder in assessing the risks related to SSRI use during pregnancy. The few studies that have adjusted for underlying maternal psychiatric illness have used small samples and have reported inconsistent results (5, 6, 8, 20, 21). Whether the reported outcomes are due to SSRI use or to the underlying psychopathology is of major clinical importance in the treatment of pregnant women with depressive and anxiety disorders. To address this question, we conducted a study based on a national birth cohort to examine pregnancy complications in mothers exposed to SSRIs and in mothers with a psychiatric diagnosis related to SSRI use but without antidepressant treatment.

METHOD

This was a population-based prospective birth cohort study using national register data. The sampling frame was 845,345

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offspring, consisting of all singleton live births in Finland between Jan. 1, 1996, and Dec. 31, 2010, identified from the national Medical Birth Register maintained by the National Institute for Health and Welfare. A detailed description of the data sources and the study design has been published previously (1), and a summary is provided here. The registers were linked using personal identity codes assigned to each Finnish citizen at birth or immigration. Data for this study were drawn from several registers.

The Drug Reimbursement Register, which has collected data on prescription drug purchases since 1995, was used to identify the study groups. Drug purchases are recorded concomitantly with the purchase at pharmacies using the Anatomic Therapeutic Chemical (ATC) classification, and drugs are supplied for a maximum of 3 months at a time. The register covers 99% of all reimbursed prescription drug purchases in Finland (22). The Special Reimbursement Register, maintained since 1964, contains data on certain chronic illnesses requiring continuous drug treatment. Over-the-counter drugs and medications administered to institutionalized persons are not included.

The Hospital Discharge Register was used to identify mothers' psychiatric history. The register includes inpatient person-level diagnoses recorded in all somatic and psychiatric hospitals in Finland since 1969, and outpatient diagnoses in public specialized care since 1998. Diagnoses for patients treated in public primary care or in private outpatient units are not included. The diagnoses are coded using ICD (ICD-8 for 1969–1986, ICD-9 for 1987–1995, and ICD-10 since 1996).

The Medical Birth Register has collected data since 1987 on maternal demographic characteristics, reproductive and medical history, health-related behaviors, diagnoses during pregnancy and delivery, and neonatal outcome using ICD codes. Data in the register are collected in a standard form from all maternity hospitals and are virtually complete after data linkages to other governmental register resources (23).

The Register of Congenital Malformations, established in 1963, collects data from several sources, including hospitals, health care professionals, and other national registers. The register uses the ICD-9 coding and collects primarily data on major congenital malformations, using the European Surveillance of Congenital Anomalies (EUROCAT) criteria for exclusion (http://www.eurocat-network.eu/content/EUROCAT-Guide-1.4-Section-3.2.pdf).

The utilization of sensitive health register data for scientific research and the data linkages were approved by the register administrators and the data protection authority. The study protocol was approved by the Institutional Ethical Review Board at the National Institute for Health and Welfare and by the Institutional Review Board of the New York State Psychiatric Institute.

Definition of Groups

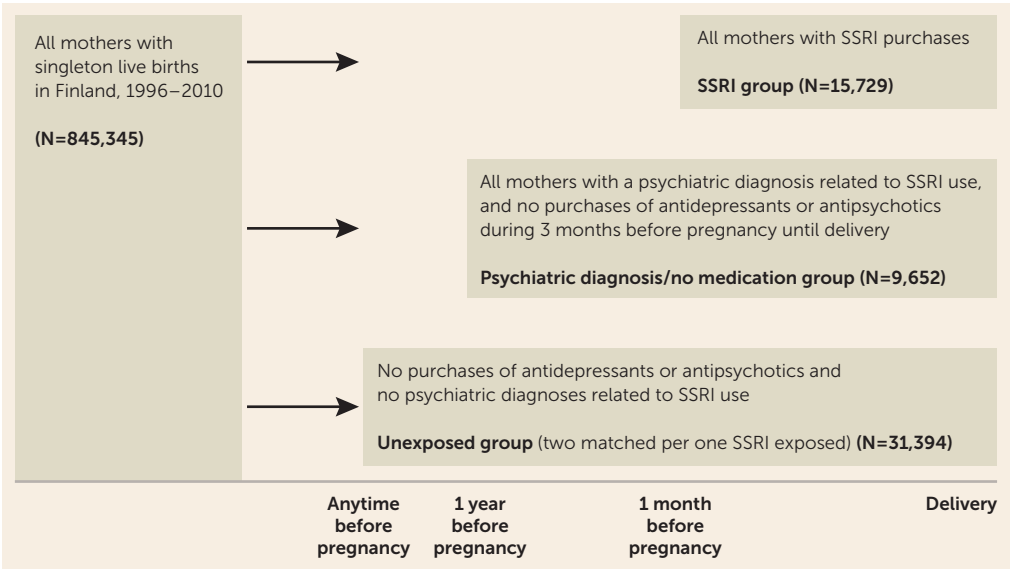
The study examined three groups (Figure 1): women who used SSRIs during pregnancy (the SSRI group), women who had a psychiatric diagnosis related to SSRIs but did not use any SSRIs (the psychiatric diagnosis/no medication group), and women who had no psychiatric diagnosis and no exposure to SSRIs (the unexposed group).

