Neonatal Morbidity After Maternal Use of Antidepressant Drugs During Pregnancy

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abstract

OBJECTIVES: To estimate the rate of admissions to NICUs, as well as infants' morbidity and neonatal interventions, after exposure to antidepressant drugs in utero.

METHODS: Data on pregnancies, deliveries, prescription drug use, and health status of the newborn infants were obtained from the Swedish Medical Birth Register, the Prescribed Drug Register, and the Swedish Neonatal Quality Register. We included 741 040 singletons, born between July 1, 2006, and December 31, 2012. Of the infants, 17 736 (2.4%) had mothers who used selective serotonin reuptake inhibitors (SSRIs) during pregnancy. Infants exposed to an SSRI were compared with nonexposed infants, and infants exposed during late pregnancy were compared with those exposed during early pregnancy only. The results were analyzed with logistic regression analysis.

RESULTS: After maternal use of an SSRI, 13.7% of the infants were admitted to the NICU compared with 8.2% in the population (adjusted odds ratio: 1.5 [95% confidence interval: 1.4–1.5]). The admission rate to the NICU after treatment during late pregnancy was 16.5% compared with 10.8% after treatment during early pregnancy only (adjusted odds ratio: 1.6 [95% confidence interval: 1.5–1.8]). Respiratory and central nervous system disorders and hypoglycemia were more common after maternal use of an SSRI. Infants exposed to SSRIs in late pregnancy compared with early pregnancy had a higher risk of persistent pulmonary hypertension (number needed to harm: 285).

CONCLUSIONS: Maternal use of antidepressants during pregnancy was associated with increased neonatal morbidity and a higher rate of admissions to the NICU. The absolute risk for severe disease was low, however.

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Ms Nörby and Dr Forsberg planned and designed the study with special emphasis on antidepressant drugs and neonatal outcomes, respectively; they also drafted the initial manuscript. Dr Källén planned and designed the study and was responsible for the data collection and statistical analysis; Drs Wide, Sjörs, and Winbladh acted as scientific advisers during the study process; and all authors critically reviewed and revised the manuscript and approved the final version as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Antidepressant drug use during pregnancy is associated with several neonatal complications. However, the severity of the symptoms and to what extent they are caused by the drugs or the disease is still unclear.

WHAT THIS STUDY ADDS: We have quantified the neonatal morbidity for infants exposed to antidepressant drugs during pregnancy in a population-based study. Our results support a causal relationship between antidepressant exposure in utero and need of specialized neonatal care and interventions.

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Treatment with antidepressant drugs during pregnancy is linked to neonatal complications such as respiratory distress, hypoglycemia, and central nervous system (CNS) disorders, as well as preterm birth, low birth weight, and low Apgar scores.[1–21] The neonatal problems are mostly transient[2,3,9,10,22] but may require treatment in a NICU.[1,4,6,12] Proposed mechanisms are withdrawal effects[5,22,23] or serotonergic overstimulation syndrome.[5,22] It is unclear to what extent these complications are caused by the antidepressant drugs[6,11,13,16,18,19] or by the underlying disease.[24–27] Persistent pulmonary hypertension in the newborn (PPHN) is a potentially serious but rare complication associated specifically with selective serotonin reuptake inhibitors (SSRIs).[28–30]

Indications for SSRI treatment are depressive and anxiety disorders, both of which are common in the pregnant population.[31,32] Approximately 4% of pregnant women in Sweden and 6% in the United States undergo treatment with SSRIs,[32–34] and their use is increasing.[33,34]

The aim of the present study was to analyze the severity of neonatal complications (primarily measured as admissions to the NICU) after fetal exposure to antidepressant drugs, with a special focus on SSRIs. By combining data from national health registers with Swedish quality registers on neonatal care, comprehensive information was obtained regarding the infants' morbidity on a population level. Another objective was to differentiate the neonatal effects of the drug treatment from the impact of the women's psychiatric conditions, as far as possible. This approach was undertaken by comparing exposure to SSRIs in late pregnancy versus early pregnancy only because neonatal adaption problems have been associated with exposure primarily during late pregnancy.[1,2,12,19,22]

METHODS

The study was register based, combining data from the Swedish Medical Birth Register (MBR),[35] the Prescribed Drug Register (PDR),[36] the Swedish Neonatal Quality Register (SNQ),[37] and the Perinatal Revision South Register (PRS).[38] Linkage between the registers was accomplished by using the Swedish personal identification numbers. Our study population consisted of all singleton births in Sweden (a total of 741 040 infants) registered in the MBR between July, 1, 2006, and December, 31, 2012. An outline of the study design is presented in Supplemental Fig 1.

