ORIGINAL ARTICLE

# Neonatal Outcomes After Prenatal Exposure to Selective Serotonin Reuptake Inhibitor Antidepressants and Maternal Depression Using Population-Based Linked Health Data

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**Context:** Prenatal exposure to selective serotonin reuptake inhibitor (SSRI) antidepressants and maternal depression both alter neonatal health, and distinguishing the effects of each influence remains challenging.

**Objective:** To determine whether exposure to SSRIs and depression differs from exposure to maternal depression alone.

**Design:** Using population health data, records of neonatal birth outcomes were linked to records of maternal health and prenatal maternal prescriptions for SSRIs.

**Setting:** Population of British Columbia, Canada.

**Participants:** Mothers and their infants, representing all live births during a 39-month period (N = 119 547) (1998-2001).

**Main Outcome Measures:** Outcomes from infants of depressed mothers treated with SSRIs (SE-D) were compared with outcomes from infants of depressed mothers not treated with medication (DE) and nonexposed controls. To control for maternal mental illness severity, propensity score matching was used to identify a comparison group of DE mothers who were similar to the SE-D mothers in characteristics in the year preceding and during pregnancy.

**Results:** Fourteen percent of mothers were diagnosed as having depression during their pregnancy, and the incidence of prenatal SSRI exposure increased from 2.3% to 5.0% during a 39-month period. Birth weight and gestational age for SE-D infants were significantly less than for DE infants, as was the proportion of infants born at less than 37 weeks (95% confidence interval [CI], –1 to –64, –0.25 to –0.45, and –0.009 to –0.04, respectively), although differences in the incidence of birth weight less than the 10th percentile for gestational age were not significant. An increased proportion of SE-D infants had neonatal respiratory distress (13.9% vs 7.8%), jaundice (9.4% vs 7.5%), and feeding problems (3.9% vs 2.4%) compared with DE infants (95% CI of difference, 0.042-0.079, 0.003-0.334, and 0.005-0.025, respectively). When outcomes were compared between SE-D and propensity score–matched DE neonates, SE-D was associated with increased incidence of birth weight below the 10th percentile and rates of respiratory distress.

**Conclusion:** With linked population health data and propensity score matching, prenatal SE-D exposure was associated with an increased risk of low birth weight and respiratory distress, even when maternal illness severity was accounted for.

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DEPRESSION OCCURS IN AN estimated 7% to 15% of all pregnancies[1] and is widely recognized as a perinatal factor that alters birth outcomes and neonatal behaviors.[2,3] However, pharmacologic management of perinatal depression is not without risk to the neonate.[4] Soon after the introduction of selective serotonin reuptake inhibitor (SSRI) antidepressants in 1988 and their use to manage mood disorders during pregnancy, studies emerged reporting adverse neonatal effects.[4-6] Some early studies suggested that SSRI use was safe,[7] with little or no risk of adverse outcomes,[8-10] while others reported neurobehavioral disturbances and increased risks of lower birth weight and preterm birth.[5,11,12] While exposure has not been associated with major anomalies,[13,14] recent scientific and public attention has focused on a cluster of symptoms often referred to as "poor neonatal adaptation," which includes respiratory distress, hypoglycemia, temperature instability, and irritability[5,15-17] that may reflect pharmacologic neurotoxic[12,16] or behavioral teratogenic[18,19] effects. An increased risk of these symptoms, including convulsions, has also been found through the use of large population-based birth registries or World Health Organization data sets.[17,20]

Two previous prospective population-based studies matching maternal prescription data with birth data yielded conflicting evidence of adverse outcomes. Using the Swedish Medical Birth Registry, Ericson et al[21] reported that prenatal exposure was not associated with an increased risk of adverse birth outcomes among 546 neonates of mothers receiving an SSRI during their pregnancy. In contrast, using US health maintenance organization data, Simon et al[22] reported that prenatal SSRI exposure was associated with earlier delivery and lower birth weight, and third-trimester SSRI exposure was particularly associated with lower Apgar scores.

While these studies were able to examine neonatal outcomes in large populations, studies to date have been subject to report bias (ie, lack of precise timing of exposure data, maternal recall, mothers calling a teratology information service, or inconsistent definitions of "neonatal withdrawal" as an adverse outcome), and they were unable to examine the influence of nonrandom maternal characteristics that may have led to SSRI use during pregnancy and that could have also influenced fetal and neonatal health (ie, low socioeconomic class, number of prenatal visits, or geographic location). None of these studies was able to link a particular medication exposure to a specific neonatal outcome nor to compare the effects of exposure to SSRIs with the effect of maternal prenatal depression itself.

