Risk of Hypertensive Disorders of Pregnancy in Women Treated With Serotonin-Norepinephrine Reuptake Inhibitors:

A Comparative Study Using the EFEMERIS Database

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ABSTRACT

Background: Among antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs) are particularly expected to increase the risk of hypertensive disorders of pregnancy (HDP) with regard to their biological mechanism. We aimed to evaluate the association between prenatal exposure to SNRI and HDP.

Methods: In EFEMERIS, a French database including pregnant women covered by the French Health Insurance System of Haute-Garonne (2004–2019), we compared the incidence of HDP among women exposed to SNRI monotherapy during the first trimester of pregnancy to the incidence among 2 control groups: (1) women exposed to selective serotonin reuptake inhibitor (SSRI) monotherapy during the first trimester and (2) women not exposed to antidepressants during pregnancy. We conducted crude and also multivariate logistic regressions.

Results: Of the 156,133 pregnancies, 143,391 were included in the study population, including 210 (0.1%) in the SNRI group, 1,316 (0.9%) in the SSRI group, and 141,865 (98.9%) in the unexposed group. After adjustment for depression severity and other mental conditions, the risk of HDP was significantly higher among women exposed to SNRIs (n = 20; 9.5%) compared to women exposed to SSRIs (n = 72; 5.5%; adjusted odds ratio [aOR] [95% CI] = 2.32 [1.28–4.20]) and to unexposed women (n = 6,224; 4.4%; aOR [95% CI] = 1.89 [1.13–3.18]).

Conclusion: This study indicated an increased risk of HDP in women treated with SNRIs versus women treated with SSRIs.

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Depression is a common pathology during pregnancy, and its prevalence varies across studies from 3% to 15%.[1] Drug utilization studies showed that 1% to 10% of women are prescribed selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs).[2–5] In a French study conducted in 2018 over a 10-year period,[6] almost 2% of pregnant women received antidepressants during pregnancy. The pharmacologic treatment for major depression is mostly based on drugs targeting the monoaminergic system. In France, SSRIs and SNRIs are recommended as first-line treatments for depression. Like SSRIs, SNRIs increase the level of serotonin, but SNRIs also increase the level of norepinephrine,[7] a catecholamine acting on α-adrenergic receptors. Increasing levels of norepinephrine in early pregnancy may lead to abnormal placentation, which can result in hypertensive disorders of pregnancy (HDP).[8,9]

HDP are a major complication affecting around 7% of pregnancies.[10,11] They represent an important cause of maternal and child morbidity and mortality.[12] Gestational hypertension is defined as high blood pressure (systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg) at or after week 20 of gestation and that goes away after delivery. A quarter of women with gestational hypertension will progress to preeclampsia, which is a complex medical disorder diagnosed by gestational hypertension accompanied by proteinuria and/or evidence of maternal acute kidney injury, liver dysfunction, neurologic features, hemolysis or thrombocytopenia, or fetal growth restriction.[13] Pathophysiologic modifications of hypertensive disorders often appear during the first trimester of pregnancy.[14]

Prior studies have compared the risk of HDP in women treated with SNRIs versus pregnant women without depression, and most of these found an increased risk of HDP after exposure to SNRIs,[15–17] with the exception of a study conducted by Avalos et al.[18] However, in Avalos and colleagues' study, the sample size of the group exposed to SNRI was low (72 pregnancies). None of these studies accounted for the severity of the depression. Yet, depression itself has been identified as a risk factor for hypertension.[19] We identified two studies that used depressed unmedicated pregnant women as controls[20,21] and have adjusted their statistical analysis for depression severity proxies. Those

Clinical Points

- Depression is a common pathology during pregnancy that needs to be treated, but previous studies have suggested that antidepressants might increase the risk of hypertensive disorders of pregnancy (HDP).
- After controlling for depression severity and other mental conditions, this study shows that exposure to serotonin-norepinephrine reuptake inhibitors during pregnancy is associated with an increased risk of HDP compared to exposure to selective serotonin reuptake inhibitors.

two studies have discordant results, since Palmsten et al[20] found an increased risk of HDP after exposure to SNRIs and Yang et al[21] did not. However, Yang et al[21] did find a potential dose-response association among antidepressant users, which supports a drug-induced effect. Palmsten et al[20] also compared the risk of HDP between women exposed to SNRIs versus women exposed to SSRIs and found that HDP risk was higher among women taking SNRIs (relative risk [RR] = 1.54; 95% CI, 1.28–1.86) compared with women receiving SSRI monotherapy after adjusting for depression severity. To date, the challenge is to identify a safe and effective class of antidepressant to best treat depressed women during pregnancy.