All pregnant women in Sweden are offered free antenatal care. At their initial visit, in 90% of the cases in the first trimester,[35] the women are interviewed by their midwife, and information regarding height, weight, medications, and smoking habits are prospectively collected and registered in the MBR. During the second trimester, the women are offered a free ultrasound examination to check for multiple pregnancies, congenital malformations, and to obtain an expected date of delivery. In total, the MBR contains data on antenatal care, delivery, and the pediatric examination of the newborn child for >97% of all births. The MBR was used in the present study to obtain information on maternal and fetal background characteristics.

Drug Exposure

Data on prescription drug exposure were acquired from the MBR (midwife interview) and the PDR. The PDR stores data on all drugs prescribed in ambulatory care and dispensed at a Swedish pharmacy but does not include medications used for in-patient care in hospitals.[36] The drugs registered in the MBR and PDR are classified according to the Anatomical Therapeutic Chemical classification system.

Antidepressant exposure was defined as drugs belonging to Anatomical Therapeutic Chemical class N06A (antidepressants). These drugs were divided into subgroups on the basis of their pharmacologic properties. For the main results, we focused the analyses on SSRIs (N06AB), which constituted 79% of the reported antidepressant drug intake.

The use of antidepressants was allocated into any use (exposure at any time during or 1 month before the pregnancy), late use (drugs dispensed during the last 90 days of the pregnancy with or without early use), and early use only (exposure 1 month before and during pregnancy but not during the last 90 days of the pregnancy). Supplemental Table 5 provides details of the antidepressant drug exposure.

We also collected data on the following neurotropic drugs known or suspected to cause neonatal problems similar to antidepressants: antiepileptics, opioids, psycholeptics, and centrally acting sympathomimetics.[21] Mild sedatives (alimemazine, promethazine, propiomazine, and hydroxyzine) were classified separately from the neurotropic drugs.

Neonatal Outcomes

Data on admissions to neonatal wards were extracted from the national SNQ[37] that covers all 37 NICUs in Sweden. Because the south of Sweden was not included in the SNQ until 2012, data from this region were collected from the PRS[38] for the years 2006 to 2011. Both registers comprise detailed information on infants treated at neonatal wards. The infants' diagnoses were obtained from SNQ/PRS and MBR, where they are registered according to the *International Classification of Diseases, 10th Revision*. We also

collected diagnoses from the SNQ that are recorded via checkboxes in the infant's medical record. A comprehensive list of neonatal outcomes and data sources is available in Supplemental Table 6.

The care at NICUs in Sweden corresponds to the American Academy of Pediatrics' classifications of neonatal care, Levels II to IV.[39] Infants with minor neonatal complications may remain in the maternity ward (equivalent to Level I care) and are not included in the SNQ or PRS. Their diagnoses are, however, registered in the MBR.

Statistical Analyses

Odds ratios (ORs) for dichotomous outcomes, any antidepressant use versus no use, the individual antidepressant substances versus no use, or late use versus early use only were obtained by using logistic regression analyses. When so specified in the tables and in the text, crude and adjusted ORs are displayed. Prefatory analyses were performed to choose the most efficient way to represent the covariates in the analyses (linear, second-degree polynomial, or division into class variables). In the final analyses, adjustments were made for maternal factors: maternal age (linear continues variable), year of birth (linear), primiparity (versus multiparity), maternal smoking (ordinal scale, 1 = no, 2 = 1–9 cigarettes per day, 3 = ≥10 cigarettes per day), BMI (linear), mother born in Sweden (no versus yes), cohabiting with the child's father (no versus yes), cesarean delivery (yes versus no), any use of mild sedatives (yes versus no), and maternal use of other neurotropic drugs (yes versus no).When so specified, adjustments were also made for fetal factors: gestational age (GA) (linear) and fetal weight for GA and sex (birth weight *z* scores, linear).[40] Missing data regarding maternal smoking and BMI were replaced by the overall means. Tests of homogeneity of the ORs across the antidepressant groups were based on weighted sums of the squared deviations of the stratum-specific log-ORs from their weighted means.