Concerns about neonatal symptoms led the Food and Drug Administration[23] and Health Canada[24] to issue warnings in 2004 regarding third-trimester SSRI use. These warnings were issued even though recent extensive reviews of the effects of prenatal SSRI exposure[4,25] have observed that neonatal outcomes in this setting are at the intersection of exposure to maternal depression and SSRI medications, highlighting the need to distinguish outcomes that are specific to each of these factors. For ethical and health reasons, it is not possible to study the effects of SSRI use during pregnancy in the absence of psychiatric illness, making it impossible to study the effects of SSRI exposure independent of exposure to depressed maternal mood. To date, a randomized controlled study of the neonatal effects of SSRI exposure in the context of depression vs depression alone has not been undertaken to differentiate drug-induced adverse effects from those induced by depression itself. However, as an alternative approach, use of population-based health data may offer a way to make comparisons between neonatal outcomes among offspring of depressed mothers who choose not to use an SSRI during their pregnancy with those who were treated with an SSRI and thereby bring us a step closer to identifying outcomes that might differ with these 2 exposures.

To examine how the effects of SSRI medication used to treat depression during pregnancy might differ from the effects of gestational exposure to maternal depression alone, we undertook a population-based study using administrative health data linking maternal health (mental health diagnoses) and prescription records to neonatal data. We expected that mothers in the SSRI group might be more severely depressed than mothers in the depression-alone group, and therefore maternal illness severity might confound our ability to examine outcomes between SSRI and depression exposure. For this reason, we used propensity score matching to control for differences in maternal illness severity between groups. We expected, while controlling for illness severity, that parental SSRI use, which might lessen the severity of maternal illness, would be associated with improved neonatal outcomes compared with the outcomes after exposure to maternal depression alone.

## METHODS

This study was undertaken with approval from the University of British Columbia Research Ethics Board, the Children's and Women's Health Centre of British Columbia Research Review Committee, the British Columbia Ministry of Health Services, and the British Columbia College of Pharmacists. Data were analyzed by 3 of us (T.F.O., W.W., and J.A.).

### DATA SET COMPILATION

Data used in this study came from 5 administrative sources housed in the British Columbia Linked Health Database[26] (British Columbia registry of births, hospital separation records, the PharmaCare registry of subsidized prescriptions, physician billing records; and the registry of Medical Services Plan subscribers) linked to PharmaNet, a province-wide network recording all prescriptions dispensed by British Columbia pharmacists. The patient is identified by means of the personal health number, a 10-digit number that uniquely identifies all subscribers to British Columbia's Medical Services Plan. In British Columbia, all users of medical services must be subscribers. The data were processed by the Centre for Health Services and Policy Research, University of British Columbia, which linked these data, replacing personal identifiers with unique, nonidentifying study numbers and attached derived variables. PharmaNet provided records with the same unique, nonidentifying study number as was provided by the Centre for Health Services and Policy Research, so the prescription data could be linked to the other health data deterministically.

A total of 203 520 registered live births in British Columbia occurred between April 1, 1997, and March 31, 2002. Of these, 200 291 (98.4%) had a valid study number that was linked to the mother's study number, and 192 725 (96.2%) of these records unambiguously matched hospital birth records. Of the 192 725, 191 452 (99.3%) reported estimated gestational ages between 11 and 59 weeks on the hospital separation record, which enabled us to estimate the date of conception. To ensure that the infants with long hospital stays were not underreported in our sample, we restricted our analysis to those with dates of conception before March 26, 2001, allowing 90 days between the last expected birth date and the last hospital separation date. To match maternal prescription records in the PharmaNet database, we further restricted the analysis to neonates with an estimated date of conception between January 1, 1998, and March 26, 2001, reducing our sample to 120 702.

Hospital separation records contain up to 16 diagnostic or procedure codes that are provided by the physician attending during the neonatal period. Physicians entered at least 1 *International Classification of Diseases, Ninth Revision (ICD-9)* diagnostic code for 40 733 (34%) and at least 2 diagnostic codes for 27 192 (23%) of the 120 702 births.

After removal of 87 records with data entry errors and 1068 records for multiple births, the study population comprised records related to 119 547 live births. To these records, we linked information about maternal prescriptions for all records of SSRI antidepressants, other antidepressants, benzodiazepines, and antipsychotic medications dispensed between January 1, 1998,

**Table 1. Maternal *ICD-9* Diagnostic Codes for Mothers in the SE-D Group**

| Code | Description |
|---|---|
| 290.2 | Senile dementia, depressed or paranoid type |
| 296 | Manic-depressive psychosis, manic type |
| 296.1 | Manic-depressive psychosis, depressed type |
| 296.2 | Manic-depressive psychosis, circular type but currently manic |
| 296.3 | Manic-depressive psychosis, circular type but currently depressed |
| 296.4 | Manic-depressive psychosis, circular type, mixed |
| 296.5 | Manic-depressive psychosis, circular type, current condition not specified |
| 296.6 | Manic-depressive psychosis, other and unspecified |
| 298 | Depressive type |
| 300.4 | Neurotic depression |
| 309 | Brief depressive reaction |
| 309.1 | Prolonged depressive reaction |
| 311 | Depressive disorder, not elsewhere classified |
| 50B | Anxiety/depression |

