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Antidepressant use during pregnancy and the risk of pregnancy-induced hypertension

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Antidepressants represent one of the most commonly used medications during pregnancy.
- There is a scarcity of information on impact of medications on maternal health outcomes.
- As the primary caregiver of the child, the mother's health and well-being should carry significant weight when making decisions regarding medication use during pregnancy.

WHAT THIS STUDY ADDS

- Antidepressant use during pregnancy is associated with increased risk of pregnancy-induced hypertension.
- These findings highlight the importance of further research evaluating the impact of gestational medication use on the health of the mother.

AIM

Due to their effect on altering physiological interactions between vasodilator and vasoconstrictor autacoids in normal pregnancies, antidepressants may be associated with the risk of pregnancy-induced hypertension. We evaluated the impact of antidepressant use during pregnancy on the risk of pregnancy-induced hypertension.

METHODS

We conducted a nested case–control study within the Quebec Pregnancy Registry, built by linkage of provincial medical, pharmaceutical, hospital and birth databases. We identified 1216 women with a diagnosis of pregnancy-induced hypertension with or without pre-eclampsia and with no history of hypertension before pregnancy. We randomly selected 10 controls for each case, matched on case index date (date of diagnosis) and gestational age. Odds ratios (OR) were calculated using conditional logistic regression models, adjusting for sociodemographic characteristics, maternal depression, anxiety, other chronic conditions, medication use and health service utilization.

RESULTS

Among cases, 45 (3.7%) had used antidepressants during pregnancy compared with 300 (2.5%) in the control group (OR 1.52, 95% CI 1.10, 2.09). After adjusting for potential confounders, use of antidepressants during pregnancy was significantly associated with increased risk of pregnancy-induced hypertension (OR 1.53, 95% CI 1.01, 2.33). In stratified analyses, use of selective serotonin re-uptake inhibitors (OR 1.60, 95% CI 1.00, 2.55), and more specifically, paroxetine (OR 1.81, 95% CI 1.02, 3.23) was associated with risk of pregnancy-induced hypertension.

CONCLUSIONS

Women who use antidepressants during pregnancy are at increased risk of pregnancy-induced hypertension with or without pre-eclampsia above and beyond the risk that could be attributed to their depression or anxiety disorders.

Introduction

Up to 14% of pregnant women use antidepressants during pregnancy [1, 2], yet there is marked inadequacy of data on the use of these drugs in this population. In particular, while epidemiologic studies have better elucidated associations with fetal and neonatal outcomes including spontaneous abortions [3], small for gestational age babies [4] and congenital abnormalities [5, 6], lack of similar data for maternal outcomes precludes overall understanding of the risks and benefits of antidepressant use during pregnancy.

Given that selective serotonin re-uptake inhibitors (SSRIs) may affect the peripheral handling of serotonin [7] and that serotonin-norephinephrine re-uptake inhibitors (SNRIs) have demonstrated noradrenergic effects [8], it is conceivable that antidepressants may be associated with pregnancy-induced hypertension. A study using maternal self-report of medication exposure from the Slone Epidemiology Center showed that women who received SSRIs 2 months before pregnancy and continued using them after the first trimester had increased risk of pregnancy-induced hypertension compared with non-SSRI users [9]. A recent study of maternal and neonatal outcomes of antidepressant use using data from the Swedish Medical Birth Register showed that women who reported use of an antidepressant since becoming pregnant or those who were prescribed antidepressants during pregnancy by antenatal care had 50% higher risk of pre-eclampsia [10]. As therapeutic uncertainty remains regarding the safety of antidepressants during gestation along with the need for information on their impact on maternal health, confirmation of these findings using objective data on medication use and health outcomes is warranted. Thus, our objective was to evaluate the impact of antidepressant use during pregnancy on the risk of pregnancy-induced hypertension in a population-based cohort of pregnant women.

