Original Investigation

Antidepressant Use Late in Pregnancy and Risk of Persistent Pulmonary Hypertension of the Newborn

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IMPORTANCE The association between selective serotonin reuptake inhibitor (SSRI) antidepressant use during pregnancy and risk of persistent pulmonary hypertension of the newborn (PPHN) has been controversial since the US Food and Drug Administration issued a public health advisory in 2006.

OBJECTIVE To examine the risk of PPHN associated with exposure to different antidepressant medication classes late in pregnancy.

DESIGN AND SETTING Cohort study nested in the 2000-2010 Medicaid Analytic eXtract for 46 US states and Washington, DC. Last follow-up date was December 31, 2010.

PARTICIPANTS A total of 3 789 330 pregnant women enrolled in Medicaid from 2 months or fewer after the date of last menstrual period through at least 1 month after delivery. The source cohort was restricted to women with a depression diagnosis and logistic regression analysis with propensity score adjustment applied to control for potential confounders.

EXPOSURES FOR OBSERVATIONAL STUDIES SSRI and non-SSRI monotherapy use during the 90 days before delivery vs no use.

MAIN OUTCOMES AND MEASURES Recorded diagnosis of PPHN during the first 30 days after delivery.

RESULTS A total of 128 950 women (3.4%) filled at least 1 prescription for antidepressants late in pregnancy: 102 179 (2.7%) used an SSRI and 26 771 (0.7%) a non-SSRI. Overall, 7630 infants not exposed to antidepressants were diagnosed with PPHN (20.8; 95% CI, 20.4-21.3 per 10 000 births) compared with 322 infants exposed to SSRIs (31.5; 95% CI, 28.3-35.2 per 10 000 births), and 78 infants exposed to non-SSRIs (29.1; 95% CI, 23.3-36.4 per 10 000 births). Associations between antidepressant use and PPHN were attenuated with increasing levels of confounding adjustment. For SSRIs, odds ratios were 1.51 (95% CI, 1.35-1.69) unadjusted and 1.10 (95% CI, 0.94-1.29) after restricting to women with depression and adjusting for the high-dimensional propensity score. For non-SSRIs, the odds ratios were 1.40 (95% CI, 1.12-1.75) and 1.02 (95% CI, 0.77-1.35), respectively. Upon restriction of the outcome to primary PPHN, the adjusted odds ratio for SSRIs was 1.28 (95% CI, 1.01-1.64) and for non-SSRIs 1.14 (95% CI, 0.74-1.74).

CONCLUSIONS AND RELEVANCE Evidence from this large study of publicly insured pregnant women may be consistent with a potential increased risk of PPHN associated with maternal use of SSRIs in late pregnancy. However, the absolute risk was small, and the risk increase appears more modest than suggested in previous studies.

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The high pulmonary vascular resistance characteristic of fetal circulation fails to decrease at birth in 10 to 20 newborns in every 10 000 live births, resulting in right-to-left shunting of blood through fetal channels, diminished pulmonary blood flow, and profound hypoxemia.[1,2] Such persistent pulmonary hypertension of the newborn (PPHN) typically occurs in term or near-term infants and presents within hours of birth with severe respiratory failure requiring intubation and mechanical ventilation.[2] Persistent pulmonary hypertension of the newborn is associated with substantial morbidity and mortality: 10% to 20% of affected infants will not survive, and infants who survive face serious long-term sequelae including chronic lung disease, seizures, and neurodevelopmental problems due to both the hypoxemia and the aggressive treatments it often requires.[1,3-6]

In 2006, the US Food and Drug Administration (FDA) issued a public health advisory on a potential increased risk of PPHN associated with late pregnancy exposure to selective serotonin reuptake inhibitors (SSRIs) based on a single epidemiologic study that found a 6-fold increase in risk associated with SSRI use after the 20th week of pregnancy.[7,8] Based on a review of additional studies with conflicting findings (2 studies reported an increase in risk, whereas 3 did not), the FDA concluded in 2011 that it was premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN and updated the advisory accordingly.[9-13] The negative studies tended to be small, raising the possibility that they had insufficient power to detect an increased risk.[10,11]

Given the ongoing controversy regarding the association between SSRI exposure in late pregnancy and the risk of this highly morbid pregnancy outcome, we examined the risk of PPHN associated with both SSRI and non-SSRI antidepressants in a large cohort of publicly insured pregnant women across the United States.

Methods

Data Source and Study Cohort

The study cohort was extracted from the Medicaid Analytic eXtract (MAX) for 46 US states and the District of Columbia for 2000-2010. Montana, Connecticut, and Michigan were excluded because of insufficient data to create a linked cohort of mothers and infants, and data from Arizona were not available. The MAX data set records demographic and Medicaid enrollment information for all Medicaid beneficiaries, as well as their health care use including recorded diagnoses and procedures for all physician services and hospitalizations and filled outpatient medication prescriptions.

The approach used for the development of our study cohort has previously been described in detail.[14] We identified all completed pregnancies in women aged 12 to 55 years and linked these pregnancies to live-born infants. We estimated the date of last menstrual period (LMP) based on the delivery date and diagnostic codes for preterm delivery using a validated algorithm.[15] To ensure complete ascertainment of exposures, outcomes, and covariates, we required all women to be Medicaid eligible, without supplementary insurance, restricted benefits, or certain capitated managed care plans that underreport claims to MAX, from 2 months or fewer after the LMP through at least 1 month after delivery.