The discordant results of previous studies, as well as the high prevalence of antidepressant use during pregnancy and the potentially serious consequences of HDP, present a need for additional studies. In a French population–based cohort of pregnant women, we evaluated the association between HDP and exposure to SNRIs during pregnancy compared to exposure to SSRIs and to no exposure to antidepressants. Our hypothesis was that women exposed to SNRIs during pregnancy have an increased risk of HDP compared to both women exposed to SSRIs and women not exposed to antidepressants.

METHODS

Design

We performed a population-based cohort study. The risk of gestational hypertension in women exposed to SNRIs during pregnancy (SNRI group) was compared to the risk of gestational hypertension in (1) women exposed to SSRIs during pregnancy (SSRI group) and (2) women not exposed to antidepressants (Anatomic Therapeutic Chemical Classification [ATC] code N06A) up to 3 months before and during pregnancy (unexposed group).

Data Source

This study was performed using data on pregnant women in Haute-Garonne (Southwestern France) from the EFEMERIS database.[22,23]

EFEMERIS consists of anonymous data on (*a*) all drug prescriptions dispensed at pharmacies by patients receiving outpatient care, prior to and during pregnancy (names, ATC codes, dispensing dates, etc), provided by the French Health Insurance System; (*b*) administrative and medical information on the mother (professional status, parity, smoking) and the child (birth weight, congenital anomaly) through children's certificates filled out during the compulsory medical examinations at birth and at 9 and 24 months, provided by the Mother and Child Protection Center; (*c*) maternal medical discharge diagnosis codes from hospital, as well as date of hospitalization, provided by the linkage with the French National Uniform Hospital Discharge Data Set Database (PMSI); and (*d*) medical terminations of pregnancy that has been considered in the maternity wards of the region and centralized by the Prenatal Diagnosis Center.

A document ("declaration of pregnancy"), which contains this accurate starting date of pregnancy, is completed by the physician and sent to the French Health Insurance System for reimbursement of health care costs of women during pregnancy. The ultrasound performed at the end of the first trimester of pregnancy is the medical examination that allows the physician to know the exact starting date (date of conception). The French Health Insurance System is universal and manages all reimbursements of health care for all people affiliated with a health insurance scheme in France, supplemented by mutual funds or private insurance companies. The main system is for salaried workers and covers about 80% of the population. Expenses for most of the medications, except those deemed not to contribute much to health, are partially or totally covered by the Health Insurance System. The French list of refundable medicines is available on the French Health Insurance System website.[24] During the first 6 months of pregnancy, medications are reimbursed at a rate of 35% or 65%. Thereafter, medical care and medications are provided free of charge until the end of pregnancy.

The EFEMERIS database was approved by the French Data Protection Authority on April 7, 2005 (authorization number 05–1140). This study was performed using anonymized patient data. The women included in the EFEMERIS database were informed of their inclusion and of the potential use of their anonymized data for research purposes. They could oppose the use of their data at any time.

Study Population

The eligible study participants were women included in EFEMERIS, a population-based cohort of pregnant women. The inclusion period was between 2004 and 2019. Exclusion criteria were (1) pregnancies leading to spontaneous abortions (before week 20 of amenorrhea), since the outcome (HDP) occurs after week 20 of gestation; (2) exposure to antidepressants other than SSRIs or SNRIs 3 months before and during pregnancy; (3) receipt of both SSRIs and SNRIs 3 months before and during pregnancy; (4) exposure to SSRIs or SNRIs during the second and/or the third trimester but not during the first trimester; and (5) hypertension (diagnosis established during hospitalization and/or prescription and dispensation of antihypertensive medications) before week 20 of gestation.

Outcome

The outcome was HDP. Based on several validated algorithms and previous publications,[25–30] women with gestational hypertension were identified based on (*i*) diagnosis established during hospitalization, from week 20 of gestation (*ICD-10* codes: I10 to I16 "hypertensive disease," O13 "gestational hypertension without significant proteinuria," O14 "pre-eclampsia," O15.0 "eclampsia complicating pregnancy," O15.1 "eclampsia complicating labor," O15.2 "eclampsia complicating the puerperium," and O16 "unspecified maternal hypertension"); (*ii*) out- or inpatient diagnosis of "gestational hypertension," "pre-eclampsia," "eclampsia," or "HELLP syndrome" specified in the children's health certificates or in the Prenatal Diagnosis Center's medical files; and (*iii*) new onset, from week 20 of gestation, and dispensing of antihypertensive medications (ATC codes: C02 "antihypertensives," C03 "diuretics," C07 "beta-blocking agents," C08 "calcium channel blockers," and C09 "agents acting on the renin-angiotensin system").