The SSRI group (N=15,729). All women who purchased SSRIs (ATC code N06AB, including fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, and escitalopram) during the period from 30 days before the beginning of gestation until the end of pregnancy were considered exposed, the date of purchase marking the beginning of each exposure (see Figure 1). The beginning of gestation corresponding to the last menstrual period was calculated from the best clinical estimate of gestational age at birth, primarily based on ultrasound and registration in the Medical Birth Register. Pregnancy trimesters were defined as follows: the first trimester lasted until day 84 of gestation, the second covered days 85–182, and the third from day 183 until birth. Information on psychiatric diagnosis in the Hospital Discharge Register was available only for those women who had been treated in a hospital or in public specialized care, and diagnosis was not available for those women in this group who had been treated solely in public primary care or in private medical care.

The psychiatric diagnosis/no medication group (N=9,652). This group included all mothers who had a diagnosis of a psychiatric disorder related to SSRI use from 1 year before the beginning of gestation until discharge (≤3 weeks) from hospital after delivery but who had no purchases of antidepressants (ATC codes N06A, N06CA) or antipsychotics (N05A) from 3 months before the beginning of gestation until delivery (see Figure 1). The diagnoses included nonaffective and undefined psychoses (ICD-10 codes F20–F29; ICD-9 codes 295, 297, 298); bipolar disorder (ICD-10 codes F30–F31; ICD-9 codes 2962, 2963, 2964, 2967A); depression or undefined affective disorders (ICD-10 codes F32–F39; ICD-9 codes 2961, 2968A, 3004A), and anxiety and other emotional disorders (ICD 10 codes F40–F48; ICD-9 codes 300.x, excluding 3004A). This group was derived exclusively from specialized services.

The unexposed group (N=31,394). This group included mothers who had made no purchases of antidepressants or antipsychotics and had no psychiatric diagnoses related to SSRI use at any time prior to or during pregnancy. The unexposed group served as a background control group. Two unexposed subjects per one SSRI-exposed subject were selected randomly from a cohort matched for offspring date of birth within a period of ±6 months (see Figure 1). We compared pregnancy outcomes in the SSRI group to outcomes in the psychiatric diagnosis/no medication group to control for maternal underlying illness, and to the unexposed group. Because fluoxetine and paroxetine are the SSRIs most commonly associated with the neonatal behavioral syndrome (13), we also compared outcomes after fluoxetine or paroxetine exposure during the second or third trimester to outcomes after exposure to other SSRIs.

FIGURE 1. Flow Chart of the Register-Based Information and the Time Window Criteria for Definition of Exposure Groups in a Study of Prenatal Exposure to SSRIs or Maternal Psychiatric Disorders[a]



[a] SSRI=selective serotonin reuptake inhibitor. The SSRI group included all mothers with one or more SSRI purchases 1 month prior to or during pregnancy. The psychiatric diagnosis/no medication group included all mothers who had a psychiatric diagnosis related to SSRI use during pregnancy or within 1 year before pregnancy but who had no purchases of antidepressants or antipsychotics 3 months before or during pregnancy. The unexposed group included mothers with neither a history of psychiatric diagnoses related to SSRI use (in the Hospital Discharge Register) nor any purchases of antidepressants or antipsychotics.

Maternal Characteristics and Covariates

Data on covariates were derived from the registers described above. Covariates included maternal demographic, social, and medical characteristics.

Outcome Variables

The outcomes of interest were selected based on clinical importance, for which divergent results have been published (3–13): 1) diagnoses related to pregnancy and delivery, including hypertension of pregnancy/preeclampsia, mode of delivery (vaginal delivery or cesarean section), and bleeding during or after delivery; and 2) neonatal outcomes, including categorically defined late preterm (32–36 gestational weeks) and very preterm birth (<32 weeks), small for gestational age (birth weight more than two standard deviations below national standards for sex and length of gestation) (24), and neonatal problems, including a 5-minute Apgar score <7, neonatal breathing problems, monitoring in a neonatal (intensive) care unit, and hospital stay at 7 days of age. We also assessed the risk for persistent pulmonary hypertension of the newborn, a rare outcome, and major congenital anomalies in an analysis of first-trimester SSRI exposure.

Statistical Analysis

We used logistic regression models within the generalized linear modeling framework to examine relationships of pregnancy complications to SSRI use and to maternal psychiatric disorders related to SSRI use but not treated with antidepressants. Using generalized estimating equation models, we were able to specify a covariance structure to take into account correlations between siblings to control for nonindependent observations. The crude model included adjustment for sex and the birth periods 1996–2000, 2001–2005, and 2006–2010. For the adjusted analyses, clinically relevant and plausible covariates were first tested for association with the three-class exposure status. When associated with exposure at a significance threshold of 0.1, the covariate was tested separately for association with each outcome. Rather than including a specific set of covariates for each of the 13 outcomes, we included as potential confounders in the logistic regression model those covariates that were associated with exposure and several of the outcomes at $p<0.1$ (see Table S1 in the data supplement that accompanies the online edition of this article). The "unknown" category for socioeconomic status (18%) was included because we anticipated the missing observations to occur completely at random. Because maternal height and prepregnancy weight were only available from 2004 (missing data prevalence, 35%), body mass index was not included in the analyses. All analyses were performed in SAS, version 9.4 (SAS Institute, Cary, N.C.).