Antidepressant Medications

The hypothesized etiologically relevant window for exposures that might lead to PPHN is early in the third trimester to delivery.[16] To avoid differential opportunity for exposure in term and preterm pregnancies, the exposure window for the study was therefore defined from 90 days before delivery through delivery. Women were considered exposed if they filled at least 1 prescription for an antidepressant medication during this time frame. Antidepressants were classified as SSRI therapy and non-SSRI therapy (see eTable 1 in the Supplement for a list of medications). Women exposed to both SSRIs and non-SSRIs were excluded from the cohort. The reference group consisted of women without exposure to antidepressants at any time during pregnancy. To facilitate comparison with earlier studies, we also conducted an analysis in the subgroup of term deliveries in which women were considered exposed if they filled a prescription after the 20th week of pregnancy.

Persistent Pulmonary Hypertension of the Newborn

Persistent pulmonary hypertension of the newborn was defined based on the presence of inpatient *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9*) diagnostic codes for persistent fetal circulation (747.83) or primary pulmonary hypertension (416.0x) in the maternal or infant records during the first 30 days after delivery. We used both maternal and infant codes because an infant's claims may be recorded under the mother's identification number for the first several months after birth.[17] Although PPHN is typically diagnosed at birth, we extended the window to 30 days after delivery to allow for late submission of health care claims. The positive predictive value (PPV) for this outcome definition was 89.6% in a validation study based on primary medical record review in cases treated at the delivery hospital.[18]

To assess the relationship between antidepressant medications and PPHN due to pulmonary vascular remodeling or maladaptation to circulatory transition (referred to hereafter as primary PPHN), we conducted additional analyses excluding infants with congenital cardiac malformations (except for those expected to be secondary to PPHN, such as patent ductus arteriosus, patent foramen ovale; eTable 2 in the Supplement) or lung abnormalities (ie, pulmonary hypoplasia, congenital diaphragmatic hernia because it could compress the lungs), and restricted the cohort to term deliveries. This definition resembles that of previous publications.[8,19]

Covariates

Information on comorbidities and other medications was obtained during the baseline period (any time before the end of pregnancy), unless otherwise noted. Covariates considered for confounding adjustment included year of delivery, age, race, multiple gestation, antidepressant indications (depression, other mental health disorders, pain-related diagnoses, migraine, sleep disorders, premenstrual tension syndrome, smoking, chronic fatigue syndrome), proxies for depression sever-

ity (number of outpatient and inpatient depression diagnoses), other chronic maternal illness (hypertension, preexisting diabetes, gestational diabetes, epilepsy, renal disease, asthma, obesity), other psychotropic medication use (anticonvulsants, antipsychotics, anxiolytics, benzodiazepines, other hypnotics, barbiturates, lithium), antidiabetic, antihypertensive and asthma medications, and nonsteroidal anti-inflammatory drugs. The number of distinct prescription drugs excluding antidepressants dispensed, number of physician outpatient visits, and number of hospital days (measured between 60 and 140 days after LMP to avoid measuring health care use intensity during the exposure window) were used as a general marker of comorbidity.[20] Cesarean delivery was not adjusted for because it has been shown that conditioning on such an intermediate perinatal factor is susceptible to overadjustment bias.[21,22]

Data Analyses

We compared the sociodemographic, clinical, and health care use characteristics between exposure groups and determined the frequency of PPHN in exposed and unexposed women. Logistic regression analysis was used to estimate odds ratios (ORs) and their 95% confidence intervals (CIs) for PPHN associated with antidepressant exposure. Results are presented for 4 levels of adjustment: (1) unadjusted, (2) restricted to women with a depression diagnosis to control for the potential effect of the underlying illness or factors associated with it, (3) restricted to women with a depression diagnosis, using propensity score stratification to further control for proxies of depression severity and other potential confounders,[23] and (4) restricted to women with a depression diagnosis, using high-dimensional propensity score stratification to further reduce residual confounding by controlling for proxies of unmeasured confounders.[24] Propensity scores were determined based on logistic regression models that estimated the probability of having filled a prescription for an antidepressant medication on the basis of all covariates listed above. Discrimination between treated and untreated patients was measured by the area under the receiver operating characteristic curve or *C* statistic, which ranges from 0.5 (no discrimination) to a theoretical maximum of 1 (perfect discrimination). We created 100 propensity score strata of equal width, removed strata that did not contain at least 1 treated woman and 1 untreated woman because they are uninformative, and stratified the outcome models by these propensity score strata.[25] The high-dimensional propensity score algorithm evaluates thousands of inpatient and outpatient diagnoses, procedures, and pharmacy claims and prioritizes those covariates that may act as proxies for unmeasured confounders. These empirically identified confounders (n = 200) were combined with the investigator-specified covariates listed above in a propensity score model to improve confounding adjustment.[24]

Sensitivity Analyses

To evaluate the statistical effect of potential exposure misclassification, we redefined exposure status as having filled at least 2 prescriptions during the 90 days before delivery. To evaluate the statistical effect of potential outcome misclassification as well as the potential association between exposure and the severity of the condition, we restricted the outcome to cases of severe PPHN, defined as a diagnosis of PPHN in the presence of a procedure code for respiratory assistance, extracorporeal membrane oxygenation, or inhaled nitric oxide therapy. To help assess whether outcomes were properly ascertained, we also evaluated some known associations in our data set, between maternal diabetes, obesity, cesarean delivery, black race, and PPHN.[19,26] Precision around the estimates of absolute risk and the measures of association are provided using 95% confidence intervals.