Exposure

The time-window for exposure to SNRIs or SSRIs was defined as the first trimester of pregnancy, because HDP might be the consequence of abnormal placentation due to uterine, placental, and umbilical vasoconstriction during the first trimester of pregnancy.[9,14] The first trimester of pregnancy was defined as the period from the date of last menstrual period (LMP) to LMP + 97 days (13 weeks + 6 days of gestation), as defined by the American College of Obstetricians and Gynecologists.[31]

Drug classification was based on the ATC Classification System.[32] Women receiving at least one prescription during the first trimester of pregnancy of an SNRI (ATC codes were N06AX16 for venlafaxine, N06AX17 for milnacipran, and N06AX21 for duloxetine) were included in the SNRI group. Women receiving at least one prescription during the first trimester of pregnancy of an SSRI (ATC code N06AB) were included in the SSRI group. Women receiving no prescriptions for an SNRI nor SSRI up to 3 months before and during pregnancy were included in the unexposed group.

Potential Confounders

Potential confounding factors were identified in the literature[33]: maternal age (≤ 20 years, >20 to 30 years, >30 to 40 years, and > 40 years), parity, multiple pregnancy (yes/no), gestational diabetes (defined as the prescription and dispensing of at least one antidiabetic medication [ATC code A10] only during the second and/or third trimester[s]), history of diabetes (defined as the prescription and dispensing of at least one antidiabetic medication [ATC code A10] only before pregnancy and/or during the first trimester of pregnancy), folic acid dispensed during the 3 months prior to conception,[34] dispensing during pregnancy of medications known to induce hypertension (nonsteroidal anti-inflammatory drugs [NSAIDs] [ATC code M01], triptans [ATC code N02CC], and vasoconstrictors used as nasal decongestants [ATC code R01A]), and assisted medical procreation (clomiphene dispensed during the 3 months prior to conception). The number of hospitalizations for depression (*ICD-10* codes F30 to F39) was used as a proxy of mental illness severity. As EFEMERIS provided only medical discharge diagnosis codes from hospital, we used proxies to adjust for other comorbid psychiatric conditions or pain: (*i*) coprescription during pregnancy of medications used to treat anxiety (anxiolytics [ATC class N05B]) (at least one prescription during pregnancy: yes/no); (*ii*) coprescription during pregnancy of medications used to treat schizophrenia and/or bipolar disorder (antipsychotics [ATC class N05A]) (at least one prescription during pregnancy: yes/no); and (*iii*) coprescription during pregnancy of medications used to treat neuropathic pain (N02AX02 [tramadol], N01BX04 [capsaicin], N01BB02 [lidocaine plaster], N02AA01 [morphine], N02AA05 [oxycodone], N02AX06 [tapentadol], N02BG08 [ziconotide]) (at least one prescription during pregnancy: yes/no).

Among these factors, confounders were identified using univariate analysis. The variables with a significance of 20% were introduced into the multivariate model. Whatever the univariate analysis, the following covariates were entered into the model: maternal age, parity, multiple pregnancy, gestational diabetes, history of diabetes, number of hospitalizations for depression, coprescription during pregnancy of medications used to treat anxiety, coprescription during pregnancy of medications used to treat schizophrenia and/or bipolar disorder, and coprescription during pregnancy of medications used to treat neuropathic pain.

Statistical Analysis

Maternal characteristics were described in the 3 groups. Continuous variables were expressed as means (± SD; SD and range) and categorical variables as numbers (percentages).

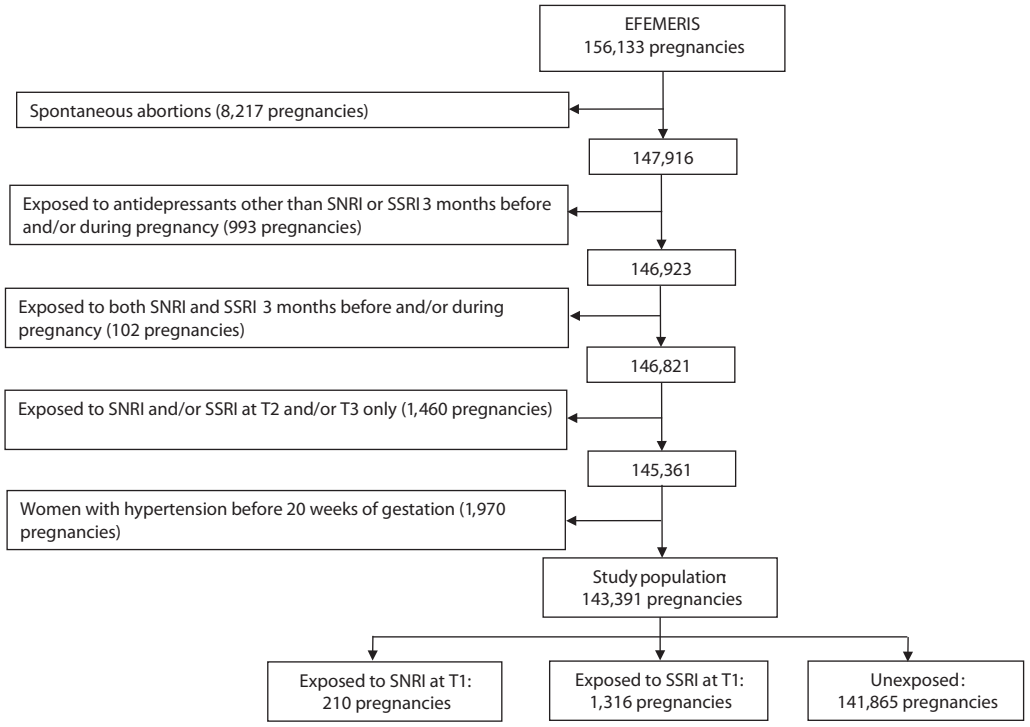
Logistic regression models were used to analyze the association between exposure to SNRIs during pregnancy and gestational hypertension by calculating odds ratios (ORs) and their 95% CIs. Cases with missing data for any of the covariates selected in the crude analysis were excluded from the multivariable analyses; we applied complete case analyses. The analyses were carried out using SAS version 9.4 software (SAS Institute Inc; Cary, NC). A 2-sided 5% level of significance was applied.