RESULTS

A total of 12,817 women purchased SSRIs during the first trimester or 30 days before the beginning of gestation, and 9,322 (59.3%) made two or more purchases. Use of the individual SSRIs during the study years is summarized in Figure S1 in the online data supplement. The maternal characteristics of the three groups are presented in Table 1. Information on psychiatric diagnosis was available for 4,811 (30.6%) of mothers in the SSRI group; mothers in the psychiatric diagnosis/no medication group were all identified

TABLE 1. Maternal Characteristics Tested as Covariates in a Study of Prenatal Exposure to SSRIs or Maternal Psychiatric Disorders[a]

	Covariate Associated With Exposure	SSRI Group (N=15,729)		Psychiatric Diagnosis/ No Medication Group (N=9,652)		Unexposed Group (N=31,394)	
Characteristic	p	N	%	N	%	N	%
Age (years)	<0.001						
≤19		524	3.3	954	9.9	775	2.5
20–24		2,747	17.5	2,117	21.9	5,162	16.4
25–29		4,679	29.8	2,414	25.0	10,361	33.0
30–34		4,459	28.4	2,378	24.6	9,518	30.3
35–39		2,564	16.3	1,390	14.4	4,441	14.2
≤40		756	4.8	399	4.1	1,137	3.6
Place of residence	0.01						
Urban		10,687	67.9	6,707	69.5	21,233	67.6
Semiurban		2,552	16.2	1,512	15.7	5,050	16.1
Rural		2,489	15.8	1,427	14.8	5,054	16.1
Marital status	<0.001						
Married, in relationship, divorced, or widowed		13,364	89.6	7,919	88.1	28,832	95.5
Unmarried		1,546	10.4	1,074	11.9	1,347	4.5
Parity	<0.001						
One or more previous births		9,189	58.4	5,194	53.8	18,569	59.2
No previous births		6,534	41.6	4,455	46.2	12,817	40.8
Smoking during pregnancy	<0.001	4,575	29.9	2,737	29.1	3,947	12.9
Socioeconomic status	<0.001						
Upper white collar worker		1,857	11.8	1,219	12.6	5,360	17.1
Lower white collar worker		4,954	31.5	2,825	29.3	10,479	33.4
Blue collar worker		2,493	15.9	1,435	14.9	4,271	13.6
Other[b]		3,669	23.3	2,365	24.5	5,728	18.3
Unknown		2,756	17.5	1,802	18.7	5,556	17.7
Purchases of other psychiatric drugs[c]	<0.001	3,223	20.5	553	5.7	278	0.9
Prepregnancy diabetes	<0.001	108	0.7	88	0.9	154	0.5
Other chronic diseases[d]	<0.001	1,325	8.4	756	7.8	1,666	5.3
Artificial reproduction	0.4	335	2.1	227	2.4	716	2.3
Body mass index	<0.001						
<18.5		422	4.0	311	5.8	789	3.8
18.5–24.9 (reference)		5,982	56.4	3,266	60.8	13,465	64.1
25–29.9		2,462	23.2	1,139	21.2	4,466	21.3
≥30		1,734	16.4	653	12.2	2,282	10.9

[a] SSRI=selective serotonin reuptake inhibitor. Percentages were calculated from nonmissing data. Missing values were as follows: place of residence, N=64 (0.1%); marital status, N=2,693 (4.7%); previous births, N=17 (<0.1%); smoking during pregnancy, N=1,458 (2.6%); body mass index (available only from 2004 onward), N=19,804 (34.9%).
[b] The "other" category included students, housewives, entrepreneurs, and unemployed.
[c] Other psychiatric drugs included anxiolytics, sedative-hypnotics, and antiepileptic drugs.
[d] Other chronic diseases, drawn from the Special Reimbursement Register, included the following, recorded at any time: thyroid insufficiency, posttransplantation conditions, disseminated connective tissue diseases (including rheumatoid arthritis), chronic asthma, chronic obstructive pulmonary disease, chronic hypertension, and inflammatory bowel diseases.

from the Hospital Discharge Register, and therefore all had a diagnosis. Among mothers in the SSRI group who had a diagnosis, 4,713 (98.0%) had a diagnosis related to affective disorders (depression, anxiety, bipolar disorder), compared with 9,407 (97.5%) in the psychiatric diagnosis/no medication group. A total of 265 (5.5%) mothers in the SSRI group and 424 (4.4%) in the psychiatric diagnosis/no medication group had a diagnosis of non-affective or undefined psychosis (see Table S2 in the data supplement).