We added the current study to the most recent meta-analysis evaluating the association between SSRI use late in pregnancy and PPHN, which included 5 nonrandomized studies and estimated a pooled OR of 2.50 (95% CI, 1.32-4.73).[27] We assessed between-study heterogeneity on the basis of the χ^2 statistic and the I^2 statistic, and, consistent with the approach used in the original analyses, we pooled estimates using the DerSimonian and Laird random effects model. We conducted the analysis under 2 alternative scenarios: (1) using our base-case estimate, and (2) using our estimate for primary PPHN.

All analyses were conducted using SAS Software, version 9.3 (SAS System for Unix, SAS Institute Inc). The research was approved by the institutional review board of Brigham and Women's Hospital, which granted a waiver of informed consent.

Results

Among 3 789 330 eligible pregnancies, 128 950 women (3.4%) used an antidepressant during the 90 days before delivery: 102 179 (2.7%) were exposed to an SSRI and 26 771 (0.7%) to a non-SSRI antidepressant.

There were substantial differences in the baseline characteristics of the patients exposed to antidepressants compared with those unexposed (**Table 1**). Compared with women who took no antidepressant, women who filled a prescription for an antidepressant were more likely to be older and white, to use other psychotropic medications, to have a chronic illness, to be obese, to be smokers, and to have greater health care use. Baseline characteristics were more comparable between users of SSRI and non-SSRI antidepressants, although the non-SSRI users had a higher burden of illness overall, having more comorbidities, comedication use, and greater health care use. Antidepressant users were more likely to deliver preterm and by cesarean.

Overall, 20.8 (95% CI, 20.4-21.3) per 10 000 infants not exposed to antidepressants during the last 90 days of pregnancy had PPHN compared with 31.0 (95% CI, 28.1-34.2) per 10 000 infants exposed to antidepressants. This higher unadjusted risk among exposed infants was observed for both SSRI (31.5; 95% CI, 28.3-35.2 per 10 000 infants) and non-SSRI (29.1; 95% CI, 23.3-36.4 per 10 000 infants) antidepressants. After restricting to women with a depression diagnosis, the risks were 24.9 (95% CI, 23.7-26.1), 33.8 (95% CI, 29.7-38.6), and 34.4 (95% CI, 26.5-44.7) per 10 000 for unexposed, SSRI-exposed and non-SSRI exposed infants, respectively (**Table 2**).

Table 1. Characteristics of Women in the Study Cohort

Characteristic	No. (%) of Women in Study		
	Antidepressant Exposure		
	SSRI (n = 102 179)	Non-SSRI (n = 26 771)	Unexposed (n = 3 660 380)
Age, mean (SD), y	25.69 (5.48)	26.29 (5.68)	24.15 (5.49)
Year of delivery			
2000-2002	14 818 (14.50)	3069 (11.46)	623 464 (17.03)
2003-2005	37 102 (36.31)	8902 (33.25)	1 134 797 (31.00)
2006-2007	19 732 (19.31)	6645 (24.82)	768 457 (20.99)
2008-2010	30 527 (29.88)	8155 (30.46)	1 133 662 (30.97)
Race[a]			
White	81 339 (79.60)	21 398 (79.93)	1 720 307 (47.00)
Black	9153 (8.96)	2574 (9.61)	986 416 (26.95)
Hispanic	6148 (6.02)	1317 (4.92)	664 138 (18.14)
Other or unknown	5211 (5.10)	1407 (5.26)	278 816 (7.62)
Multiple gestation	3121 (3.05)	913 (3.41)	105 102 (2.87)
Preterm birth[b]	16 174 (15.83)	4654 (17.38)	431 096 (11.78)
Cesarean delivery[b]	29 806 (29.17)	8350 (31.19)	988 459 (27.00)
Antidepressant indications			
Depression	65 316 (63.92)	16 283 (60.82)	657 515 (17.96)
Other mental health disorders	15 297 (14.97)	4498 (16.80)	245 020 (6.69)
Pain-related diagnoses	9762 (9.55)	3235 (12.08)	171 913 (4.70)
Sleep disorders	6551 (6.41)	2259 (8.44)	65 493 (1.79)
Premenstrual tension syndrome	778 (0.76)	183 (0.68)	8 683 (0.24)
Smoking	20 766 (20.32)	7249 (27.08)	340 440 (9.30)
Chronic fatigue syndrome	18 291 (17.90)	5091 (19.02)	295 965 (8.09)
Migraine/headache	32 189 (31.50)	9594 (35.84)	690 775 (18.87)
Proxies for depression severity, No. of depression diagnoses, median (range)			
Outpatient	0 (0-180)	0 (0-180)	0 (0-180)
Inpatient	0 (0-16)	0 (0-7)	0 (0-8)
Chronic maternal illness			
Hypertension	6524 (6.38)	2162 (8.08)	148 158 (4.05)
Diabetes	5475 (5.36)	1618 (6.04)	132 761 (3.63)
Gestational diabetes	11 787 (11.54)	3222 (12.04)	310 142 (8.47)
Epilepsy	1831 (1.79)	472 (1.76)	29 323 (0.80)
Renal disease	652 (0.64)	207 (0.77)	16 084 (0.44)
Asthma	16 785 (16.43)	4872 (18.20)	377 275 (10.31)
Obesity	8179 (8.00)	2351 (8.78)	199 783 (5.46)
Other psychotropic medications			
Anticonvulsants	11 190 (10.95)	4158 (15.53)	118 575 (3.24)
Antipsychotics	15 199 (14.87)	4996 (18.66)	172 453 (4.71)
Anxiolytics	5081 (4.97)	1700 (6.35)	29 959 (0.82)
Benzodiazepines	21 869 (21.40)	6647 (24.83)	170 271 (4.65)
Other hypnotics	28 367 (27.76)	8213 (30.68)	474 318 (12.96)
Barbiturates	8241 (8.07)	2858 (10.68)	120 171 (3.28)
Lithium	1670 (1.63)	624 (2.33)	10 972 (0.30)
Other medications			
Antihypertensives	14 819 (14.50)	4792 (17.90)	262 457 (7.17)
Antidiabetics	4988 (4.88)	1502 (5.61)	102 283 (2.79)
Asthma medications	50 073 (49.01)	14 036 (52.43)	1 264 376 (34.54)
NSAIDs	46 632 (45.64)	13 368 (49.93)	1 358 600 (37.12)
No. of distinct prescription drugs, excluding antidepressants, median (range)	3 (0-31)	3 (0-43)	1 (0-39)
No. of outpatient physician visits, mean (SD)	12.61 (7.25)	13.05 (7.71)	10.37 (5.29)
No. of days hospitalized, median (range)	0 (0-85)	0 (0-89)	0 (0-90)