Differences regarding the length of stay at the NICU and the number of days on a ventilator or continuous positive airway pressure (CPAP) were evaluated by using Mann-Whitney *U* tests or Kruskal-Wallis tests. Statistical analyses were conducted by using SPSS version 22 (IBM SPSS Statistics, IBM Corporation, Armonk, NY) and Gauss (Aptech Systems Inc, Maple Valley, WA; http://www.aptech.com,version 10).

Ethics

The study was approved by the regional ethical review board in Lund (dnr. 2013/342-31/5).

RESULTS

Table 1 summarizes maternal and fetal background characteristics for the subcohorts maternal use of SSRIs and no antidepressant drug use. Corresponding data for exposure to other antidepressant drugs are displayed in Supplemental Table 7. Pregnant women who used SSRIs tended to be older, were to a higher extent smokers, more often had a BMI >30, and more frequently gave birth by cesarean delivery. Exposed neonates were to a higher extent born moderately preterm, with birth weight <2500 g and/or low Apgar scores. The crude OR in Table 1 indicated an increased risk for stillbirth among SSRI-exposed infants. After adjustment for maternal factors, the association between maternal use of antidepressants and stillbirth was no longer statistically significant (OR: 1.2 [95% confidence interval (CI): 1.0–1.5]; *P* = .08).

Admission to NICU

Infants exposed to SSRIs were more often treated at a NICU than infants not exposed to antidepressants (OR: 1.5 [95% CI: 1.4–1.5]; number needed to harm [NNH]: 29; adjusted for maternal factors) (Table 2). Adjustment for fetal factors (GA and small for gestational age [SGA]), in addition to maternal factors, did not change the OR. The risk was highest after exposure to SSRIs during late pregnancy (adjusted OR: 1.8 [95% CI: 1.7–1.9]; NNH: 17). Comparison between late and early SSRI exposure only yielded an OR of 1.6 (95% CI: 1.5–1.8) and an NNH of 18, adjusted for maternal factors (Supplemental Table 8).

There was a heterogeneity between the different antidepressant drug groups (*P* = .002) (Supplemental Table 8). The risks for treatment at the NICU were highest for serotonin norepinephrine reuptake inhibitors and tricyclic antidepressants (ORs: 2.7 [95% CI: 2.0–3.5] and 2.6 [95% CI: 1.7–3.4], respectively) comparing late exposure with early exposure and adjusted for maternal factors.

Duration of NICU Care

The median duration of stay among infants treated at a NICU was 5 days for SSRI-exposed infants compared with 7 days for non-exposed (*P* < .001). The corresponding figures for term infants only were 4 days and 5 days, respectively (*P* < .001). Infants exposed to other neurotropic drugs were excluded from this analysis.

Neonatal Morbidity and Treatment

Table 3 displays diagnoses and treatments after SSRI use compared with no antidepressant exposure, and Table 4 displays exposure to SSRIs in late versus early pregnancy only. An increased frequency of any respiratory disorder (but not for respiratory distress syndrome) was seen, especially after use of SSRIs during late pregnancy. Treatment with CPAP was also

TABLE 1 Background Characteristics of the Study Population: Maternal Use of SSRIs Versus No Antidepressant Drug Use During Pregnancy