Abbreviations: *ICD-9, International Classification of Diseases, Ninth Revision*; SE-D, depressed mothers treated with selective serotonin reuptake inhibitors.

and March 31, 2002. This was derived from 363 641 records with 915 distinct drug identity numbers; 98.1% of these records had a unique combination of date, drug identity number, and study number, leaving 356 727 prescriptions. The file identified the drug by brand name and generic name, the date that the drugs were dispensed, and the number of days supplied, together with a unique study number for the mother.

Prenatal exposure occurred if the period from the date the drugs were dispensed until that date plus the number of days for which drugs were supplied overlapped with the pregnancy. We excluded the date of birth from the pregnancy to eliminate drugs taken after the baby had been born. Of the total 356 727 prescriptions, we identified 75 456 for one of the following SSRIs: citalopram hydrobromide, fluoxetine hydrochloride, fluvoxamine maleate, paroxetine, sertraline hydrochloride, and venlafaxine hydrochloride.

Information on medical histories, including diagnosis of maternal mood both during pregnancy and in the 12 months before conception, was obtained from Ministry of Health Services, Medical Services Plan billing records. Records for all medical services outside a hospital in British Columbia are submitted electronically with a valid *ICD-9* diagnostic code.[27]

## STUDY GROUP IDENTIFICATION

To distinguish between the effects of SSRIs and the effects of depression and to ensure that our results were not confounded by the effects of other psychotropic medications taken by the mothers, we identified 3 mutually exclusive and homogeneous groups of neonates based on the maternal mental health and medication records: (1) The *SSRI group* (SE-D) consisted of neonates of depressed mothers who had filled a prescription for an SSRI 49 days or more after conception but who had not received any other antidepressants, benzodiazepines, or antipsychotics during pregnancy. Ninety percent of the mothers in this group had been diagnosed as having depression (on one 3- or 4-digit *ICD-9* code [**Table 1**]) either during pregnancy or during the year before becoming pregnant. We observed that at day 112 of the pregnancy, the proportion of mothers using SSRIs was 49.7% of those using an SSRI on day 1 of their pregnancy. Therefore, to ensure that we studied outcomes after substantial prenatal SSRI exposure, we selected for analysis in this study only women and their infants who had filled a prescription more than 49 days after conception. (2) The *depressed-only group* (DE) included neonates of mothers diagnosed as having depression during pregnancy who had not received antidepressants, benzodiazepines, or antipsychotic medications during their pregnancy. (3) The *nonexposed control group* consisted of neonates of mothers who had received neither a diagnosis of depression nor antidepressants, benzodiazepines, or antipsychotics during their pregnancy.

## NEONATAL OUTCOMES

On the basis of previous work,[6,11,12] 4 key neonatal outcomes were identified: birth weight (grams and incidence of birth weight less than the 10th percentile for gestational age), percentage born at gestational age less than 37 weeks, length of stay in the hospital greater than 3 days, and incidence of adverse neonatal symptoms (respiratory distress [*ICD-9* codes, 769, 770.6, and 770.8], jaundice [774], convulsions [779.0], or feeding difficulties [779.3]).

## DATA ANALYSIS

Data analysis was undertaken by 2 approaches. First, to address our primary question regarding the effects of SSRI exposure vs exposure to depression alone, analysis was undertaken to examine differences in mean outcomes between the SE-D and DE groups; 2-tailed *t* tests and Fisher exact tests were used where appropriate. Second, to control for background maternal characteristics that also influenced neonatal outcomes, propensity score matching[28,29] was used to draw a comparison subgroup from the DE group that was similar in all measured maternal characteristics to the SE-D group. Maternal characteristics used for propensity score matching were as follows:

- Prepregnancy (the year before becoming pregnant)
- Number of visits to a psychiatrist
- Number of times diagnosed as depressed
- Number of times receiving a 3-digit *ICD-9* code that might include depression
- Number of times diagnosed as having a mental health disorder, excluding those diagnosed as having depression
- Number of times provided counseling by a general practitioner
- Number of visits to a physician
- Income decile
- Drugs subsidized
- Prenatal (during pregnancy)
- Age
- Number of prenatal visits
- Diagnosed as depressed
- Diagnosed with 3-digit *ICD-9* code that might include depression
- Number of times diagnosed as depressed
- Number of treatments by a psychiatrist
- Filled a prescription for an antipsychotic drug
- Filled a prescription for a tricyclic antidepressant