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitor.

[a] Race or ethnic group was determined on the basis of information submitted to the Centers for Medicare & Medicaid Services by individual states, which was based on information that had been collected and coded from Medicaid applications.

[b] Relates to current pregnancy.

In initial unadjusted analyses, the OR for PPHN was 1.51 (95% CI, 1.35-1.69) for SSRIs and 1.40 (95% CI, 1.12-1.75) for non-SSRIs (**Figure 1** and **Figure 2**). The association was attenuated after restricting the cohort to women with a depression diagnosis for SSRIs (OR, 1.36; 95% CI, 1.18-1.57), but not for non-SSRIs (OR, 1.38; 95% CI, 1.06-1.81). The *C* statistic for the pro-

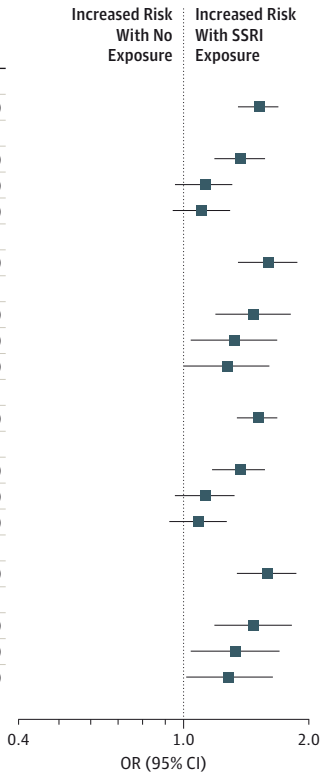
Table 2. Absolute Risk of Persistent Pulmonary Hypertension of the Newborn Among Infants of Women With and Without Antidepressant Exposure During Pregnancy by Class

	Cohort of Women With Pregnancies					
	Overall			Depression Restricted		
Exposure Groups	Unexposed	SSRI	Non-SSRI	Unexposed	SSRI	Non-SSRI
Total No. of Women	3 660 380	102 179	26 771	657 515	65 316	16 283
PPHN, No.	7630	322	78	1635	221	56
Risk per 10 000 (95% CI)	20.8 (20.4-21.3)	31.5 (28.3-35.2)	29.1 (23.3-36.4)	24.9 (23.7-26.1)	33.8 (29.7-38.6)	34.4 (26.5-44.7)

Abbreviations: PPHN, persistent pulmonary hypertension of the newborn; SSRI, selective serotonin reuptake inhibitor.

Figure 1. Risk of Persistent Pulmonary Hypertension of the Newborn Among Infants of Women Who Were and Were Not Exposed to Selective Serotonin Reuptake Inhibitors (SSRIs) During Pregnancy

	No. of Patients		No. of Outcomes		
Outcome Definition and Model	SSRI Exposed	Unexposed	SSRI Exposed	Unexposed	OR (95% CI)
Base case					
Unadjusted	102 179	3 660 380	322	7630	1.51 (1.35-1.69)
Depression restricted					
Unadjusted	65 316	657 515	221	1635	1.36 (1.18-1.57)
Propensity score stratified	65 315	657 515	221	1635	1.12 (0.95-1.31)
High-dimensional propensity score stratified	65 316	657 515	221	1635	1.10 (0.94-1.29)
Full-term deliveries					
Unadjusted	86 005	3 229 284	149	3512	1.59 (1.35-1.88)
Depression restricted					
Unadjusted	54 281	567 118	99	705	1.47 (1.19-1.81)
Propensity score stratified	54 280	567 118	99	705	1.32 (1.04-1.68)
High-dimensional propensity score stratified	54 281	567 118	99	705	1.27 (1.00-1.61)
PPHN without cardiac malformation or lung hypoplasia					
Unadjusted	102 179	3 660 380	300	7174	1.50 (1.34-1.68)
Depression restricted					
Unadjusted	65 316	657 515	205	1523	1.36 (1.17-1.57)
Propensity score stratified	65 315	657 515	205	1523	1.12 (0.95-1.32)
High-dimensional propensity score stratified	65 316	657 515	205	1523	1.08 (0.92-1.27)
Primary PPHN (PPHN without cardiac malformation or lung hypoplasia in full-term deliveries)					
Unadjusted	86 005	3 229 284	141	3348	1.58 (1.34-1.87)
Depression restricted					
Unadjusted	54 281	567 118	94	669	1.47 (1.18-1.82)
Propensity score stratified	54 280	567 118	94	669	1.33 (1.04-1.70)
High-dimensional propensity score stratified	54 281	567 118	94	669	1.28 (1.01-1.64)