Pregnancy and delivery diagnoses by exposure status are presented in Table 2. Compared with the psychiatric diagnosis/no medication group and after adjustment for confounders, women in the SSRI group had a lower risk of cesarean section, emergency or urgent cesarean section, and bleeding; the risk of hypertension of pregnancy did not differ between the two groups. Compared with the unexposed group, the SSRI group had a higher risk of cesarean section, and the psychiatric diagnosis/no medication group had a higher risk of cesarean section, emergency or urgent cesarean section, and bleeding during or after delivery.

Neonatal outcomes are presented in Table 3. Compared with the psychiatric diagnosis/no medication group, the SSRI group had a 16% lower risk of late preterm birth and a 48% lower risk of very preterm birth, but the risk of offspring being born small for gestational age did not differ between the two

TABLE 2. Comparisons of Pregnancy and Delivery Diagnoses, by Exposure Group, in a Study of Prenatal Exposure to SSRIs or Maternal Psychiatric Disorders[a]

	SSRI Group (N=15,729)		Psychiatric Diagnosis/ No Medication Group (N=9,652)		Unexposed Group (N=31,394)		SSRI Group Versus Psychiatric Diagnosis/No Medication Group		SSRI Group Versus Unexposed Group		Psychiatric Diagnosis/ No Medication Group Versus Unexposed Group	
Outcome	N	%	N	%	N	%	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Hypertension of pregnancy	813	5.2	434	4.5	1,413	4.5						
Crude							1.13*	1.00–1.28	1.13**	1.03–1.24	1.00	0.89–1.12
Adjusted							1.10	0.97–1.26	1.09	0.98–1.20	0.99	0.87–1.11
Cesarean section	3,004	20.9	2,387	26.5	4,984	17.3						
Crude							0.77***	0.73–0.82	1.22***	1.16–1.29	1.58***	1.49–1.67
Adjusted							0.70***	0.66–0.75	1.18***	1.11–1.25	1.68***	1.57–1.79
Cesarean section, emergency or urgent	1,600	12.3	977	12.9	2,869	10.7						
Crude							0.96	0.88–1.05	1.13***	1.06–1.21	1.17***	1.08–1.27
Adjusted							0.88 **	0.80–0.97	1.05	0.97–1.14	1.19***	1.09–1.30
Bleeding during or after delivery	520	3.3	342	3.5	903	2.9						
Crude							0.88	0.77–1.01	1.15*	1.03–1.29	1.31*	1.15–1.49
Adjusted							0.83*	0.71–0.96	1.07	0.95–1.21	1.29***	1.13–1.48

[a] SSRI=selective serotonin reuptake inhibitor. Percentages were calculated from nonmissing data. Crude odds ratios were adjusted for sex and birth period (1996–2000, 2001–2005, and 2006–2010). Adjusted odds ratios were adjusted for sex, birth period, maternal age at delivery, place of residence, marital status, parity, smoking, socioeconomic status, purchase of anxiolytics, sedative-hypnotics, or antiepileptic drugs, prepregnancy diabetes, and other chronic diseases (see Table 1 footnotes). For cesarean section, the reference group was those with vaginal cephalic delivery.

* $p<0.05$. ** $p<0.01$. *** $p<0.001$.

groups. The SSRI group had a higher risk of all neonatal problems, but not hospital stay at 7 days of age. Compared with the unexposed group, the SSRI group had a higher risk of all neonatal problems, including hospital stay at 7 days age. Compared with the unexposed group, the psychiatric diagnosis/no medication group had a higher risk of late preterm and very preterm birth, need for monitoring in a neonatal care unit, and hospital stay at 7 days of age. Twelve infants in the SSRI group (0.1%) had a diagnosis of persistent pulmonary hypertension, compared with three (<0.1%) in the psychiatric diagnosis/no medication group (odds ratio=2.49, 95% CI=0.71–8.70) and 21 (0.1%) in the unexposed group (odds ratio=1.14, 95% CI=0.56–2.33).

In subanalyses in which the SSRI group included only women with two or more SSRI purchases, comparison with the psychiatric diagnosis/no medication group yielded adjusted results similar to those obtained for women with any SSRI purchases for all outcomes except that the risk of hypertension of pregnancy was now marginally higher (odds ratio=1.16, 95% CI=1.01–1.35, p=0.04) and the lower risk of urgent or emergency cesarean section was now insignificant (see Table S3 in the data supplement). There was also a tendency for slightly higher risks than those observed in the overall SSRI group for 5-minute Apgar score <7, neonatal breathing problems, and needing monitoring in a neonatal care unit (see Table S3).

In the trimester-specific analyses comparing the subgroup of mothers with SSRI use during the first trimester with the psychiatric diagnosis/no medication group, SSRI use was associated with a lower risk of preterm birth (<37 weeks) (Table 4), but the association was marginally insignificant after second- and/or third-trimester exposure. The risks of neonatal problems and major congenital anomalies were not higher after first-trimester exposure, but exposure during the second and/or third trimester was associated with a higher risk of neonatal problems, including 5-minute Apgar score <7, neonatal breathing problems, and monitoring in a neonatal care unit, with odds ratios higher than those observed for SSRI use at any time during pregnancy. A subanalysis that was restricted to full-term infants and compared second- and/or third-trimester fluoxetine or paroxetine use with use of other SSRIs revealed no significant differences for 5-minute Apgar score <7, neonatal breathing problems, or monitoring in a neonatal care unit.