Sensitivity Analysis

We performed two sensitivity analyses to assess the robustness of our findings.

Nifedipine and nicardipine (two calcium channel blockers) can be used both to treat hypertension and as tocolytics in preterm labor.[35] This may have led to a misclassification bias because some women may have been wrongly classified as having the outcome even though they were prescribed nifedipine or nicardipine for preterm labor. To limit this misclassification bias, we repeated the main analysis after exclusion of women exposed once to nifedipine (ATC code C08CA05) or nicardipine (ATC code C08CA04)

Figure 1. Flowchart of the Selected Population



Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, T1 = first trimester, T2 = second trimester, T3 = third trimester.

after week 20 of gestation and who received a diagnosis code of preterm labor (*ICD-10* code O60).

We repeated the main analysis including women exposed to SNRIs or SSRIs during the first trimester only (and not during the second and/or the third trimester) to assess the robustness of our findings and to support the role of SNRI exposure during early pregnancy in the occurrence of HDP.

RESULTS

A total of 156,133 pregnancies (158,486 fetuses/children) were included in EFEMERIS between 2004 and 2019. After applying exclusion criteria, the study population consisted of 143,391 pregnancies (Figure 1). Among those pregnancies, in 210 (0.1%) did women receive at least one prescription for an SNRI during the first trimester of pregnancy; in 1,316 (0.9%), at least one prescription for an SSRI during the first trimester of pregnancy; and in 141,865 (98.9%), no prescription for an antidepressant (N06A) 3 months before and during pregnancy.

Of the 210 pregnancies exposed to an SNRI, the most frequently prescribed medication was venlafaxine (181; 86.2%), followed by duloxetine (25; 11.9%) and milnacipran (4; 1.9%). Women received a mean ± SD of 3.6 ± 3.3 (minimum = 1, maximum = 17) prescriptions of an SNRI during the first trimester, and 81 (38.6%) received only one prescription.

Among the 1,316 pregnancies exposed to an SSRI, the most frequently prescribed medication was escitalopram (428; 32.5%), followed by paroxetine (373; 28.3%), fluoxetine (183; 13.9%), citalopram (172; 13.1%), sertraline (158; 12.0%), and fluvoxamine (3; 0.2%). Women received a mean ± SD of 3.0 ± 2.9 (minimum = 1, maximum = 16) prescriptions of an SNRI during first trimester, and 681 (51.7%) received only one prescription.

Baseline characteristics of the pregnant women in the 3 groups are shown in Table 1. Compared to unexposed women, women exposed to SNRIs or SSRIs during the first trimester of pregnancy were slightly older (SNRI: 33.5 years, SSRI: 32.5 years, unexposed: 30.5 years). The percentage of women diagnosed with gestational diabetes was higher in the SNRI- and SSRI- exposed groups than in the unexposed group (SNRI: n = 10 [4.8%], SSRI: n = 66 [5.0%], unexposed: n = 3,592 [2.5%]). They also received more prescriptions for medications that could induce arterial hypertension (NSAIDs, triptans, and vasoconstrictors used as nasal decongestants) (SNRI: n = 38 [18.1%], SSRI: n = 281 [21.4%], unexposed: n = 17,682 [12.5%]). Likewise, the percentage of women receiving medication used to treat anxiety (SNRI: n = 89 [42.4%], SSRI: n = 535 [40.7%], unexposed: n = 3,673 [2.6%]) as well as schizophrenia and/or bipolar disorder (SNRI: n = 104 [7.9%], SSRI: = 21 [10.0%], unexposed: n = 790 [0.6%]) was higher in the SNRI and SSRI group than in the unexposed group. There were no statistically significant differences between the SNRI and the SSRI group for all the baseline characteristics, except for the number of hospitalizations for depression (SNRI: n = 23 [11.0%], SSRI: n = 49 [3.7%], unexposed: n = 105 [0.1%], $P < .0001$).