Results are presented with different levels of confounding adjustment and varying the outcome definition. PPHN indicates persistent pulmonary hypertension of the newborn

pensity score models in the cohort of women with a depression diagnosis was 0.83 for both medication classes, indicating there were remaining differences in patient characteristics between nonusers and users of both classes of antidepressants. Fine stratification by propensity score resulted in groups with very similar measured characteristics, as evidenced by the small standardized differences (**Table 3**). Associations were further attenuated after adjustment for the propensity score. The adjusted OR was 1.12 (95% CI, 0.95-1.31) for women exposed to SSRIs and 1.01 (95% CI, 0.76-1.35) for women exposed to non-SSRIs. Stratification on the high-dimensional propensity score yielded similar results (OR, 1.10; 95% CI, 0.94-1.29 for SSRIs and OR, 1.02; 95% CI, 0.77-1.35 for non-SSRIs) (Figure 1 and Figure 2).

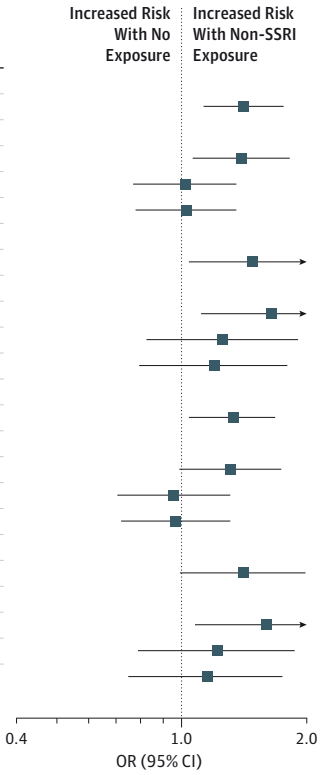
Restricting the cohort to term deliveries and redefining the outcome as PPHN in the absence of congenital cardiac malformations and lung hypoplasia generated slightly increased point estimates of risk for both SSRIs (high-dimensional adjusted OR, 1.28; 95% CI, 1.01-1.64) and non-SSRIs (high-dimensional adjusted OR, 1.14; 95% CI, 0.74-1.74) (Figure 1 and Figure 2). Restricting the cohort to term deliveries and defining exposure as having filled a prescription after the 20th week of pregnancy resulted in a high-dimensional adjusted OR of 1.14 (95% CI, 0.90-1.43) for SSRIs and 1.14 (95% CI, 0.77-1.69) for non-SSRIs.

Sensitivity Analyses

Requiring women to have filled at least 2 prescriptions in the 90 days before delivery did not result in stronger associations

Figure 2. Risk of Persistent Pulmonary Hypertension of the Newborn Among Infants of Women Who Were and Were Not Exposed to Antidepressants Other Than Selective Serotonin Reuptake Inhibitors (SSRIs) During Pregnancy

Outcome Definition and Model	No. of Patients		No. of Outcomes		OR (95% CI)
	Non-SSRI Exposed	Unexposed	Non-SSRI Exposed	Unexposed	
Base case					
Unadjusted	26 771	3 660 380	78	7630	1.40 (1.12-1.75)
Depression restricted					
Unadjusted	16 283	657 515	56	1635	1.38 (1.06-1.81)
Propensity score stratified	16 274	657 515	54	1635	1.01 (0.76-1.35)
High-dimensional propensity score stratified	16 274	657 515	55	1635	1.02 (0.77-1.35)
Full-term deliveries					
Unadjusted	22 117	3 229 284	35	3512	1.46 (1.04-2.03)
Depression restricted					
Unadjusted	13 356	567 118	27	705	1.63 (1.11-2.39)
Propensity score stratified	13 348	567 118	27	705	1.25 (0.82-1.90)
High-dimensional propensity score stratified	13 353	567 118	27	705	1.19 (0.79-1.79)
PPHN without cardiac malformation or lung hypoplasia					
Unadjusted	26 771	3 660 380	69	7174	1.32 (1.04-1.67)
Depression restricted					
Unadjusted	16 283	657 515	49	1523	1.30 (0.98-1.73)
Propensity score stratified	16 274	657 515	47	1523	0.95 (0.70-1.30)
High-dimensional propensity score stratified	16 274	657 515	48	1523	0.96 (0.71-1.30)
Primary PPHN (PPHN without cardiac malformation or lung hypoplasia in full-term deliveries)					
Unadjusted	22 117	3 229 284	32	3348	1.40 (0.99-1.98)
Depression restricted					
Unadjusted	13 356	567 118	25	669	1.59 (1.07-2.37)
Propensity score stratified	13 348	567 118	25	669	1.21 (0.78-1.86)
High-dimensional propensity score stratified	13 355	567 118	25	669	1.14 (0.74-1.74)



Results are presented with different levels of confounding adjustment and varying the outcome definition.