Propensity score matching was carried out in 6 stages. First the parameters of a model predicting SSRI exposure were estimated by maximum likelihood probit analysis. Second, these parameters were used to calculate the *propensity score* for each individual in our sample. Third, for each exposed mother, the unexposed mother with the most similar propensity score was selected for comparison purposes, without replacement. Where there was no comparable unexposed mother, the exposed mother was dropped from the analysis. Fourth, the propensity score

**Table 2. Maternal Characteristics***

| | Group Characteristics, Mean (SD) | | | Group Differences | | | |
|---|---|---|---|---|---|---|---|
| | | | | SE-D – DE | | DE – Nonexposed | |
| | SE-D (n = 1451) | DE (n = 14 234) | Nonexposed (n = 92 192) | Difference (95% CI) | *P* Value | Difference (95% CI) | *P* Value |
| Age during pregnancy, y | 29.9 (5.8) | 29.5 (5.7) | 29.5 (5.5) | 0.43 (0.11 to 0.74) | .008† | 0.02 (–0.08 to 0.12) | .71† |
| No. of prenatal visits | 10.5 (4.0) | 11.2 (3.7) | 10.7 (4.0) | –0.7 (–0.91 to –0.48) | <.001† | 0.55 (0.48 to 0.62) | <.001† |
| No. of visits to psychiatrist in year before becoming pregnant | 0.77 (3.0) | 0.16 (2.0) | 0.02 (0.41) | 0.62 (0.46 to 0.78) | <.001† | 0.14 (0.11 to 0.18) | <.001† |
| No. of times diagnosed as having depression in year before becoming pregnant | 2.53 (3.6) | 0.67 (2.3) | 0.16 (0.67) | 1.9 (1.7 to 2.1) | <.001† | 0.50 (0.47 to 0.54) | <.001† |
| No. of times receiving 3-digit *ICD-9* code that might include depression in year before becoming pregnant | 0.72 (2.2) | 0.17 (1.0) | 0.09 (0.47) | 0.55 (0.44 to 0.66) | <.001† | 0.08 (0.06 to 0.09) | <.001† |
| No. of times diagnosed with mental health disorder, excluding those diagnosed with depression, in year before becoming pregnant | 0.36 (4.0) | 0.13 (2.6) | 0.05 (1.2) | 0.23 (0.02 to 0.44) | .03† | 0.07 (0.04 to 0.06) | .001† |
| No. of times provided counseling by GP in previous year | 0.89 (1.2) | 0.45 (0.89) | 0.22 (0.59) | 0.43 (0.37 to 0.50) | <.001† | 0.23 (0.22 to 0.25) | <.001† |
| Drugs subsidized through welfare program in year before becoming pregnant | 0.16 (0.37) | 0.08 (0.27) | 0.06 (0.24) | 0.08 (0.10 to 0.06) | <.001‡ | 0.02 (0.01 to 0.02) | <.001‡ |
| Income decile | 5.5 (5.7) | 5.3 (4.9) | 5.6 (6.7) | 0.2 (–0.13 to 0.48) | .27† | –0.28 (–0.38 to –0.19) | <.001† |

Abbreviations: CI, confidence interval; DE, depressed mothers not treated with medication; GP, general practitioner; *ICD-9, International Classification of Diseases, Ninth Revision*; SE-D, depressed mothers treated with selective serotonin reuptake inhibitors.
*Numbers do not always sum because of rounding.
†Two-tailed *t* test, without assuming equal variances.
‡Two-tailed Fisher exact test.

equation was reestimated on these exposed and unexposed mothers. The propensity score equation passed the balancing test as implemented by Becker and Ichino.[30] Fifth, the average agreement effect was estimated using radius matching with a radius of 0.05. Sixth, the standard errors were bootstrapped with 500 repetitions. In this way, each infant born to an SSRI-exposed mother was compared with infants born to nonexposed, but depressed, mothers with similar scores.

We made our estimates with propensity score matching for 3 reasons. First, propensity score matching does not require functional form assumptions that underlie regression methods. Second, propensity score matching highlights the "support condition"; it identifies the part of the untreated population that can be compared with the treated population without extrapolation. Inaccurate functional form and violations of the support condition, separately and in combination, will introduce bias in the regression methods. Recent empiric work has shown that this bias can be substantial.[31,32] Third, we used propensity score matching because it is a transparent method for eliminating bias due to measured confounders. The results are easily understood because the comparison group has the same average characteristics as the treatment group. With the matched comparison group, the influence of the treatment can be estimated by comparing the means of the treatment and comparison groups.