Table 1. Maternal and Newborn Characteristics of the EFEMERIS Cohort in the 3 Exposure Groups, Haute-Garonne, France, 2004–2019 (143,391 Pregnancies)[a]

Characteristic	SNRI During T1 (210 Pregnancies)	SSRI During T1 (1,316 Pregnancies)	Unexposed (141,865 Pregnancies)	*P* Value SSRI vs SNRI	*P* Value SNRI vs Unexposed
Maternal					
Sociodemographic and Professional					
Age at delivery, mean ± SD [min–max], y	33.5 ± 5.1 [18–46]	32.5 ± 5.0 [18–46]	30.5 ± 5.0 [14–57]	.01	<.0001
≤ 20	2 (1.0)	11 (0.8)	3,150 (2.2)	.01	<.0001
> 20–30	60 (28.6)	435 (33.1)	68,244 (48.1)		
> 30–40	126 (60.0)	808 (61.4)	67,283 (47.4)		
> 40	22 (10.5)	62 (4.7)	3,188 (2.2)		
	(110 Pregnancies)	(661 Pregnancies)	(77,360 Pregnancies)		
Pregnant women with a profession	63 (57.3)	359 (54.3)	46,540 (60.2)	.56	.54
	(202 Pregnancies)	(1,201 Pregnancies)	(132,140 Pregnancies)		
Long-term adverse health condition[b]	20 (9.9)	126 (10.5)	2,570 (1.9)	.80	<.0001
Medically assisted procreation	3 (1.4)	16 (1.2)	1,637 (1.2)	.80	.71
	(88 Pregnancies)	(510 Pregnancies)	(55,931 Pregnancies)		
Smoking	19 (21.6)	99 (19.4)	6,145 (11.0)	.65	.002
Obstetric Disorders and History					
Gestational diabetes (second and/or third trimester)	10 (4.8)	66 (5.0)	3,592 (2.5)	.88	.04
History of diabetes (before and/or during first trimester)	1 (0.5)	30 (2.3)	1,170 (0.8)	.08	.58
Hospitalization with depression (*ICD-10* codes F30–F39)	23 (11.0)	49 (3.7)	105 (0.1)	<.0001	<.0001
	(163 Pregnancies)	(973 Pregnancies)	(108,511 Pregnancies)		
Parity, mean ± SD [min–max]	1.8 ± 1.1 [1–6]	1.9 ± 1.0 [0–7]	1.7 ± 0.9 [0–13]	.65	.18
Medications					
Prescription folic acid (before pregnancy)	30 (14.3)	168 (12.8)	20,537 (14.5)	.54	.94
Prescription of teratogenic medications[c]	6 (2.9)	20 (1.5)	124 (0.1)	.16	<.0001
Prescription during pregnancy for medication that could induce arterial hypertension[d]	38 (18.1)	281 (21.4)	17,682 (12.5)	.28	.01
Medication used to treat neuropathic pain during pregnancy	3 (1.4)	25 (1.9)	1,514 (1.1)	.64	.61
Medication used to treat anxiety during pregnancy	89 (42.4)	535 (40.7)	3,673 (2.6)	.64	<.0001
Medication used to treat schizophrenia and/or bipolar disorder during pregnancy	104 (7.9)	21 (10.0)	790 (0.6)	.30	<.0001
Pregnancy Outcomes					
Pregnancy termination (≥ 20 WA)	0 (0.0)	10 (0.8)	760 (0.5)	.62	.76
Multiple pregnancy	5 (2.4)	22 (1.7)	2,207 (1.6)	.48	.34
Newborns	(215 Newborns)	(1,327 Newborns)	(143,301 Newborns)		
Preterm birth (< 37 WA)	21 (9.8)	116 (8.7)	8,813 (6.1)	.62	.03
Low birth weight (< 2,500 g)	16 (7.4)	110 (8.3)	7,763 (5.4)	.72	.15

[a]Data are presented as n (%) unless otherwise noted. The total numbers of pregnancies for each column are those listed in the column head except when indicated by a separate value within the column for individual variables.
[b]Long-term adverse health conditions (ALD: *affection de longue durée* in French) are 30 long-term and serious health conditions for which patients are fully covered by the national health care scheme.
[c]Included prescription of valproic acid during the first trimester of pregnancy, vitamin K antagonists during the first trimester of pregnancy, antineoplastic agents 1 month before and/or during the first trimester of pregnancy, mycophenolic acid during the first trimester of pregnancy, retinoids for systemic use 3 months before and/or during the first trimester of pregnancy, and thalidomide during the first trimester of pregnancy.
[d]Included prescription during pregnancy of nonsteroidal anti-inflammatory drugs (NSAIDs) (ATC code M01), triptans (ATC code N02CC), and vasoconstrictors used as nasal decongestants (ATC code R01A).
Abbreviations: ATC = Anatomical Therapeutic Chemical, Max = maximum, Min = minimum, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = Selective serotonin reuptake inhibitor, T1 = first trimester, WA = week of amenorrhea.