(eTable 3 in the Supplement). There was no evidence of an association between SSRI or non-SSRI antidepressants and severe PPHN, either for the base-case definition or for primary PPHN (eTable 4 in the Supplement).

There were statistically significant associations between PPHN and maternal diabetes (OR, 2.93; 95% CI, 2.72-3.15), obesity (OR, 2.02; 95% CI, 1.88-2.17), cesarean delivery (OR, 3.20; 95% CI, 3.06-3.35), and black race (OR, 1.30; 95% CI, 1.24-1.36). These findings are consistent with well-established associations. Adding our study to the meta-analysis using a random effects model reduced the pooled OR from 2.50 (95% CI, 1.32-4.73) to 1.95 (95% CI, 1.08-3.54) for our base-case estimate, and to 2.03 (95% CI, 1.21-3.41) for the estimate of PPHN in the absence of cardiac malformations, hypoplastic lung, or prematurity (primary PPHN) (eFigures 1 and 2 in the Supplement). The I^2 was 82% when using the base-case estimate and 71% when using the estimate for primary PPHN, suggesting there may be substantial heterogeneity between studies. The *P* value for the χ^2 statistic was <.05 in both cases.

Discussion

In this cohort of 3 789 330 pregnancies in the Medicaid program from 46 US states and the District of Columbia, of which 128 950 were exposed to antidepressants late in pregnancy, after control for depression and other potential confounding factors, we found that SSRI exposure in late pregnancy may be associated with an increase in the risk of PPHN, but the magnitude of that risk is smaller than previous studies have suggested. Sensitivity analyses applying more stringent definitions of exposure (>1 dispensing) and outcome (PPHN with ventilatory assistance or extracorporeal membrane oxygenation) did not amplify the degree of observed risk. There was no evidence of a significantly increased risk associated with non-SSRI antidepressant medication use.

Persistent pulmonary hypertension of the newborn can result from cardiac malformations, prematurity (eg, lungs with insufficient surfactant, meconium aspiration), structural lung abnormalities (eg, pulmonary hypoplasia), pulmonary vascular remodeling involving increased muscularization of pulmonary arterioles, or pulmonary vasoconstriction (eg, decreased production of or responsiveness to vasodilators such as nitric oxide and prostacyclin, or increased release of or responsiveness to vasoconstrictors).[1,28-30] Analyses that focused on the outcome of PPHN in the absence of cardiac malformations, hypoplastic lung, or prematurity (thereby focusing on PPHN due to pulmonary vascular remodeling or maladaptation to circulatory transition) resulted in slightly increased point estimates for risks associated with SSRIs.

The study that carried most weight in the recent meta-analysis[27] was a population-based cohort study con-

Table 3. Characteristics of Women in the Depression Restricted Cohort, Accounting for Propensity Score Strata