Methods

Data sources

We used data from the Quebec Pregnancy Registry, a longitudinal cohort established with the linkage of three administrative databases: (i) *Régie de l'Assurance Maladie du Québec* (RAMQ), (ii) MED-ECHO and (iii) *Institut de la Statistique du Québec* (ISQ). The RAMQ provides medical coverage to all 7.8 million Quebec residents and pharmaceutical coverage to 43% (e.g. welfare recipients, individuals ≥65 years, individuals not insured by their employer or spouse's employer) through Quebec's Public Prescription Drug Insurance Plan; 36% of women between 15–45 years of age are covered by the RAMQ drug plan [11]. Data holdings in the RAMQ include (i) prospectively collected data on physician-based diagnoses (according to International Classification of Diseases, ninth revision [ICD-9] [12]), visits to physicians and emergency departments, health care provider characteristics and patient characteristics in the Medical Services File and (ii) validated and reliable data on filled medications including drug name, dosage, quantity and date and duration of dispensing in the Prescription Drug File [11, 13]. The MED-ECHO hospital database records all acute care hospitalizations, including length of gestation, which is defined from the first day of the last menstrual period to the end of pregnancy and confirmed by ultrasound, providing exact gestational age at the end of pregnancy. Data on physician-based medical diagnoses in MED-ECHO have demonstrated validity [14]. The ISQ database contains demographic information on the mother, father and baby. Data recorded in the ISQ database have been compared with medical charts and found to be complete and valid [15]. Overall, the Quebec Pregnancy Registry contains data on all pregnancies between January 1 1997 and December 31 2003 that were covered by Quebec's Public Prescription Drug Insurance Plan for at least 12 months before pregnancy and during pregnancy.

Study population

To be included in this study, women in the Quebec Pregnancy Registry had to be 15 years of age or more at the beginning of pregnancy and continuously insured by Quebec's Public Prescription Drug Insurance Plan for at least 12 months before and during pregnancy. If a woman had more than one pregnancy during the study period, then only the first pregnancy meeting the eligibility criteria was considered as pregnancy-induced hypertension is more common among primiparous women [16].

Study design and outcome definition

We applied the nested case–control design which yields similar effect sizes as a time-dependent cohort study but with greater computational efficiency [17]. Cases of pregnancy-induced hypertension were defined as women with a diagnosis of gestational hypertension (ICD-9: 642.3, 642.0), pre-eclampsia (ICD-9: 642.4, 642.5) or eclampsia (ICD-9: 642.6) after the 20th week of gestation [18, 19]. A study of a population-based medical birth registry reported positive predictive values of 93% for diagnostic codes for pregnancy-induced hypertension with pre-eclampsia and 84% for pregnancy-induced hypertension without pre-eclampsia [19]. Women with a diagnostic code for hypertension (ICD-9: 401.0–405.9, 362.1, 416.0, 437.2, 796.2) or prescriptions for antihypertensive medication (e.g. selective and non-selective β-adrenoceptor blockers, α-adrenoceptor blockers, α- and β-adrenoceptor blockers) in the 12 months before pregnancy and during the first 20 weeks of pregnancy were considered to have chronic hypertension and excluded. We also excluded women with a diagnostic code for pregnancy-induced hypertension before the 20th week of pregnancy. This definition is consistent with clinical guidelines as the Society of Obstetricians and Gynaecologists of Canada state that pre-existing

hypertension pre-dates pregnancy or appears before 20 weeks of gestation and pregnancy-induced hypertension appears at or after 20 weeks gestation [16]. For each case, we defined the index date as the earliest date of diagnosis of pregnancy-induced hypertension. Using the nested case–control design, we selected controls among women in the Quebec Pregnancy Registry who did not have a diagnosis of pregnancy-induced hypertension at or before the same gestational age as their matched case did. The index date for controls was assigned as the matched index date for their corresponding case, thereby matching cases and controls on gestational age.

Exposure to antidepressants

As in our previous work on gestational antidepressant use and fetal/neonatal outcomes [3, 5, 6, 20], we used the RAMQ Prescription Drug File to define exposure to antidepressants as at least one prescription filled between the first day of gestation and index date. Prescriptions filled before pregnancy but whose duration overlapped the first day of gestation were also considered. Antidepressants evaluated included (i) SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline), (ii) tricyclic antidepressants (amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline and trimipramine), (iii) SNRIs (venlafaxine) and (iv) 'other antidepressants' (serotonin modulators, monoamine oxidase inhibitors, tetracyclic piperazino-azepines, and dopamine and norepinephrine re-uptake inhibitors). Combined use of antidepressants was defined as the filling of a prescription for at least one dose of two or more different antidepressant classes or types between the first day of gestation and index date.