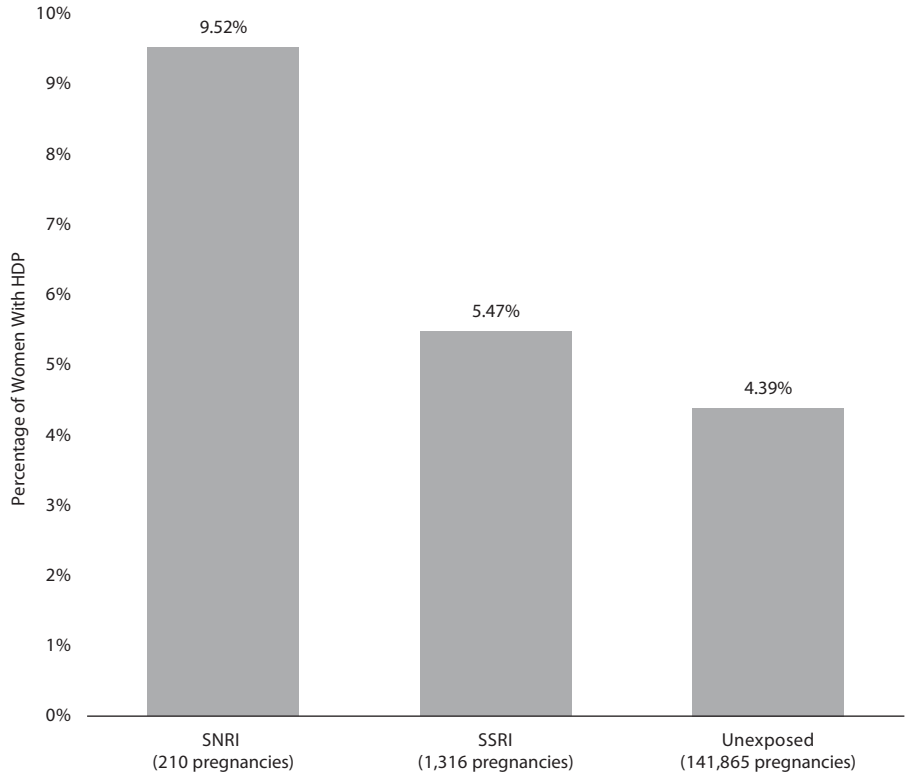
HDP was identified in 20 of 210 pregnancies in the SNRI group (9.5%), 72 of 1,316 pregnancies in the SSRI group (5.5%; *P* = .021), and 6,224 of 141,865 pregnancies in the unexposed group (4.4%; *P* = .0003) (Figure 2).

Table 2 presents the results of the crude and multivariate analyses. Exposure to SNRI during pregnancy was statistically associated with an increased risk of HDP, compared to SSRI-exposed pregnancies (adjusted OR [aOR] [95% CI] = 2.32 [1.28–4.20]; *P* = .01) and to unexposed pregnancies (aOR [95% CI] = 1.89 [1.13–3.18]; *P* = .02).

In the first supplementary analysis, we excluded 49 women exposed once to nifedipine or nicardipine after week 20 of gestation and with a diagnosis of preterm labor. Exposure to an SNRI during pregnancy was still statistically associated with an increased risk of HDP, compared to SSRI-exposed pregnancies (aOR [95% CI] = 2.32 [1.28–4.20]; *P* = .01) and to unexposed pregnancies (aOR [95% CI] = 1.92 [1.14–3.22]; *P* = .01). The results of this supplementary analysis did not change from the main analysis. Outcome misclassification bias is therefore limited for this study.

In the second supplementary analysis, we included only women exposed to SNRIs or SSRIs during the first trimester but not thereafter. Among the 210 pregnancies in the SNRI group, 96 (45.7%) were exposed to SNRIs during the first

Figure 2. Prevalence of Pregnancies (total = 145,391) Identified With HDP



Abbreviations: HDP = hypertensive disorders of pregnancy, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

trimester only, and among the 1,316 pregnancies in the SSRI group, 613 (46.6%) were exposed to SSRIs during the first trimester only. Exposure to SNRI during the first trimester only was still statistically associated with an increased risk of HDP compared to exposure to SNRI during the first trimester only (aOR [95% CI] = 3.14 [1.37–7.20]; $P = .01$).