	No. (%) of Women					
	SSRI Exposed vs Unexposed Cohort[a]			Non-SSRI Exposed vs Unexposed Cohort[a]		
	SSRI	Unexposed	Standardized Difference	Non-SSRI	Unexposed	Standardized Difference
No. of Women	65 315	657 515		16 274	657 515	
Age, mean (SD), y	23.95 (5.44)	23.90 (5.53)	0.01	23.99 (5.31)	23.79 (5.51)	0.04
Year of delivery						
2000-2002	5833 (8.93)	55 284 (8.41)	0.02	1421 (8.73)	52 752 (8.02)	0.03
2003-2005	17 330 (26.53)	178 152 (27.09)	−0.01	4365 (26.82)	174 195 (26.49)	0.01
2006-2007	16 137 (24.71)	158 311 (24.08)	0.01	3998 (24.57)	160 940 (24.48)	0.00
2008-2010	26 014 (39.83)	265 767 (40.42)	−0.01	6490 (39.88)	269 628 (41.01)	−0.02
Race[b]						
White	37 829 (57.92)	388 642 (59.11)	−0.02	10 339 (63.53)	379 150 (57.66)	0.12
Black	14 287 (21.87)	139 888 (21.28)	0.01	3034 (18.64)	145 699 (22.16)	−0.09
Hispanic	9096 (13.93)	88 712 (13.49)	0.01	1771 (10.88)	92 155 (14.02)	−0.10
Other or unknown	3683 (5.64)	37 546 (5.71)	0.00	1040 (6.39)	37 744 (5.74)	0.03
Multiple gestation	2065 (3.16)	21 280 (3.24)	0.00	553 (3.40)	21 269 (3.23)	0.01
Preterm birth[c]	10 314 (15.79)	91 583 (13.93)	0.05	2654 (16.31)	90 875 (13.82)	0.07
Cesarean delivery[c]	18 589 (28.46)	188 722 (28.70)	−0.01	4693 (28.84)	187 906 (28.58)	0.01
Antidepressant indications						
Depression	65 315 (100.00)	657 515 (100.00)		16 274 (100.00)	657 515 (100.00)	
Other mental health disorders	17 273 (26.45	160 964 (24.48)	0.05	4241 (26.06)	163 067 (24.80)	0.03
Pain-related diagnoses	7958 (12.18)	75 476 (11.48)	0.02	2060 (12.66)	75 457 (11.48)	0.04
Sleep disorders	4927 (7.54)	44 508 (6.77)	0.03	1285 (7.89)	43 870 (6.67)	0.05
Premenstrual tension syndrome	490 (0.75)	4722 (0.72)	0.00	111 (0.68)	4585 (0.70)	0.00
Smoking	15 647 (23.96)	142 270 (21.64)	0.06	4258 (26.17)	141 373 (21.50)	0.11
Chronic fatigue syndrome	14 422 (22.08)	137 003 (20.84)	0.03	3747 (23.02)	135 962 (20.68)	0.06
Migraine/headache	26 438 (40.48)	256 899 (39.07)	0.03	6687 (41.09)	257 701 (39.19)	0.04
Proxies for Depression Severity, No. of depression diagnoses, median (range)						
Outpatient	0 (0 to 180)	0 (0 to 180)	0.02	0 (0 to 180)	0 (0 to 180)	0.04
Inpatient	0 (0 to 16)	0 (0 to 8)	0.03	0 (0 to 7)	0 (0 to 8)	0.04
Chronic maternal illness						
Hypertension	4802 (7.35)	47 451 (7.22)	0.01	1214 (7.46)	47 449 (7.22)	0.01
Diabetes	3727 (5.71)	35 857 (5.45)	0.01	911 (5.60)	35 562 (5.41)	0.01
Gestational diabetes	5941 (9.10)	61 399 (9.34)	−0.01	1571 (9.65)	60 089 (9.14)	0.02
Epilepsy	1593 (2.44)	13 646 (2.08)	0.02	452 (2.78)	13 456 (2.05)	0.05
Renal disease	608 (0.93)	5648 (0.86)	0.01	124 (0.76)	5687 (0.87)	−0.01
Asthma	14 774 (22.62)	138 776 (21.11)	0.04	3707 (22.78)	139 337 (21.19)	0.04
Obesity	7249 (11.10)	69 226 (10.53)	0.02	1716 (10.54)	69 456 (10.56)	0.00
Other psychotropic medications						
Anticonvulsants	9258 (14.17)	81 958 (12.46)	0.05	2233 (13.72)	81 177 (12.35)	0.04
Antipsychotics	11 936 (18.27)	106 030 (16.13)	0.06	2867 (17.62)	104 607 (15.91)	0.05
Anxiolytics	2733 (4.18)	26 266 (3.99)	0.01	747 (4.59)	25 072 (3.81)	0.04
Benzodiazepines	12 794 (19.59)	122 329 (18.60)	0.03	3129 (19.23)	118 102 (17.96)	0.03
Other hypnotics	19 229 (29.44)	187 929 (28.58)	0.02	4652 (28.59)	186 045 (28.30)	0.01
Barbiturates	5196 (7.96)	48 757 (7.42)	0.02	1310 (8.05)	48 203 (7.33)	0.03
Lithium	1412 (2.16)	11 083 (1.69)	0.03	328 (2.02)	10 791 (1.64)	0.03
Other medications						
Antihypertensives	9617 (14.72)	91 169 (13.87)	0.02	2392 (14.70)	90 232 (13.72)	0.03
Antidiabetics	2763 (4.23)	26 422 (4.02)	0.01	700 (4.30)	25 804 (3.92)	0.02
Asthma medications	38 938 (59.62)	384 043 (58.41)	0.02	9733 (59.81)	385 862 (58.68)	0.02
NSAIDs	42 368 (64.87)	419 104 (63.74)	0.02	10 417 (64.01)	424 005 (64.49)	−0.01

(continued)

Table 3. Characteristics of Women in the Depression Restricted Cohort, Accounting for Propensity Score Strata (continued)

	No. (%) of Women					
	SSRI Exposed vs Unexposed Cohort[a]			Non-SSRI Exposed vs Unexposed Cohort[a]		
	SSRI	Unexposed	Standardized Difference	Non-SSRI	Unexposed	Standardized Difference
No. of distinct prescription drugs, excluding antidepressants, median (range)	2 (0 to 31)	2 (0 to 33)	0.06	2 (0 to 43)	2 (0 to 33)	0.12
No. of outpatient physician visits, mean (SD)	12.42 (7.01)	11.94 (6.57)	0.07	12.53 (7.09)	11.83 (6.49)	0.10
No. of days hospitalized, median (range)	0 (0 to 85)	0 (0 to 90)	0.02	0 (0 to 89)	0 (0 to 90)	0.03

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitor.

[a] To account for the propensity score, the untreated observations were weighted using the distribution of the treated among propensity score strata. Propensity score strata that did not contain at least 1 treated woman and 1 untreated woman (ie, uninformative strata) were removed.

[b] Race or ethnic group was determined on the basis of information submitted to the Centers for Medicare & Medicaid Services by individual states, which was based on information that had been collected and coded from Medicaid applications.