Covariates

We assessed the history of the following conditions: depression (ICD-9: 296.x, 300.4, 309, 311); anxiety (ICD-9: 300.0), diabetes (ICD-9: 250.0–250.9, 271.4, 790.2 or use of insulin or oral hypoglycaemic agents), cardiovascular disease (ICD-9: 414.0–414.9, 710.0–710.9, 404.0–404.9, 429.2, 794.3, 648.6, 425.4, 440.9, V174) and asthma (ICD-9: 648.5–648.6, 390.0–459.9, 490.9–519.9, 745.0–748.9). We assessed other medication use in the 12 months before pregnancy and during pregnancy including non-steroidal anti-inflammatory drugs (NSAIDs), systemic anti-infective agents and all other medications excluding antidepressants. Healthcare utilization variables including hospitalizations and emergency department visits were selected as markers of health status and were measured in the 12 months before and during pregnancy. We also considered pregnancy related variables including prenatal visits and visits to obstetricians/gynaecologists. Finally, we determined the following sociodemographic variables at index date: maternal age, region of residence and RAMQ insurance status (welfare beneficiary *vs.* adherent).

Statistical analysis

To estimate the effect of antidepressant use during pregnancy on the risk of pregnancy-induced hypertension, we used conditional logistic regression models and calculated crude and adjusted odds ratios (OR) with 95% confidence intervals. Multivariable models were adjusted for sociodemographic variables, depression, anxiety, other comorbid medical conditions, medication use and health care utilization. In primary analyses, we evaluated gestational antidepressant use as a dichotomous exposure (yes/no) and in secondary analyses, we evaluated exposure according to antidepressant class and type. In sensitivity analyses, we compared women who received antidepressants in the 2 months before pregnancy and continued treatment after the first trimester (continuers) with women who discontinued before the end of the first trimester (discontinuers) and non users [9].

Ethics approval

This study was approved by the Ethics Committee of Ste-Justine's Hospital and the linkages between databases were approved by the Commission d'accès à l'information du Québec.

Results

Among 61 735 women in the Quebec Pregnancy Registry who met study inclusion criteria, we identified 1216 cases of pregnancy-induced hypertension including 457 women with pregnancy-induced hypertension without pre-eclampsia, 795 women with pregnancy-induced hypertension with pre-eclampsia and four women with eclampsia. Characteristics of cases and their matched controls are shown in Table 1. Cases had higher frequency of diabetes, hospital visits before pregnancy, and higher frequency of encounters with psychiatrists and obstetricians/gynaecologists during pregnancy compared with controls.

Overall, 345 women filled at least one prescription for an antidepressant during pregnancy, 45 (3.7%) were cases and 300 (2.5%) were controls. When modelling antidepressant exposure dichotomously and adjusting for potential confounders including indication for use, antidepressant use during pregnancy was associated with a 53% increased risk of pregnancy-induced hypertension (adjusted OR 1.53, 95% CI 1.01, 2.33) (Table 2).

When modelling exposure according to antidepressant class, we found that use of SSRIs alone was significantly associated with the risk of pregnancy-induced hypertension (adjusted OR 1.60, 95% CI 1.00, 2.55) (Table 3). Use of other antidepressants (serotonin modulators, monoamine oxidase inhibitors, tetracyclic piperazino-azepines, and dopamine and norepinephrine re-uptake inhibitors) was also significantly associated with risk of pregnancy-induced hypertension (adjusted OR 3.71, 95% CI 1.25, 10.98).

Table 1

Study population characteristics*

Characteristic	Cases of pregnancy-induced hypertension n = 1 216	Controls n = 12 160	P value†
Age (years), mean (SD)	27.4 ± 5.9	27.2 ± 5.5	0.61
Gestational age at index date‡ (weeks), mean (SD)	36.3 ± 3.5	36.3 ± 3.5	1.00
Urban residence	892 (73.4)	9 386 (77.2)	0.003
Recipient of social assistance	314 (25.8)	3 686 (30.3)	0.001
Psychiatric diagnosis			
Depression	60 (4.9)	508 (4.2)	0.21
Anxiety	80 (6.6)	784 (6.5)	0.86
Comorbid conditions			
Diabetes mellitus	22 (1.8)	77 (0.6)	<0.0001
Cardiovascular disease§	3 (0.3)	12 (0.1)	0.14
Asthma	150 (12.3)	1 465 (12.1)	0.77
During year before pregnancy			
Medication use			
Antidepressant use	70 (5.8)	593 (4.9)	0.18
NSAIDs	2105 (16.9)	1 801 (14.8)	0.06
Systemic anti-infective agents	327 (26.9)	3 280 (26.9)	0.95
Other medications excluding antidepressants	898 (73.9)	8 724 (71.7)	0.12
Health care utilization			
Visited psychiatrists	34 (2.8)	360 (2.9)	0.75
Number of visits to physicians			
0–2	397 (32.7)	4 010 (32.9)	0.67
3–5	316 (25.9)	3 020 (24.8)	
≥6	503 (41.4)	5 130 (42.2)	
Number of prescribers			
0–2	869 (71.5)	8 982 (73.9)	0.07
≥3	347 (28.5)	3 178 (26.1)	
Inpatient or emergency visit	120 (9.9)	1 747 (14.4)	<0.0001
During pregnancy (first day of gestation to index date)			
Medication use			
Antidepressants	45 (3.7)	300 (2.5)	0.009
NSAIDs	38 (3.1)	347 (2.9)	0.59
Systemic anti-infective agents	327 (26.9)	3 280 (26.9)	0.95
Other medications excluding antidepressants	772 (63.5)	7 314 (60.2)	0.02
Health care utilization			
Visited psychiatrists	34 (2.8)	230 (1.9)	0.03
Visited obstetricians/gynaecologists	1 008 (82.9)	9 394 (77.3)	<0.0001
Number of prenatal visits			
0–2	84 (6.9)	923 (7.6)	0.39
≥3	1 132 (93.1)	11 237 (92.4)	