## RESULTS

Maternal characteristics are presented in **Table 2**. In the 39 months from January 1998 to March 2001, the incidence of diagnosis of depression remained stable at 14%, but the incidence of SSRI medication during pregnancy increased from 2.3% to 5.0% of all pregnancies. The most common SSRI medications used were paroxetine (44.7%), fluoxetine (27.2%), sertraline (25.6%), fluvoxamine (4.6%), and citalopram (3.3%). In our sample, venlafaxine was used only in combination with other non-SSRI medications and therefore was not included in our study sample. Maternal age, number of prenatal visits, and income decile were very similar among the 3 groups. Mothers who took SSRIs, however, were substantially different from both other groups in ways that suggest that their depression was more severe than the depression of mothers who did not take SSRIs (Table 2). These mothers were diagnosed as having depression about 4 times more frequently than the DE group, had visited a psychiatrist about 5 times more frequently, and had been diagnosed as having a mental illness other than depression about 3 times more frequently than mothers diagnosed as having depression but who did not take SSRIs while pregnant.

### NEONATAL CONDITION

Neonatal outcomes are tabulated in **Table 3**. Infants exposed to SSRIs had shorter gestations, lower birth weights, and longer hospital stays than nonexposed infants. With the exception of birth weight for gestational age, a similar pattern of differences in neonatal outcomes was also observed when SSRI-exposed infants were compared with infants exposed to depression alone.

**Table 3. Infant Characteristics***

| | Neonatal Outcomes, Mean | | | Outcome Differences: SE-D – DE | | Outcome Differences: DE – Nonexposed | |
|---|---|---|---|---|---|---|---|
| | SE-D | DE | Nonexposed | Difference (95% CI) | *P* Value | Difference (95% CI) | *P* Value |
| Incidence of cesarean section | 0.24 | 0.21 | 0.19 | 0.03 (0.01 to 0.05) | .01† | 0.01 (0.01 to 0.02) | <.001† |
| Birth weight, g | 3397 | 3429 | 3453 | –32 (–1 to –64) | .05‡ | –24 (–14 to –39) | <.001‡ |
| Gestational age, wk | 38.8 | 39.1 | 39.2 | –0.35 (–0.25 to –0.45) | <.001‡ | –0.06 (–0.02 to –0.09) | <.001‡ |
| Incidence of preterm birth (<37 wk) | 0.090 | 0.065 | 0.059 | 0.02 (0.009 to 0.04) | <.001† | 0.006 (0.002 to 0.010) | .007† |
| Incidence of birth weight <10th percentile for gestational age | 0.085 | 0.081 | 0.074 | 0.005 (–0.01 to 0.02) | .51† | 0.007 (0.002 to 0.011) | .005† |
| Length of hospital stay, d | 3.31 | 2.88 | 2.76 | 0.43 (0.12 to 0.74) | .007‡ | 0.12 (0.03 to 0.20) | .006‡ |
| Incidence of hospital stay >3 d | 0.23 | 0.18 | 0.17 | 0.05 (0.03 to 0.07) | <.001† | 0.01 (0.01 to 0.02) | <.001† |
| Incidence of hospital stay >3 d, infants born by vaginal birth | 0.16 | 0.12 | 0.11 | 0.036 (0.01 to 0.06) | <.001† | 0.01 (0.01 to 0.02) | <.001† |
| Incidence of respiratory distress | 0.139 | 0.078 | 0.074 | 0.063 (0.042 to 0.079) | <.001† | 0.004 (–0.0004 to 0.009) | .07† |
| Incidence of feeding problems | 0.039 | 0.024 | 0.021 | 0.015 (0.005 to 0.025) | .002† | 0.003 (0.0004 to 0.006) | .02† |
| Incidence of respiratory distress, infants born by vaginal birth | 0.132 | 0.071 | 0.068 | 0.058 (0.038 to 0.079) | <.001† | 0.006 (0.0004 to 0.011) | .03† |
| Incidence of jaundice | 0.094 | 0.075 | 0.079 | 0.019 (0.003 to 0.034) | .01† | –0.004 (–0.009 to 0.0004) | .08† |
| Incidence of convulsions | 0.0014 | 0.0009 | 0.0011 | 0.0005 (–0.0015 to 0.0025) | .64† | –0.0002 (–0.0008 to 0.0003) | .49† |

Abbreviations: CI, confidence interval; DE, depressed mothers not treated with medication; SE-D, depressed mothers treated with selective serotonin reuptake inhibitors.

*Numbers do not always sum because of rounding.

†Two-tailed Fisher exact test.

‡Two-tailed *t* test, without assuming equal variances.