Characteristic	SSRI Without Other Neurotropic Drugs (*n* = 12 516)	SSRI + Other Neurotropic Drugs[a] (*n* = 5220)	Total SSRI Use (*n* = 17 736)	No Antidepressant Use (*n* = 718 533)	Total SSRI Versus No Antidepressant Use	
	%	%	%	%	OR	95% CI
Maternal characteristics						
Year of child's birth						
2005–2008	33.7	35.9	34.2	42.0	0.7	0.7–0.7
2009–2012	66.3	64.1	65.8	58.0	1.4	1.4–1.4
Maternal age, y						
<20	1.8	1.7	1.8	1.7	1.1	1.0–1.2
≥35	26.1	26.6	26.3	21.5	1.3	1.2–1.3
Parity						
Primipara	46.2	45.4	45.8	45.3	1.0	1.0–1.0
Multipara	53.8	54.6	54.2	54.7	1.0	1.0–1.0
BMI						
<18.5[b]	2.3	2.4	2.3	2.4	1.0	0.9–1.1
>30[b]	16.1	20.8	17.6	12.1	1.6	1.5–1.6
Missing	7.6	8.9	8.1	8.5	0.9	0.9–1.0
Maternal smoking[b]	11.8	17.9	14.1	6.4	2.4	2.3–2.5
Missing	3.7	4.2	3.9	4.7	0.8	0.8–0.9
Maternal country of birth						
Sweden	88.2	83.9	87.0	76.0	2.1	2.0–2.2
Other Nordic	1.6	1.8	1.7	2.0	0.8	0.7–0.9
Non-Nordic	10.2	14.3	11.3	20.6	0.5	0.5–0.5
Not living with father of child	9.5	14.5	11.1	5.8	2.0	1.9–2.1
Maternal disease						
Diabetes	0.8	1.1	0.9	0.5	1.7	1.4–2.0
Gestational diabetes	1.3	1.6	1.5	1.1	1.3	1.2–1.5
Hypothyroidism	3.0	3.1	3.1	1.6	2.0	1.8–2.2
Essential hypertension	0.4	0.8	0.5	0.4	1.4	1.1–1.7
Severe preeclampsia	1.2	1.1	1.2	0.9	1.3	1.2–1.5
Crohn's disease	0.4	0.6	0.5	0.2	2.0	1.6–2.5
Use of neurotropic drugs[c]						
Opioids (N02A)	—	35.6	12.7	5.1	2.7	2.6–2.8
Antiepileptics (N03A)	—	4.3	3.0	0.4	7.8	7.1–8.6
Psycholeptics (N05)	—	57.7	19.0	1.4	17.0	16.3–17.8
Centrally acting sympathomimetics (N06BA)	—	2.3	1.1	0.1	11.8	10.1–13.9
Use of mild sedatives[d]	21.0	39.2	27.5	3.5	10.5	10.2–10.9
Cesarean delivery	20.8	25.3	22.4	16.5	1.5	1.4–1.5
Infant characteristics						
Male sex	51.3	51.7	51.5	51.2	1.0	1.0–1.0
GA, wk						
<32	0.9	1.1	1.0	1.2	0.8	0.7–1.0
32–36	2.7	3.1	2.9	1.9	1.6	1.4–1.7
37–41	88.6	88.0	88.2	88.0	1.0	1.0–1.1
≥42	4.8	3.4	4.3	6.7	0.6	0.6–0.7
Birth weight						
<2500 g	4.2	5.2	4.6	3.2	1.5	1.4–1.6
SGA	2.4	2.9	2.6	2.3	1.1	1.0–1.2
LGA	4.3	4.7	4.5	4.0	1.1	1.0–1.2
Apgar score <7 at 5 min	2.7	2.6	2.7	1.3	2.2	2.0–2.4
Birth defects (weeded)[e]						
Total	2.2	2.3	2.2	2.2	1.0	0.9–1.2
Heart malformation	0.8	0.7	0.8	0.8	1.0	0.9–1.2
Perinatal death[f]	0.5	0.7	0.5	0.4	1.2	1.0–1.5
Stillbirth	0.4	0.6	0.5	0.3	1.4	1.1–1.7
Neonatal death[g]	0.1	0.2	0.1	0.1	1.0	0.7–1.5

LGA, large for gestational age.

[a] Opioids (N02A), antiepileptics (N03A), psycholeptics (N05), and centrally acting sympathomimetics (N06BA).

[b] Percentages were based on records with valid information.

[c] Anatomical Therapeutic Chemical classification system codes given within parentheses.

[d] Alimemazine, propiomazine, promethazine, and hydroxyzine.

[e] Birth defects (weeded), malformations defined as *International Classification of Diseases, 10th Revision,* diagnoses beginning with Q, excluding the following minor conditions: preauricular appendix, patent ductus arteriosus in a preterm infant, single umbilical artery, tongue tie, undescended testicle, hip dislocation/subluxation, and nevus.

[f] Stillbirth and death within 7 days from birth.

[g] Death within 28 days after birth.