DISCUSSION

The study highlighted an increased risk of HDP in pregnancies exposed to SNRIs compared to pregnancies exposed to SSRIs or to unexposed pregnancies.

Comparison of the Findings With the Existing Literature

This study adds to the conflicting literature on antidepressant-related gestational hypertension. Numerous studies have shown a higher risk of HDP after exposure to SNRIs compared to unexposed pregnancies,[15–17,20] whereas some studies did not.[18,21] Depression itself has been associated with a greater risk of HDP,[19] through a dysregulation of the autonomic nervous system and altered excretion of neuroendocrine transmitters.[36] For this reason, some authors selected pregnancies with unmedicated depression as controls. Despite the use of this design, the results remain conflicting.[20,21] In France, SSRIs and SNRIs are both recommended as first-line treatments for depression. Palmsten et al[20] found that HDP risk was higher among women receiving an SNRI compared with women receiving SSRI monotherapy. Using women exposed to an SSRI as a control group plays a role in mitigating the confounding effect for indication. However, our descriptive analysis showed that SNRIs might be given as second-line treatment by some practitioners in case of more severe depression, since we observed a smaller number of women exposed and a higher percentage of women with hospitalization for depression in the SNRI group.

To further limit the bias due to the confounding effects of depression severity and indication, we controlled for proxies of disease severity and other mental conditions. Our results are comparable to those of the studies by Palmsten et al[20] and Yang et al,[21] as these also accounted for maternal depression using untreated depressed women as controls. Our findings of an increased risk of gestational hypertension following SNRI exposure during pregnancy are in line with those of the study by Palmsten et al.[20] Although Yang et al[21] did not find this association, the authors provided evidence of a dose-response relationship between exposure to antidepressants during pregnancy and hypertensive disorders. Our findings are supported by the pharmacodynamic properties of SNRIs. SNRIs inhibit both serotonin and norepinephrine transporters and increase extracellular concentrations of these monoamines.[7] Serotonin and norepinephrine induce vasoconstriction, including uterine, placental, and umbilical vasoconstriction,[8,9] which is a biological pathway for HDP. As abnormal placentation may drive the development of

Table 2. Association Between SNRI Exposure During Pregnancy and HDP[a]

Analysis	Total, n	Outcome, n	OR (95% CI) Crude	OR (95% CI) Adjusted[b]	*P* Value (Adjusted)
Main Analysis					
SSRI group (reference)	965	53	1	1	
SNRI group	163	19	**2.27 (1.30–3.94)**	**2.32 (1.28–4.20)**	**.01**
Unexposed group (reference)	107,843	4940	1	1	
SNRI group	163	19	**2.74 (1.70–4.43)**	**1.89 (1.13–3.18)**	**.02**
Supplementary Analysis (excluding exposure once to nifedipine or nicardipine after 20 weeks of gestation and with a diagnosis of preterm labor)					
SSRI group (reference)	965	53	1	1	
SNRI group	163	19	**2.27 (1.30–3.94)**	**2.32 (1.28–4.20)**	**.01**
Unexposed group (reference)	107,805	4902	1	1	
SNRI group	163	19	**2.76 (1.71–4.47)**	**1.92 (1.14–3.22)**	**.01**
Supplementary Analysis (exposure to SNRIs or SSRI during the first trimester only)					
SSRI group (reference)	613	25	1	1	
SNRI group	96	10	**2.73 (1.26–5.89)**	**3.14 (1.37–7.20)**	**.01**

[a]Boldface indicates statistical significance.
[b]Multivariate logistic regression model adjusted for maternal age, parity, presence of gestational of diabetes, history of diabetes, presence of multiple pregnancy, prescription of potentially hypertensive medications during pregnancy, hospitalization with depression, medication used to treat neuropathic pain during pregnancy, medication used to treat anxiety during pregnancy, and medication used to treat schizophrenia and/or bipolar disorder during pregnancy.
Abbreviations: HDP = hypertensive disorders of pregnancy, OR = odds ratio, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

preeclampsia, our time window for exposure to SNRIs or SSRIs was the first trimester of pregnancy. The result of our second sensitivity analysis supported the role of SNRI exposure in early pregnancy in the onset of HDP.