The most common reported complication was respiratory distress, and a significantly greater incidence was observed among SSRI-exposed neonates (13.9%) than the other neonates (Table 3). A total of 117 convulsions were reported, and rates did not differ between groups (2 in the SE-D group, 12 in the DE group, and 103 in the nonexposed infants). The SSRI-exposed infants were significantly more likely to have jaundice than the depressed-only infants, while the nonexposed and DE groups did not significantly differ. Feeding difficulties were significantly more frequently reported in the SE-D group than the DE group (95% confidence interval for difference in proportions, 0.005-0.025).

The proportion of infants born by cesarean section was higher among the SE-D group; however, the difference in rates of cesarean section accounts for only a small portion of the differences in outcomes. For vaginally born infants, the incidence of respiratory distress was significantly higher for infants with SSRI exposure than nonexposed infants. In addition, the length of stay in hospital was significantly longer, suggesting that SSRIs had affected outcomes independent of their effect on mode of birth.

### PROPENSITY SCORE MATCHING

To account for differences in maternal characteristics that may have led to SSRI use during pregnancy (ie, illness severity), propensity score matching was used to identify a subgroup of mothers in the DE group who were similar to the mothers in the SE-D group (see the list of characteristics in the "Data Analysis" subsection of the "Methods" section). While the simple (unmatched) comparison between SE-D and DE showed significant differences in birth outcome, when outcomes were compared between the SE-D group and the DE subgroup with propensity score matching, the incidence of birth weight less than the 10th percentile and respiratory distress (even among infants born by vaginal delivery) remained significantly different (**Table 4**).

## COMMENT

Using population-based health data linking records of maternal prescriptions for SSRI antidepressants dispensed during pregnancy with neonatal birth outcomes, we observed differences in birth outcome between infants with exposure to SSRIs and depression and with exposure to maternal depression alone. Importantly, SE-D was still associated with an increased incidence of birth weight below the 10th percentile and increased rates of respiratory distress, even when illness severity was accounted for by means of propensity score matching. These findings are contrary to the expectation that treating depressed mothers with SSRIs during pregnancy would be associated with lessening of the adverse neonatal consequences associated with maternal depression.

There are 2 possible reasons for these findings: (1) Neonates born to mothers who were treated with SSRIs may have had adverse outcomes because their mothers had more severe depression (bias due to illness severity). If the SSRIs lessened the effect of maternal depression, then in the absence of treatment with an SSRI, outcomes for these infants may have been even worse. (2) Alternatively, SSRIs could have affected outcomes separate from the effect of depression.

**Table 4. Comparisons Using Propensity Score Matching: Outcomes for SE-D vs DE Neonates**

| | Outcome Differences, SE-D – DE | | | |
|---|---|---|---|---|
| | Unmatched | | Propensity Score Matched* | |
| | Difference (95% CI) | *P* Value | Difference (95% CI) | *P* Value† |
| Incidence of cesarean section | 0.03 (0.01 to 0.05) | .01‡ | –0.009 (–0.050 to 0.036‡) | .69 |
| Birth weight, g | –32 (–1 to –64) | .05† | 10 (–43 to 70‡) | .72 |
| Gestational age, wk | –0.35 (–0.25 to –0.45) | <.001† | –0.14 (–0.34 to 0.06‡) | .18 |
| Incidence of preterm birth (<37 wk) | 0.02 (0.01 to 0.04) | <.001‡ | 0.007 (–0.018 to 0.034‡) | .61 |
| Incidence of birth weight <10th percentile for gestational age | 0.005 (–0.010 to 0.020) | .51‡ | 0.033 (0.007 to 0.059‡) | .02 |
| Length of hospital stay, d | 0.43 (0.12 to 0.74) | .007† | 0.055 (–0.610 to 0.410‡) | .83 |
| Incidence of hospital stay >3 d | 0.05 (0.03 to 0.07) | <.001‡ | 0.037 (–0.004 to 0.075‡) | .07 |
| Incidence of hospital stay >3 d, infants born by vaginal birth‡ | 0.036 (0.014 to 0.059) | <.001‡ | 0.035 (–0.005 to 0.072‡) | .08 |
| Incidence of respiratory distress | 0.063 (0.042 to 0.079) | <.001‡ | 0.044 (0.013 to 0.077‡) | .006 |
| Incidence of feeding problems | 0.015 (0.004 to 0.025) | .002‡ | 0.011 (–0.009 to 0.030‡) | .28 |
| Incidence of respiratory distress, infants born by vaginal birth‡ | 0.058 (0.038 to 0.079) | <.001‡ | 0.049 (0.017 to 0.088‡) | .006 |
| Incidence of jaundice | 0.019 (0.003 to 0.034) | .01‡ | 0.01 (–0.02 to 0.04‡) | .45 |
| Incidence of convulsions | 0.0005 (–0.0015 to 0.0025) | .64‡ | 0.00077 (–0.0010 to 0.0036§) | .30 |

Abbreviations: CI, confidence interval; DE, depressed mothers not treated with medication; SE-D, depressed mothers treated with selective serotonin reuptake inhibitors.