[c] Relates to current pregnancy; these variables were not included in the propensity score.

ducted using Scandinavian health registries.[31] Among 1.6 million pregnancies of at least 33 gestational weeks, 11 014 mothers (0.7%) had filled a prescription for an SSRI late in pregnancy. Thirty-three exposed women vs 1899 unexposed women had a diagnosis of PPHN, for an unadjusted OR of 2.5 (95% CI, 1.8-3.6) and an adjusted OR of 2.1 (95% CI, 1.5-3.0). Although the unadjusted estimates differ between the Scandinavian study and this study (OR, 2.5 vs 1.5, respectively), this is entirely driven by the risk among the unexposed. The risk among the exposed was 30.0 per 10 000 in the Scandinavian study and 31.5 per 10 000 in the current study, whereas the risk among the unexposed was 12.0 per 10 000 and 20.8 per 10 000, respectively. Since the referent in the Scandinavian study is the general population (as opposed to low-income Medicaid beneficiaries), the burden of comorbid illness is likely to be much lower in their reference group. Similar to the current study, the Scandinavian study accounted for a range of predefined potential confounding variables, including sociodemographic characteristics and chronic maternal disease in the adjusted analysis. However, in contrast to the current study, the population was not restricted to women with a diagnosis of depression in order to mitigate potential confounding by the underlying psychiatric illness and its associated conditions and behaviors, and proxies for unmeasured confounders were not considered.

This study has several strengths, including its very large size, the objective assessment of drug exposure, access to medical records for outcome validation, the availability of information on a wide range of potential confounders, and the use of advanced epidemiologic methods to mitigate confounding. These characteristics allowed exploration of whether differences among earlier studies in design and analytic features could have explained the discrepant findings, including the consideration of PPHN secondary to congenital heart disease, prematurity, or both and the potential confounding role of the underlying depression and its associated factors. In addition, the study's large size enabled examination of the association for the less frequently used non-SSRIs.

This study also has some limitations. One concern is that the modest associations can be attributed to misclassification, because nondifferential misclassification of the exposure or the outcome will tend to bias results toward the null.[32] This appears unlikely to explain the results. Although filling 1 prescription does not ensure that the medication was taken as prescribed, women who go through the effort to refill a prescription are more likely to be taking the medication. Sensitivity analyses in which women were required to have filled at least 2 prescriptions during the last 90 days before delivery did not result in stronger associations. We used a validated outcome definition with high positive predictive value to define PPHN.[18] There was no evidence of an increased risk when the outcome was redefined as severe PPHN. Our ability to reproduce the association between established risk factors (diabetes, obesity, cesarean delivery, black race) and PPHN suggests the outcome is defined with high specificity in the study.

Adjusting for a large set of predefined and empirical potential confounding variables through use of propensity score stratification resulted in exposure groups with very similar measured characteristics, including important risk factors for PPHN such as diabetes, and nonsteroidal anti-inflammatory drug use. Nevertheless, information on some potential confounding factors is incomplete (eg, smoking) or absent (eg, maternal body mass index, diabetes severity), which may have resulted in residual confounding to the extent that these factors were not accounted for through adjustment for correlated variables (ie, proxies) identified in the high-dimensional propensity score analysis. Since most associations were null and these factors are expected to be more common among antidepressant-exposed women than among unexposed women, this is not a major concern. We cannot exclude the possibility, however, that the small increase in risk of primary PPHN observed for SSRIs is attributable to residual confounding.

Medicaid covers close to half of all births in the United States, making publicly insured pregnant women an important yet understudied population. The Medicaid population is younger and more racially diverse than commercially insured populations. Nevertheless, the etiologic findings from this study should be generalizable to other populations as these factors are not expected to affect the biologic relations studied.[32]

It has been suggested that higher circulating levels of serotonin in the fetus might result in the vasoconstriction and smooth muscle cell proliferation that is characteristic of PPHN.[28,33-36] That could explain why the association was slightly stronger when PPHN cases potentially attributable

to other causes like prematurity were excluded from the analyses. If so, the outcome definition could explain some of the discrepancies among previous studies. However, we cannot rule out the possibility that the slightly stronger association observed in the subgroup of full-term deliveries is attributable to selection bias; ie, stratifying on preterm delivery could have induced an association between antidepressant use and PPHN.

The findings in the largest cohort studied to date, using advanced epidemiologic methods to mitigate confounding by the underlying psychiatric illness and its associated conditions and behaviors, suggest that the risk of PPHN associated with late pregnancy exposure to SSRI antidepressants—if present—is smaller than previous studies have reported. Clinicians and patients need to balance the potential small increase in the risk of PPHN, along with other risks that have been attributed to SSRI use during pregnancy,[37,38] with the benefits attributable to these drugs in improving maternal health and well-being.[39]

Conclusions

Evidence from this large study of publicly insured pregnant women may be consistent with a potential increased risk of PPHN associated with maternal use of SSRIs in late pregnancy. However, the absolute risk was small and the risk increase appears more modest than suggested in previous studies.

ARTICLE INFORMATION

Author Contributions: Dr Huybrechts had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Huybrechts, Bateman, Palmsten, Desai, Patorno, Hernandez-Diaz.
Acquisition, analysis, or interpretation of data: All the authors.
Drafting of the manuscript: Huybrechts, Bateman.
Critical revision of the manuscript for important intellectual content: All the Authors.
Statistical analysis: Huybrechts, Palmsten, Desai, Gopalakrishnan, Levin, Mogun, Hernandez-Diaz.
Obtained funding: Huybrechts, Hernandez-Diaz.
Administrative, technical, or material support: Huybrechts.
Study supervision: Patorno, Hernandez-Diaz.

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