TABLE 2 Admission to NICU Among Infants Exposed to SSRIs Compared With Infants Not Exposed to Antidepressant Drugs During Pregnancy

Exposure Group	Crude					Adjusted for Maternal Factors,[a] Including Use of Other Neurotropic Drugs[b]		Adjusted for Maternal and Fetal Factors[c]	
	Total	NICU	%	OR	95% CI	OR	95% CI	OR	95% CI
No antidepressant	718 533	59 210	8.2	1.0	Ref	1.0	Ref	1.0	Ref
SSRI, any use	17 736	2437	13.7	1.8	1.7–1.9	1.5	1.4–1.5	1.5	1.4–1.5
SSRI, early use only[d]	8636	936	10.8	1.4	1.3–1.4	1.1	1.0–1.2*	1.2	1.1–1.2
SSRI, late use[e]	9100	1501	16.5	2.2	2.1–2.3	1.8	1.7–1.9	1.7	1.6–1.8

Exposure information acquired from self-reported use in early pregnancy or any prescription during pregnancy or 1 month before. ORs were obtained by using multiple logistic regression analyses.

[a] Maternal age, year of birth, primiparity (versus multiparity), maternal smoking, BMI, mother born in Sweden, cohabiting with the child's father, cesarean delivery, and any use of mild sedatives during pregnancy.

[b] Opioids (N02A), antiepileptics (N03A), psycholeptics (N05), and centrally acting sympathomimetics (N06BA).

[c] GA and fetal weight for GA and sex (birth weight *z* scores).

[d] Exposure 1 month before and during pregnancy but not for the last 90 days of the pregnancy.

[e] Drugs dispensed during the last 90 days of the pregnancy with or without use during early pregnancy.

* Statistically significant ($P < .05$).

more frequent for infants exposed to SSRIs. The median treatment time with CPAP was 2 days for both exposed and nonexposed infants. Ventilator treatment was slightly more common in infants born to mothers who used SSRIs during late pregnancy compared with early pregnancy only. The median time on a ventilator was 3 days for SSRI-exposed infants and 4 days for nonexposed infants (*P* value for difference: .16). Analysis of neonatal morbidity according to GA for late SSRI use versus early SSRI use revealed that the ORs for respiratory disorders were more pronounced in term infants than in preterm infants (Supplemental Tables 9 and 10).

PPHN was more common both when comparing SSRI exposure versus nonexposure (OR: 1.3 [95% CI: 1.0–1.6]; $P = .03$) and treatment during late versus early pregnancy (OR: 2.1 [95% CI: 1.3–3.2]) (Tables 3 and 4). The corresponding NNH was 285 comparing late and early exposure, adjusted for maternal factors. Restricting the analysis to term infants, the OR for PPHN, SSRI late exposure versus early exposure, was 2.6 (95% CI: 1.4–4.8), and the NNH was 322. The mortality rate among infants with PPHN was 3.4% (3 of 89) for SSRI-exposed infants and 8.3% (171 of 2051) for nonexposed infants (OR: 0.4 [95% CI: 0.1–1.2]).The need for ventilator treatment among children with PPHN was significantly less in infants exposed to SSRIs (47% [42 of 89]) than among nonexposed infants (62% [1267 of 2051]; OR: 0.6 [95% CI: 0.4–0.9]). When GA was adjusted for, no difference between the need for ventilator treatment was indicated (OR: 0.9 [95% CI: 0.5–1.4]). Exposure to SSRIs did not affect the median length of stay in the NICU, which was 11 days for term infants with PPHN ($P = .7$ for difference in exposed/nonexposed) and 63 days for preterm infants with PPHN ($P = .5$).

An increased occurrence of hypoglycemia, CNS symptoms, and feeding difficulties after maternal use of SSRIs was also reported (Table 3 and 4).

DISCUSSION

Poor neonatal adaptation is well described as a consequence of maternal use of antidepressant drugs during pregnancy.[1–5,7–15,17,33] Our study adds information concerning the need for neonatal care associated with antidepressant exposure; for SSRIs, it provides detailed data on morbidity as well as neonatal interventions. We observed an increased risk of admission to the NICU in all groups exposed to antidepressant drugs, with the highest proportion of neonatal care after exposure to serotonin norepinephrine reuptake inhibitors or tricyclic antidepressants in late pregnancy. Because the median duration of NICU stay for the SSRI-exposed infants was ~1 week (just slightly shorter than that for the nonexposed infants), we believe that they were admitted due to substantial neonatal problems and not only as a precaution. This theory is supported by the fact that CPAP treatment was more common than in nonexposed infants, and ventilator treatment more frequent, after exposure during late pregnancy compared with early pregnancy only.