DISCUSSION

We found that SSRI use during pregnancy is associated with a lower risk of late preterm and very preterm birth compared with women who had a psychiatric diagnosis but were not treated with antidepressants during pregnancy. To our knowledge, this is a novel finding. We also observed a lower risk of cesarean section in SSRI users. In addition, we confirmed an increased risk of a 5-minute Apgar score <7, neonatal breathing problems, and need for monitoring in a neonatal care unit.

TABLE 3. Comparisons of Neonatal Outcomes, by Exposure Group, in a Study of Prenatal Exposure to SSRIs or Maternal Psychiatric Disorders[a]

	SSRI Group (N=15,729)		Psychiatric Diagnosis/No Medication Group (N=9,652)		Unexposed Group (N=31,394)		SSRI Group Versus Psychiatric Diagnosis/No Medication Group		SSRI Group Versus Unexposed Group		Psychiatric Diagnosis/No Medication Group Versus Unexposed Group	
Outcome	N	%	N	%	N	%	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Preterm birth												
32–36 weeks	741	4.7	515	5.4	1,193	3.8						
Crude							0.89*	0.79–1.00	1.24***	1.13–1.37	1.40***	1.26–1.57
Adjusted							0.84*	0.74–0.96	1.07	0.96–1.20	1.27***	1.13–1.44
<32 weeks	80	0.5	93	1.0	186	0.6						
Crude							0.53***	0.39–0.72	0.85	0.65–1.11	1.60***	1.23–2.08
Adjusted							0.52***	0.37–0.74	0.78	0.57–1.07	1.50**	1.12–2.01
Small for gestational age	393	2.5	245	2.5	673	2.2						
Crude							1.00	0.85–1.17	1.17*	1.03–1.33	1.17*	1.01–1.36
Adjusted							0.92	0.77–1.10	0.86*	0.74–0.99	0.93	0.79–1.10
5-minute Apgar score <7	376	3.9	113	2.3	383	2.1						
Crude							1.72***	1.39–2.13	1.96***	1.70–2.27	1.14	0.92–1.41
Adjusted							1.68***	1.34–2.12	1.72***	1.46–2.02	1.02	0.81–1.28
Breathing problems	763	4.9	310	3.2	874	2.8						
Crude							1.50***	1.31–1.72	1.77***	1.60–1.96	1.18*	1.04–1.35
Adjusted							1.40***	1.20–1.62	1.60***	1.43–1.79	1.15	1.00–1.32
Neonatal care unit	2,405	15.3	1,160	12.0	3,032	9.7						
Crude							1.31 ***	1.22–1.42	1.68***	1.58–1.78	1.28***	1.19–1.38
Adjusted							1.24***	1.14–1.35	1.38***	1.29–1.48	1.12**	1.03–1.21
In hospital at 7 days of age	1,315	8.4	821	8.6	1,760	5.6						
Crude							0.98	0.89–1.08	1.53***	1.42–1.65	1.56***	1.43–1.71
Adjusted							0.89*	0.80–0.99	1.22***	1.12–1.33	1.37***	1.24–1.51

[a] SSRI=selective serotonin reuptake inhibitor. Percentages were calculated from nonmissing data. Crude odds ratios were adjusted for sex and birth period (1996–2000, 2001–2005, and 2006–2010). Adjusted odds ratios were adjusted for sex, birth period, maternal age at delivery, place of residence, marital status, parity, smoking, socioeconomic status, purchase of anxiolytics, sedative-hypnotics, or antiepileptic drugs, prepregnancy diabetes, and other chronic diseases (see Table 1 footnotes). Five-minute Apgar scores were available from 2004 to 2010. For preterm (32–36 weeks) and very preterm (<32 weeks) birth, the reference group was birth at ≥37 gestational weeks.

* $p<0.05$. ** $p<0.01$. *** $p<0.001$.

The risk of preterm birth was 16% lower, and the risk of very preterm birth nearly 50% lower, for women using SSRIs during pregnancy compared with mothers who had a psychiatric diagnosis but no medication use. This finding remained even when we restricted the analyses to women with two or more SSRI purchases, a sign of continuous use and greater adherence. Given that less than 0.1% of women in the whole birth cohort purchased the first-generation antipsychotics prochlorperazine and dixyrazine, used for treating morning sickness during pregnancy, a condition associated with a reduced risk of preterm birth (25), their use is unlikely to have biased the results.