*For SE-D group, n = 817; DE group, n = 805.

†*P* values calculated by means of 2-tailed normal distribution and bootstrapped standard errors (500 repetitions).

‡Bootstrapped bias-corrected 95% CIs.

§Calculated from bootstrapped standard errors.

Our findings that neonates born to the propensity score–matched, non–SSRI-exposed depressed mothers were similar to neonates born to SSRI-exposed depressed mothers (ie, in gestational ages, birth weights, incidence of feeding problems, convulsions, and jaundice) may suggest that previous studies failed to account for maternal illness severity, thereby attributing adverse neonatal outcomes to SSRI exposure rather than to maternal depression. Furthermore, our finding that prenatal SSRI exposure was associated with reduced birth weight for gestational age and an increased incidence of neonatal respiratory distress, even after controlling for potential confounders, suggests that exposure to both SSRIs and a depressed maternal mood had an additive negative effect beyond the effect of exposure to depression alone for these outcomes. Finally, when the effect of depression alone was compared with the apparent effect of SSRIs (DE minus nonexposed vs SE-D minus DE in Table 3), the effect of SSRIs appeared in similar areas but to a greater degree. The main exception to this was the incidence of respiratory distress. Despite our large sample sizes, the difference in the incidence of respiratory distress among the DE group was not statistically significantly different from the incidence among the nonexposed group. When we controlled for variables that reflect the severity of illness, we found that the apparent effects of SSRIs generally disappeared, except that the effect on respiratory distress remained large and statistically significant. It seems unlikely that our attempts to control for illness severity could have succeeded for some outcomes and yet failed for respiratory distress. This also suggests that the effect on respiratory distress may be due to SSRI exposure rather than to maternal depression.

During a 39-month period, the diagnosis of depression during pregnancy remained stable at 14%, which is consistent with the Avon cross-sectional study that found 13.5% of mothers depressed at 32 weeks' gestation.[1] While the rate of SSRI use during pregnancy averaged less than 2.5% in 1998, it doubled in British Columbia during our study period to levels greater than the 1% to 3.5% previously reported.[33,34] The most common SSRIs used were paroxetine, sertraline, and fluoxetine.

A number of recent studies have linked maternal health data to study neonatal outcomes following prenatal SSRI exposure.[21,22,33,35] Previous results have been mixed, some showing reduced birth weight and shortened gestational age[22,35] and increased risk for fetal death and convulsions,[35] while the others report no increase in adverse outcomes.[21,33] None of these studies was able to account for the concurrent effects of depressed maternal mood. The importance of differentiating the effects of exposure to maternal depression from SSRI effects and of understanding the role that maternal health characteristics (ie, maternal psychotropic medication use, concurrent illness) play in influencing birth outcomes has been highlighted in a recent review.[4] We used propensity score matching to compare outcomes following exposure to SSRIs and depression with outcomes among neonates exposed to depression alone specifically to control for these major potential confounders. Using administrative health data, we were not able to directly control for alcohol, illicit drug use, smoking, socioeconomic conditions beyond income decile, and the severity of depression or effect of comorbid psychiatric conditions (ie, anxiety) that could also influence neonatal outcomes.

Specific mechanisms that may account for our findings remain to be studied; however, the reduced birth weight for gestational age and increased risk of respiratory distress after prenatal SSRI exposure observed in this study are consistent with increasing reports from separate studies on the effects of SSRI exposure[4] and depres-

sion.[2,36,37] However, given that outcomes among SSRI-exposed infants were typically worse than for infants exposed to depression only, it is possible that SSRIs affect outcomes via an additive and/or distinct set of direct and indirect mechanisms.

Maternal mood influences fetal and infant development in complex ways that include direct biological, genetic, and indirect environmental effects that extend from early pregnancy well into infancy. There is mounting evidence that maternal psychological functioning is translated into altered fetal and neonatal physiological outcomes.[38] Maternal stress may disrupt fetal neurobehavioral development,[39-41] reduced birth weight, and increased incidence of prematurity.[42-46] This may be due to exposure to increased levels of adrenal hormones, which adversely influence glucocorticoid receptors in the developing fetal brain,[47,48] which in turn alter regulation of stress responses.[48-50] Newborns of depressed mothers may show more irritability[51] and greater right frontal electroencephalographic activation[52] and may have reduced dopaminergic levels[53] compared with controls. Furthermore, both animal and human studies have linked serotonin (5HT) to the effects of chronic unpredictable physiological stress during pregnancy with lasting effects on monoaminergic system function[54] and behavior in offspring.[3,55,56]