Some earlier reports suggested that severity of maternal depression per se is of greater importance than the drug effects.[24,25] Untreated depression and anxiety disorders have been linked to similar outcomes as treatment with antidepressant agents (eg, neonatal adaptation difficulties, preterm birth, SGA).[41–45] We found increased odds for admission to the NICU after exposure to antidepressants during late pregnancy compared with exposure during early pregnancy only. This finding was an attempt to account for the underlying psychiatric condition, and the clearly increased risk after

TABLE 3 Neonatal Morbidity Among Infants Exposed to SSRIs Compared With No Antidepressant Drug Exposure During Pregnancy

Outcome	Any SSRI (n = 17 736)		No Antidepressants (n = 718 533)		Crude		Adjusted for Maternal[a] Factors, Including Use of Other Neurotropic Drugs[b]		Adjusted for Fetal[c] and Maternal Factors, Including Use of Other Neurotropic Drugs	
	n	%	n	%	OR	95% CI	OR	95% CI	OR	95% CI
Any respiratory disorder	1 019	5.7	20 922	2.9	2.0	1.9–2.2	1.6	1.5–1.7	1.6	1.5–1.7
RDS	127	0.7	3744	0.5	1.4	1.2–1.6	1.0	0.8–1.2	1.0	0.8–1.2
Transient tachypnea/other respiratory disease	819	4.6	15 860	2.2	2.1	2.0–2.3	1.7	1.6–1.9	1.7	1.6–1.9
PPHN	89	0.5	2051	0.3	1.8	1.4–2.1	1.3	1.0–1.6*	1.3	1.0–1.7*
MAS	42	0.2	969	0.1	1.8	1.3–2.4	1.6	1.1–2.1	1.8	1.3–2.4
Ventilator treatment	140	0.8	3849	0.5	1.5	1.2–1.8	1.1	1.0–1.4	1.2	1.0–1.4
CPAP	749	4.2	15 690	2.2	2.0	1.8–2.1	1.5	1.4–1.6	1.5	1.4–1.7
Hypoglycemia	701	4.0	17 439	2.4	1.6	1.5–1.8	1.3	1.2–1.4	1.3	1.2–1.4
Hyperbilirubinemia	918	5.2	32 481	4.5	1.1	1.1–1.2	1.0	1.0–1.1	1.0	0.9–1.1
CNS-related disorders	94	0.5	2082	0.3	1.8	1.5–2.2	1.5	1.2–1.9	1.5	1.2–1.8
Intracranial hemorrhage	52	0.3	1897	0.3	1.1	0.8–1.5	0.9	0.7–1.2	0.9	0.7–1.2
Feeding difficulties	227	1.3	6777	0.9	1.4	1.2–1.6	1.0	0.9–1.2	1.0	0.9–1.2
Treated PDA	50	0.3	1362	0.2	1.5	1.1–2.0	1.2	0.9–1.6	1.3	1.0–1.8
Verified infections	91	0.5	2539	0.4	1.4	1.2–1.8	1.2	1.0–1.5	1.2	1.0–1.6

ORs were obtained by using multiple logistic regression analyses. MAS, meconium aspiration syndrome; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome.

[a] Maternal age, year of birth, primiparity (versus multiparity), maternal smoking, BMI, mother born in Sweden, cohabiting with the child's father, cesarean delivery, and any use of mild sedatives during pregnancy.

[b] Opioids (N02A), antiepileptics (N03A), psycholeptics (N05), and centrally acting sympathomimetics (N06BA).

[c] GA and fetal weight for GA and sex (birth weight z scores).

* Statistically significant ($P < .05$).

antidepressant use in late pregnancy suggests a true association with the drug treatment.

The higher risk of admittance to the NICU in exposed infants compared with nonexposed infants remained largely unchanged after adjustment for GA and SGA, indicating that the association between exposure to antidepressants and neonatal morbidity is not primarily mediated via preterm birth or intrauterine growth restriction. In fact, all estimates remained and were, in most cases, more pronounced when restricting the analysis to term infants only.