Preterm birth is the single most important cause of neonatal and infant death and is associated with long-term neurological disabilities in surviving infants (26). Several previous studies have reported an increased risk of preterm birth associated with SSRI use during pregnancy (3–8). Although SSRI use usually occurs in the context of maternal depressive and anxiety disorders, only a few studies have adjusted for these factors, yielding conflicting results (5, 6, 8, 20, 21). Three of these studies were prospective; one observed a twofold higher risk of preterm birth in SSRI users (N=329) (5), and another reported similarly elevated risks of preterm birth between SSRI users (N=48) and women with untreated depression (6). The third study, a population-based study from Norway, reported a 50% higher risk of preterm birth in SSRI users (N=572), but the risk was no longer significant after adjustment for maternal depressive symptoms (20). Yet another study, based on pharmacy records (N=221), reported an increased risk of preterm birth in SSRI users compared with women who had a psychiatric illness but no SSRI use (8). Methodological limitations of previous studies include small sample sizes (5, 6, 8) and selection bias. Underestimation of SSRI exposure and maternal psychiatric illness (8) and low response rates (20) may also have biased the findings. Another population-based study found an increased risk of preterm birth in SSRI users (N=1,500), but after adjusting for depression severity, the risk became nonsignificant, suggesting that maternal depression confounded the association (21). None of the previous studies that controlled for maternal

TABLE 4. Comparison of Pregnancy and Neonatal Outcomes Between SSRI-Exposed Mothers and Those With a Psychiatric Diagnosis But No Antidepressant Use, By Gestational Period of SSRI Exposure[a]

	SSRI Exposure During First Trimester Only (N=7,069)		SSRI Exposure at Least During Second and/or Third Trimester (N=8,660)	
Outcome	Odds Ratio	95% CI	Odds Ratio	95% CI
Hypertension of pregnancy	1.04	0.89–1.21	1.16	1.00–1.35
Cesarean section	0.66***	0.61–0.72	0.73***	0.67–0.79
Cesarean section, emergency or urgent	0.84**	0.75–0.95	0.90	0.81–1.01
Bleeding during or after delivery	0.82*	0.69–0.99	0.84*	0.71–1.00
Preterm birth <37 weeks[b]	0.71***	0.61–0.83	0.87	0.76–1.01
Small for gestational age	0.89	0.72–1.11	0.96	0.78–1.17
5-minute Apgar score <7	1.04	0.77–1.40	2.15***	1.68–2.74
Breathing problems	0.99	0.82–1.19	1.76***	1.50–2.07
Neonatal care unit	0.97	0.87–1.07	1.51***	1.37–1.66
In hospital at 7 days of age	0.73***	0.64–0.83	1.03	0.92–1.16
Major congenital anomaly[c]	1.03	0.88–1.20		

[a] SSRI=selective serotonin reuptake inhibitor. Odds ratios were adjusted for sex, birth period, maternal age at delivery, place of residence, marital status, parity, smoking, socioeconomic status, purchase of anxiolytics, sedative-hypnotics, or antiepileptic drugs, prepregnancy diabetes, and other chronic diseases (see Table 1 footnotes).
[b] Preterm birth <37 weeks only was included because very preterm birth (<32 weeks) would exclude the possibility of purchasing SSRIs at later gestational weeks.
[c] Only first-trimester exposures to SSRIs were assessed.
* p<0.05. **p<0.01. ***p<0.001.

psychiatric illness found a protective effect of SSRI use on preterm birth.

Prenatal stress, associated with maternal depression, affects regulation of the hypothalamic-pituitary-adrenal axis, resulting in increased corticosteroid production and release of vasoactive amines, potentially reducing umbilical blood flow and predisposing to hypoxia and preterm birth (27). Hence, the protective effect observed in our cohort could be related to relief of symptoms and stress secondary to the antidepressant effect of SSRIs, and it may be consistent with the increased risk of preterm birth in mothers with untreated depression, which was also observed in our study.

Our findings also suggest that treating maternal depression with SSRIs may lower the risk of cesarean section; we observed a 30% lower risk in SSRI users compared with mothers who had a psychiatric diagnosis but were not treated with antidepressants. Although one previous study observed an increased risk of cesarean section in women using antidepressants, the authors did not control for maternal depression (4).

A recent study in low-income women (10) reported a 40% higher risk of postpartum hemorrhage in women using SSRIs close to delivery, controlling for maternal depression severity. Contrary to this, we found a marginally protective effect of SSRI use compared with the psychiatric diagnosis/no medication group, and SSRI use during the second and/or third trimester was not associated with bleeding even when compared with the unexposed group (odds ratio=1.10, 95% CI=0.95–1.28). These findings are in line with the observed lower risk of cesarean section because these two outcomes are strongly related. These findings are also consistent with a recent population-based study from Norway that reported no increased risk for postpartum hemorrhage, controlling for maternal depression (28). While SSRI use may increase the risk of some bleeding events due to drug-induced platelet dysfunction, normal hemostatic mechanisms after delivery, including uterine contractions and uterine sinus thrombosis, are unlikely to be affected by SSRIs (29).