Values represent the number (percentage) unless otherwise indicated. SD standard deviation, NSAIDs non-steroidal anti-inflammatory drugs. *Data are taken from the Quebec Pregnancy Registry 1997–2003. †P value by chi-squared test or t-test. ‡Index date = date of diagnosis of pregnancy-induced hypertension for cases and matched date for controls. §Cardiovascular disease includes physician-based diagnosis of coronary atherosclerosis, generalized and unspecified atherosclerosis, primary cardiomyopathy and diffuse cardiac disease of connective tissue disorders.

In subgroup analyses involving SSRIs, we found that use of paroxetine alone was significantly associated with an 81% increased risk of pregnancy-induced hypertension (adjusted OR 1.81, 95% CI 1.02, 3.23) (Table 3). The point estimate for combined use of two or more SSRIs suggested a five-fold risk, but did not reach statistical significance.

Finally, in sensitivity analyses, we identified 414 women who used antidepressants 2 months before pregnancy. Of these, 385 discontinued antidepressant treatment before the end of the first trimester and 32 continued treatment after the first trimester. Compared with non users, discontinued use (OR 1.30, 95% CI 0.83, 2.03) and continued use (OR 1.64, 95% CI 0.57, 4.77) of antidepressants were not statistically significantly associated with the risk of pregnancy-induced hypertension.

Discussion

In this study of pregnant women within a large population-based registry, we found a 53% increased risk of pregnancy-induced hypertension associated with antidepressant use during pregnancy, independent of maternal age, depression, anxiety, comorbidities, medication use and health care utilization before and during pregnancy. Findings also suggest independent associations with use of SSRIs, particularly paroxetine, as well as other anti-

Table 2

Risk of pregnancy-induced hypertension associated with use of antidepressants during pregnancy

Variable	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Primary exposure		
Antidepressant use during pregnancy (yes *vs.* no)	1.52 (1.10, 2.09)	1.53 (1.01, 2.33)
Covariates		
Age (per year)	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)
Urban residence (*vs. rural residence*)	0.81 (0.71, 0.93)	0.83 (0.73, 0.95)
Recipient of social assistance (*vs.* RAMQ adherent†)	0.80 (0.70, 0.92)	0.81 (0.71, 0.93)
Psychiatric diagnosis		
Depression (yes *vs.* no)	1.19 (0.91, 1.57)	1.18 (0.85, 1.62)
Anxiety (yes *vs.* no)	1.02 (0.81, 1.29)	0.96 (0.75, 1.24)
Comorbid conditions		
Diabetes mellitus (yes *vs.* no)	2.90 (1.80, 4.68)	3.09 (1.90, 5.02)
Cardiovascular disease‡ (yes *vs.* no)	2.51 (0.71, 8.89)	2.62 (0.73, 9.40)
Asthma (*yes vs.* no)	1.03 (0.86, 1.23)	1.02 (0.85, 1.23)
During the year before pregnancy		
Medication use		
Antidepressants (yes *vs.* no)	1.19 (0.92, 1.54)	0.90 (0.63, 1.29)
NSAIDs (yes *vs.* no)	1.17 (1.00, 1.37)	1.16 (0.99, 1.36)
Health care utilization		
Visited psychiatrists (yes *vs.* no)	0.94 (0.66, 1.35)	0.91 (0.61, 1.33)
Inpatient or emergency visit (yes *vs.* no)	0.65 (0.54, 0.79)	0.64 (0.52, 0.78)
During pregnancy (first day of gestation to index date)		
Medication use		
Other medications excluding antidepressants (yes *vs.* no)	1.15 (1.02, 1.30)	1.14 (1.01, 1.29)