Central to understanding the influence of SSRIs on neonatal development and behavior is the role of the neurochemical 5HT. Half-life, potency, and the inhibition of 5HT reuptake at presynaptic neurons[57,58] differ among SSRIs; however, they all increase central synaptic 5HT concentrations[58] and readily cross the placenta,[59] thereby potentially also inhibiting 5HT reuptake in the developing fetus. During gestation, 5HT plays roles as a neurotransmitter regulating cardiovascular function, respiratory function,[60] circadian rhythms, and arousal[61] and as a trophic signal in the developing brain by directing the development of the 5HT and other components of the monoamine system.[62,63] In the fetal lung, 5HT has a direct role in the development of pulmonary artery smooth muscle in animal models and the genesis of pulmonary hypertension.[64] Serotonergic neurons are found in key regions of the brainstem that regulate respiration and central chemoreception.[60,65,66] In animal models, prenatal fluoxetine exposure is associated with decreased postnatal weight gain, reduced uterine blood flow and transient fetal hypoxemia, and increased quiet sleep.[67,68] Importantly, these SSRI effects were observed in the absence of a depressed mood in sheep. Increased levels of 5HT in the fetus, secondary to SSRI exposure, could conceivably be expressed at sites where 5HT plays a role in brain and lung development. Elevated drug levels[12,16] and suppressed levels of the 5HT metabolite 5-hydroxyindoleacetic acid, reflecting increased central 5HT activity,[16] may also have a role in affecting neonatal outcomes. Respiratory distress and neurobehavioral symptoms have been associated with increased levels of maternal and neonatal paroxetine, particularly when this SSRI was used in combination with the benzodiazepine clonazepam.[12] Altering 5HT levels during crucial periods of development might alter respiratory maturation or adaptation to the extrauterine environment, leading to neonatal respiratory distress.

Use of administrative health data to study the effects of prenatal SSRI exposure posed a number of methodologic challenges. With these population-based data, we could not directly assess the level, severity, or course of prenatal depression, nor was it possible to accurately or precisely determine how or when the physician made his or her diagnosis. Furthermore, we were not able to control directly for the effects of alcohol use or smoking. However, smoking is strongly correlated both with depression[69] and with low income[70]; by controlling for income decile between groups, we may have been able to indirectly control for smoking, and the fact that the propensity score analysis found no evidence of an effect on birth weight suggests that we were successful. Because SSRI use occurs in the context of maternal mental illness, we were not able to directly study the effects of SSRI use alone, independent of exposure to maternal depression. The best we could do was to control for the effects of illness severity by selecting maternal characteristics that we believed were associated with an increased propensity to receive an SSRI medication. While these may reflect some aspect associated with the severity of maternal mental illness, they are at best only an approximation of illness severity in the absence of a direct assessment as would be possible in a cohort study. Futhermore, while it was assumed that a filled prescription led to the medication being taken, the actual medication consumption could not be verified.

Because SSRI use occurs in the context of maternal mental illness, we were not able to study the effects of SSRI exposure independent of exposure to depression alone. Finally, the difference in birth weight for gestational age is small and the long-term clinical significance of our findings remains to be studied.

This study was undertaken to attempt to distinguish differences in the effects of maternal depression from exposure to prenatal SSRI and depression on neonates and not to address the question of whether SSRIs are safe to use during pregnancy. Our findings suggest that combined exposure to SSRIs and depression is associated with an outcome profile that appears to differ from that of exposure to depression alone. Further research is needed to identify the exact influence of gestational exposure to maternal depression and how it differs from exposure to SSRI medications alone. The results of this study do, however, bring into focus the central question of whether the adverse effects on the neonates justify the benefits of treating a depressed mother during her pregnancy with an SSRI. Depression itself may have adverse effects on the fetus and neonate, and the risk of not medically treating depression may outweigh the risk of adverse consequences associated with prenatal SSRI exposure. The conceptual model by Wisner et al[71] may offer a helpful way to guide clinical decision making in this ambiguous and challenging context. Although a discussion of the risk-benefit of antenatal SSRI treatment is beyond the scope of this article, these data and increasing reports of risks of adverse effects[4,17] suggest the need for research that clearly establishes the benefits and defines the clinical indications of SSRI use during pregnancy.

These data also highlight the frequency of depression and the possible influence of nonpharmacologic treat-

ment, and they suggest that the effect of treatment with an SSRI medication is not without risks. While the benefits of SSRI treatment during pregnancy remain to be determined, we emphasize that none of these findings should diminish the clinical urgency of recognizing and treating maternal depression during pregnancy by using a variety of available pharmacologic and nonpharmacologic strategies. At present, the need to use antidepressants must be weighed against the risks of untreated or undertreated disease, and the decision should made by an informed patient with her physician on a case-by-case basis.[71]

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