The rate of admissions to the NICU varied between the drug exposure groups. This finding might be due to differences in underlying maternal psychiatric conditions between the groups, but a drug class effect cannot be excluded.

Similar to previous studies, we found a higher frequency of respiratory disorders, CNS symptoms, hypoglycemia, and feeding difficulties[3,4,9,14,17,20–22] after maternal use of SSRIs but no increased risk of respiratory distress syndrome.

Primarily in term infants, we confirmed the earlier described association between SSRI exposure and PPHN,[28–30,46] a potentially life-threatening condition with reported mortality rates up to 10%.[47] The OR for PPHN, late versus early SSRI use, was significant only among term infants. Because the absolute risk for PPHN was higher among preterm than term infants, and SSRI-exposed infants were at increased risk of being born preterm, the NNH was nevertheless higher in the subcohort of term infants than in the total cohort. Thus, the overall impact of SSRI use in late pregnancy on PPHN rates is larger if both term and preterm births are considered. In the present SSRI-exposed cohort with PPHN, neonatal

TABLE 4 Neonatal Morbidity Among Infants Exposed to SSRIs During Late Pregnancy Compared With Exposure During Early Pregnancy Only

Outcome	SSRI, Late Use[a] (n = 9100)		SSRI, Early Use Only[b] (n = 8636)		Crude		Adjusted for Maternal[c] Factors, Including Use of Other Neurotropic Drugs[d]		Adjusted for Fetal[e] and Maternal Factors, Including Use of Other Neurotropic Drugs	
	n	%	n	%	OR	95% CI	OR	95% CI	OR	95% CI
Any respiratory disorder	649	7.1	370	4.3	1.7	1.5–2.0	1.6	1.4–1.9	1.4	1.2–1.6
RDS	64	0.7	63	0.7	1.0	0.7–1.4	1.0	0.7–1.4	0.5	0.3–0.9
Transient tachypnea/other respiratory distress	536	5.9	283	3.3	1.8	1.6–2.1	1.7	1.5–2.0	1.6	1.4–1.8
PPHN	60	0.7	29	0.3	2.0	1.3–3.0	2.1	1.3–3.2	1.7	1.1–2.8
MAS	26	0.3	16	0.2	1.5	0.8–2.9	1.6	0.8–3.0	1.9	1.0–3.6
Ventilator treatment	85	0.9	55	0.6	1.4	1.0–2.1*	1.5	1.1–2.1	1.1	0.8–1.7
CPAP	480	5.3	269	3.1	1.7	1.5–2.0	1.7	1.4–2.0	1.4	1.2–1.7
Hypoglycemia	427	4.7	274	3.2	1.5	1.3–1.8	1.5	1.3–1.7	1.3	1.1–1.6
Hyperbilirubinemia	481	5.3	437	5.1	1.0	0.9–1.2	1.0	0.9–1.2	0.8	0.6–0.9
CNS-related disorders	65	0.7	29	0.3	2.1	1.4–3.3	2.0	1.3–3.1	1.9	1.2–3.0
Intracranial hemorrhage	30	0.3	22	0.3	1.3	0.7–2.2	1.3	0.7–2.3	1.0	0.6–1.8
Feeding difficulties	147	1.6	80	0.9	1.8	1.3–2.3	1.7	1.3–2.3	1.4	1.1–1.9
Treated PDA	31	0.3	19	0.2	1.6	0.9–2.7	1.6	0.9–3.0	1.0	0.5–2.1
Verified infections	50	0.5	41	0.5	1.2	0.8–1.8	1.1	0.7–1.7	0.8	0.5–1.3

ORs were obtained by using multiple logistic regression analyses. MAS, meconium aspiration syndrome; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome.

[a] Drugs dispensed during the last 90 days of the pregnancy with or without use during early pregnancy.

[b] Exposure 1 month before and during pregnancy but not for the last 90 days of the pregnancy.

[c] Maternal age, year of birth, primiparity (versus multiparity), maternal smoking, BMI, mother born in Sweden, cohabiting with the child's father, cesarean delivery, and any use of mild sedatives during pregnancy.