Regarding other key pregnancy and neonatal complications, hypertension of pregnancy (including preeclampsia) was not more common among SSRI users compared with either of the comparison groups. The risk became marginally significant in women with two or more SSRI purchases (see Table S3), suggesting no major effect, in line with a recent study controlling for maternal depression (30). Also in line with previous research was that the risk of congenital anomalies was not increased and that SSRI use was associated with an increased risk for several neonatal problems, including low Apgar score, breathing problems, and need for monitoring in a neonatal care unit (4, 11–13, 31, 32). Because the study was based on register data, we did not have information on whether these symptoms resulted from drug toxicity or from drug withdrawal (33). Consequently, the results do not provide information on how best to treat these infants. It is possible that increased vigilance based on the knowledge that the mother had been treated with an SSRI led to increased identification of neonatal maladaptation in the SSRI-exposed group. Our results suggest that the symptoms are relatively short-lived. Even in this large study, we could not confirm an increased risk of persistent pulmonary hypertension of the newborn.

Strengths of this study include comprehensive prospectively acquired data in a large national birth cohort and inclusion of a comparison group of women with a psychiatric diagnosis related to SSRI use but no antidepressant medication during pregnancy. The prevalence of SSRI use and several of the examined outcomes in our study were comparable to those reported in other countries (2, 14, 28, 30, 34, 35), suggesting that the results are generalizable to other populations. The register data allowed us to adjust for a large number of meaningful potential confounders. Moreover, exposures, outcomes, and covariates in the registers have been validated, and the quality of ascertainment of these variables is high (22, 23, 36).

One limitation of the study is that we had no information on illness severity. The Hospital Discharge Register includes comprehensive data on diagnoses but no data on symptom levels. We had information only on maternal psychiatric disorders diagnosed in inpatient or outpatient specialized care. Hence, we cannot directly evaluate the effect of SSRI

treatment on the reduction of psychiatric symptom burden and its relationship with perinatal outcomes, although we were able to adjust for several covariates that are correlated with illness severity, including smoking (37), socioeconomic status, and use of other psychiatric drugs, including mood stabilizers. Our findings should stimulate further research on samples of pregnant mothers, treated and untreated with SSRIs, for whom information on symptom severity is available.

Another limitation is the possibility of residual confounding by behavioral factors, such as alcohol and illicit drug use, which were not available in the register data. Use of these substances is strongly correlated with smoking, however, which was accounted for in the analyses. For preterm delivery, one limitation is that information was not available on the respective proportions with spontaneous and elective preterm births. Further limitations include those commonly present in register-based studies, including lack of assessment of medication adherence and possible misclassification of timing of exposure. However, our results were consistent when analyses were restricted to women with two or more SSRI purchases during pregnancy, indicating greater adherence.

CONCLUSIONS

We have provided novel evidence that SSRI use is associated with a lower risk of preterm birth and cesarean section, compared with presence of a psychiatric diagnosis but no antidepressant treatment, and we confirmed the results from previous research of a higher risk for several neonatal problems. These divergent findings reinforce the view that the decision on whether to prescribe an SSRI during pregnancy should be individualized to the mother's medical and psychiatric history.

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Supported by NIH grant P50MH090966.

Dr. Gyllenberg has received research grants from the Sigrid Juselius Foundation, the Foundation for Pediatric Research (Finland), and the Finnish Medical Foundation. The other authors report no financial relationships with commercial interests.

Received December 21, 2014; revisions received March 11 and May 4, 2015; accepted May 11, 2015; published online August 4, 2015.