Our algorithm to identify women with gestational hypertension could be compared only partially to previous studies since most published and validated algorithms concern preeclampsia specifically. The validation studies indicated that diagnosis codes for preeclampsia can be used to identify preeclampsia, but the only validation study that was conducted using European data[27] suggested that the accuracy of codes may vary across population, periods, and databases. Therefore, using data from children's certificates to supplement data about hospitalizations may improve the performance of the algorithm. Our algorithm has several similarities with that of Boucheron et al,[30] because they also identified women with gestational hypertension through both the prescription of antihypertensive medications and the hospital stay with an *ICD-10* diagnosis for HDP, and they excluded women with a diagnosis of preterm labor. In the study by Toh et al,[25] the criterion was the diagnosis of gestational hypertension by a health professional after week 20 of gestation. Palmsten et al[20] used *ICD-9* or *ICD-10* hospitalization codes to identify preeclampsia. Finally, Zakiyah et al[37] identified women with gestational hypertension through the presence of at least one antihypertensive prescription (methyldopa, nifedipine, labetalol, ketanserin, or nicardipine) between 22 weeks' gestation and 14 days after delivery. In fact, preeclampsia can also develop after delivery, although this occurs more rarely.[38] However, a study showed that the performances of algorithms identifying preeclampsia increased when restricted to diagnosis recorded before delivery.[28]

Limitations

This study has several potential limitations. First, the Health Insurance System does not record self-medication, drugs prescribed during hospitalization, indication for medication prescription, drugs that are prescribed but not reimbursed, or compliance with the prescription. A Canadian study[39] showed that, among pregnant women continuing antidepressants, the overall rate of adherence was 62.6% and that the rate differed significantly by medication class, with a rate of 75.1% for SNRIs and 60.9% for SSRIs. Second, the EFEMERIS cohort includes pregnant women in Haute-Garonne, a region in Southwest France, and we cannot exclude that patterns of prescriptions and of hospitalizations during pregnancy may vary according to French areas. However, EFEMERIS provides an observational study on drug exposure in a large sample of pregnant women (more than 169,000 over 15 years) that is representative of pregnancies, since maternal characteristics are similar to those described in the French national perinatal survey that was published in 2010 and in 2016.[40,41] Third, we used a composite unvalidated outcome for HDP measurement. However, we could compare the prevalence of HDP to that in the study conducted by Olié et al[11] and, taking into account that we applied several exclusion criteria to select our study population, the prevalence of HDP in our population is consistent with that in the study by Olié et al.[11] Fourth, we defined exposure as having at least one prescription for an SNRI during the first trimester of pregnancy, and we could not go further in the analysis (study of a potential dose-response relationship between SNRIs and HDP and study of each SNRI separately) because of sample sizes that were to small. Fifth, as information about depression severity was not explicitly available in EFEMERIS, we used hospitalizations for depression as a proxy for disease severity. Although this may not fully have reflected all levels of severity, we were able to take into account depression severe enough to lead to hospitalization. Finally, we could not rule out that a confounding bias remained, since data on some relevant clinical and lifestyle variables were not available or were

too often missing in EFEMERIS, such as body mass index and smoking status.

Strengths

This study has several strengths. First, EFEMERIS included more than 150,000 mother-child dyads and is suitable to investigate medication safety during pregnancy because it contains validated information about pregnancy starting date, pregnancy outcomes, and all medications prescribed and dispensed as well as medical and administrative information about the mother. As antidepressants are prescription-only medications and are fully reimbursed by the health care system in France, we expected to have exhaustive data about exposure. Second, we used the active comparator design, since the control group is composed of women exposed to SSRIs whose primary indication is depression. Third, we carefully defined exposure (during the first trimester of pregnancy) and outcomes (from week 20 of gestation) to ensure that the exposure precedes the outcome. Women with hypertension before week 20 of gestation were excluded. Moreover, the exposure window is supported by publications showing that HDP might be the consequence of pathophysiologic modifications of the placenta during the first trimester.[14] Fourth, although SNRIs and SSRIs were marketed for the same indications (mainly the depression) and both are recommended in France as first-line treatments for depression, SNRIs are possibly used in more severe pathologies or in pathologies with other mental disorders associated. To limit the bias due to confounding effects of depression severity and indication, we did control for proxies of disease severity and for proxies of other mental conditions.

Clinical Relevance of the Results

Depression is a common pathology during pregnancy that may lead to severe adverse pregnancy outcomes. Untreated depression during pregnancy has been associated with adverse maternal, obstetric, and fetal outcomes,[42] and studies have demonstrated that the use of antidepressants reduces the risk of adverse pregnancy outcomes.[43] It is therefore essential to treat pregnant women for their depression. The major task is to find the most effective and safe antidepressant medication. According to the French recommendations, SSRIs and SNRIs are both first-line treatments for depression in pregnancy. However, on the basis of our results, SNRIs should be used with more caution than SSRIs in depressed women during pregnancy, especially if there are cardiovascular risk factors. If SNRIs are the only medications a pregnant woman has responded to, blood pressure should be regularly monitored during pregnancy.

To conclude, our study showed that SNRI use is associated with an increased risk of HDP compared to SSRI use. This effect is supported by a biological mechanism.

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