[d] Opioids (N02A), antiepileptics (N03A), psycholeptics (N05), and centrally acting sympathomimetics (N06BA).

[e] GA and fetal weight for GA and sex (birth weight z scores).

* Statistically significant ($P < .05$).

mortality was 3%, which is lower than previously reported.[28] In our study, the neonatal mortality rates were not significantly different between exposed and nonexposed infants with PPNH. To some extent, comparing SSRI-exposed infants with PPHN versus nonexposed infants with PPHN may be partly comparing different conditions: isolated PPHN (which is probably more common in SSRI-exposed infants) and PPHN combined with severe neonatal illness.[47] However, after adjustment for GA, the need for ventilatory support and length of NICU stay did not differ between SSRI-exposed and nonexposed infants with PPHN. Therefore, our results do not suggest that SSRI-exposed infants with PPHN have less severe symptoms than other infants with this condition.

The present study had the advantage of a large, population-based, prospectively collected study cohort with high coverage of data[35,48] and detailed information on the infants' diagnoses.[37] We could adjust for known confounders such as smoking, use of other drugs with similar effects, BMI, family situation, and cesarean delivery. The registries do not contain information on alcohol or illicit drug use, which might have affected the results. Alcohol is, however, closely associated with smoking, and adjustment for smoking did not substantially alter the estimates. Only sparse data exist regarding the rate of illicit drug use among pregnant women in Sweden. According to a local report from the Stockholm area, 31 of the 29 166 women who gave birth in the region during 2014 had ongoing illicit drug use during pregnancy, and only 8 women continued their abuse throughout the pregnancy (I. Sarman, MD, PhD, written communication, 2016). Another limitation is that the PDR only provides information on drugs that have been dispensed from the pharmacies, and the compliance to the treatment is obviously unknown. It is likely that the real exposure is

lower but this outcome would only slightly affect the calculated risks. Furthermore, the timing of drug intake was approximated from the dates the drugs were dispensed. Some women might have lowered their dose before conception or during the pregnancy and therefore did not need a refill of drugs after the expected 3 months. This approach could have led to misclassification of the exposure group, which may result in an underestimation of ORs.

The main drawback with this study and other observational studies is the difficulty of adjusting for the mothers' psychiatric illness. We tried to account for the underlying psychiatric condition by comparing exposure during late pregnancy with exposure during early pregnancy only, but considerable residual confounding might exist. It is reasonable to assume that women who continued their medication during the entire pregnancy have a more severe psychiatric condition than women who discontinued treatment. Randomized, placebo-controlled studies would be valuable for determining to what extent neonatal outcomes are due to drug treatment or to the pregnant woman's mental condition. In severe depression, this approach would not be possible for ethical reasons but for moderate disease, it might be feasible.[49]

When assessing an infant prenatally exposed to antidepressant drugs, one should be particularly aware of respiratory disorders, hypoglycemia, feeding difficulties, and CNS symptoms. However, it is important to note that the risk increase for severe disease is small in the individual case. The majority (85%) of exposed infants do not have problems requiring neonatal care. The overall amount of admissions to neonatal care associated with antidepressant exposure might be substantial. If ~4% are treated in a population of 100 000 pregnant women, ~145 extra admissions to the NICU could be expected.

CONCLUSIONS

Maternal use of antidepressant drugs during pregnancy was associated with an increased risk that the newborn child would need treatment at a NICU. The association remained after adjustment for premature birth and SGA, factors that are known to be linked to maternal depression and anxiety. The study confirms previous findings of an increased risk of PPHN after SSRI exposure, primarily among term infants. The individual risk for neonatal illness linked to antidepressant drug treatment was moderate, and it must be carefully weighed against the potentially negative consequences for both the woman and her child that untreated psychiatric conditions could entail.

ABBREVIATIONS

CI: confidence interval
CNS: central nervous system
CPAP: continuous positive airway pressure
GA: gestational age
MBR: Medical Birth Register
NNH: number needed to harm
OR: odds ratio
PDR: Prescribed Drug Register
PPHN: persistent pulmonary hypertension of the newborn
PRS: Perinatal Revision South Register
RDS: respiratory distress syndrome
SGA: small for gestational age
SNQ: Swedish Neonatal Quality Register
SSRI: selective serotonin reuptake inhibitor

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