REFERENCES

1. Malm H, Artama M, Brown AS, et al: Infant and childhood neurodevelopmental outcomes following prenatal exposure to selective serotonin reuptake inhibitors: overview and design of a Finnish Register-Based Study (FinESSI). BMC Psychiatry 2012; 12:217
2. Cooper WO, Willy ME, Pont SJ, et al: Increasing use of antidepressants in pregnancy. Am J Obstet Gynecol 2007; 196: 544.e1–544.e5
3. El Marroun H, Jaddoe VW, Hudziak JJ, et al: Maternal use of selective serotonin reuptake inhibitors, fetal growth, and risk of adverse birth outcomes. Arch Gen Psychiatry 2012; 69:706–714
4. Reis M, Källén B: Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. Psychol Med 2010; 40:1723–1733
5. Lund N, Pedersen LH, Henriksen TB: Selective serotonin reuptake inhibitor exposure in utero and pregnancy outcomes. Arch Pediatr Adolesc Med 2009; 163:949–954
6. Wisner KL, Sit DK, Hanusa BH, et al: Major depression and antidepressant treatment: impact on pregnancy and neonatal outcomes. Am J Psychiatry 2009; 166:557–566
7. Huang H, Coleman S, Bridge JA, et al: A meta-analysis of the relationship between antidepressant use in pregnancy and the risk of preterm birth and low birth weight. Gen Hosp Psychiatry 2014; 36:13–18
8. Grzeskowiak LE, Gilbert AL, Morrison JL: Neonatal outcomes after late-gestation exposure to selective serotonin reuptake inhibitors. J Clin Psychopharmacol 2012; 32:615–621
9. Toh S, Mitchell AA, Louik C, et al: Antidepressant use during pregnancy and the risk of preterm delivery and fetal growth restriction. J Clin Psychopharmacol 2009; 29:555–560
10. Palmsten K, Hernández-Díaz S, Huybrechts KF, et al: Use of antidepressants near delivery and risk of postpartum hemorrhage: cohort study of low income women in the United States. BMJ 2013; 347:f4877
11. Koren G, Boucher N: Adverse effects in neonates exposed to SSRIs and SNRI in late gestation: Motherisk Update 2008. Can J Clin Pharmacol 2009; 16:e66–e67
12. Levinson-Castiel R, Merlob P, Linder N, et al: Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. Arch Pediatr Adolesc Med 2006; 160:173–176
13. Moses-Kolko EL, Bogen D, Perel J, et al: Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. JAMA 2005; 293:2372–2383
14. Kieler H, Artama M, Engeland A, et al: Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. BMJ 2012; 344:d8012
15. Källén B, Olausson PO: Maternal use of selective serotonin re-uptake inhibitors and persistent pulmonary hypertension of the newborn. Pharmacoepidemiol Drug Saf 2008; 17:801–806
16. Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al: Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. N Engl J Med 2006; 354:579–587
17. Masand PS, Gupta S: Selective serotonin-reuptake inhibitors: an update. Harv Rev Psychiatry 1999; 7:69–84
18. Melville JL, Gavin A, Guo Y, et al: Depressive disorders during pregnancy: prevalence and risk factors in a large urban sample. Obstet Gynecol 2010; 116:1064–1070
19. Grote NK, Bridge JA, Gavin AR, et al: A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. Arch Gen Psychiatry 2010; 67: 1012–1024
20. Nordeng H, van Gelder MM, Spigset O, et al: Pregnancy outcome after exposure to antidepressants and the role of maternal depression: results from the Norwegian Mother and Child Cohort Study. J Clin Psychopharmacol 2012; 32:186–194
21. Oberlander TF, Warburton W, Misri S, et al: Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. Arch Gen Psychiatry 2006; 63:898–906
22. Martikainen J, Pajunen R, Saastamoinen L, et al: Finnish Statistics on Medicines 2009. Joint publication of the Finnish Medicines Agency and the Social Insurance Institution in Finland. Tampere, Juvenes Print and Tampereen Yliopistopaino Oy, 2010. http://www.kela.fi/in/internet/suomi.nsf/NET/210503131819PN

23. Gissler M, Shelley J: Quality of data on subsequent events in a routine Medical Birth Register. Med Inform Internet Med 2002; 27:33–38
24. Sankilampi U, Hannila ML, Saari A, et al: New population-based references for birth weight, length, and head circumference in singletons and twins from 23 to 43 gestation weeks. Ann Med 2013; 45:446–454
25. Koren G, Madjunkova S, Maltepe C: The protective effects of nausea and vomiting of pregnancy against adverse fetal outcome: a systematic review. Reprod Toxicol 2014; 47:77–80
26. Saigal S, Doyle LW: An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008; 371:261–269
27. Wadhwa PD, Entringer S, Buss C, et al: The contribution of maternal stress to preterm birth: issues and considerations. Clin Perinatol 2011; 38:351–384
28. Lupattelli A, Spigset O, Koren G, et al: Risk of vaginal bleeding and postpartum hemorrhage after use of antidepressants in pregnancy: a study from the Norwegian Mother and Child Cohort Study. J Clin Psychopharmacol 2014; 34:143–148
29. Andrade C, Sandarsh S, Chethan KB, et al: Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. J Clin Psychiatry 2010; 71:1565–1575
30. Palmsten K, Huybrechts KF, Michels KB, et al: Antidepressant use and risk for preeclampsia. Epidemiology 2013; 24:682–691
31. Malm H, Artama M, Gissler M, et al: Selective serotonin reuptake inhibitors and risk for major congenital anomalies. Obstet Gynecol 2011; 118:111–120
32. Furu K, Kieler H, Haglund B, et al: Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design. BMJ 2015; 350:h1798
33. Koren G, Finkelstein Y, Matsui D, et al: Diagnosis and management of poor neonatal adaptation syndrome in newborns exposed in utero to selective seretonin/norepinephrine reuptake inhibitors. J Obstet Gynaecol Can 2009; 31:348–350
34. Hanley GE, Mintzes B: Patterns of psychotropic medicine use in pregnancy in the United States from 2006 to 2011 among women with private insurance. BMC Pregnancy Childbirth 2014; 14:242
35. Garn JV, Nagulesapillai T, Metcalfe A, et al: International Comparison of Common Risk Factors of Preterm Birth Between the US and Canada, Using PRAMS and MES (2005–2006). Matern Child Health J 2014; 19:811–818
36. Sund R: Quality of the Finnish Hospital Discharge Register: a systematic review. Scand J Public Health 2012; 40:505–515
37. Hebert KK, Cummins SE, Hernández S, et al: Current major depression among smokers using a state quitline. Am J Prev Med 2011; 40:47–53