*Adjusted for variables listed in the table. †Quebec residents <65 years old who were not receiving social assistance but whose medications were covered under the RAMQ drug plan because they did not have access to a private drug insurance programme. ‡Cardiovascular disease includes physician-based diagnosis of coronary atherosclerosis, generalized and unspecified atherosclerosis, primary cardiomyopathy and diffuse cardiac disease of connective tissue disorders. CI confidence interval, RAMQ *Régie de l'Assurance Maladie du Québec*, NSAIDs non-steroidal anti-inflammatory drugs.

Table 3

Risk of pregnancy-induced hypertension associated with antidepressants during pregnancy by drug class and type

Variable	Number (%) of cases	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Class of antidepressant†			
No use	1171 (96.3)	1.00	1.00
SSRI alone	31 (2.6)	1.59 (1.08, 2.33)	1.60 (1.00, 2.55)
Tricyclic antidepressant alone	4 (0.3)	1.10 (0.39, 3.08)	1.10 (0.38, 3.22)
SNRI alone	2 (0.2)	0.72 (0.17, 3.04)	0.75 (0.17, 3.25)
Other antidepressants alone‡	5 (0.4)	3.89 (1.39, 10.94)	3.71 (1.25, 10.98)
Combined use ≥2 antidepressant classes	3 (0.3)	1.26 (0.38, 4.20)	1.32 (0.38, 4.57)
Type of SSRI†			
No use	1171 (97.4)	1.00	1.00
Paroxetine alone	18 (0.9)	1.70 (1.03, 2.81)	1.81 (1.02, 3.23)
Sertraline alone	6 (0.3)	1.78 (0.75, 4.25)	1.89 (0.76, 4.72)
Fluoxetine alone	2 (0.2)	0.84 (0.20, 3.57)	0.98 (0.22, 4.27)
Citalopram alone	2 (0.2)	0.88 (0.21, 3.73)	0.94 (0.21, 4.10)
Fluvoxamine alone	1 (0.05)	1.69 (0.20, 14.02)	1.71 (0.20, 14.60)
Combined use ≥2 SSRIs	2 (0.03)	5.01 (0.92, 27.34)	5.34 (0.94, 30.49)

*Adjusted for maternal sociodemographic characteristics (maternal age, social assistance status and place of residence), gestational age at index date, depression, anxiety, other comorbid conditions (diabetes mellitus, cardiovascular disease, asthma), medication use before pregnancy (antidepressants, NSAIDs), health care utilization before pregnancy (visits to psychiatrists, inpatient or emergency visit) and use of other medications excluding antidepressants during pregnancy. †Categories are mutually exclusive and two different logistic regression models were conducted to obtain findings for classes and types of antidepressants. ‡Other antidepressants alone category includes serotonin modulators, monoamine oxidase inhibitors, tetracyclic piperazino-azepines, and dopamine and norepinephrine re-uptake inhibitors. CI confidence interval, SSRI selective serotonin re-uptake inhibitor, SNRI serotonin-norephinephrine re-uptake inhibitors, NSAIDs non-steroidal anti-inflammatory drugs.

depressants defined as the combination of serotonin modulators, monoamine oxidase inhibitors, tetracyclic piperazino-azepines, and dopamine or norepinephrine re-uptake inhibitors.

The burden of depression among pregnant women, affecting up to 20% [1, 2], and high frequency of antidepressant use, anywhere from 4% [20] to 14% [1, 2], underscore the importance of research on the effects of perinatal

use on both the child and mother. Despite a growing number of studies on the impact of gestational antidepressant use on fetal and neonatal outcomes [3, 5, 6], data on maternal health outcomes are scarce. In a prior study of SSRI use and pregnancy-induced hypertension, compared with non users, women who continued SSRI use after the first trimester had a 2.5 fold increased risk of pregnancy-induced hypertension while women who discontinued SSRIs before the end of the first trimester did not (adjusted relative risk 1.33, 95% CI 0.78, 2.27) [9]. In our study, fewer women continued antidepressants after the first trimester, limiting our ability to detect significant associations. Nonetheless, by comparing outcomes between women who used antidepressants during pregnancy with those who did not, our study extends understanding from periconceptional use to actual gestational use. Furthermore, objective data on dispensed medications in the RAMQ Prescription Drug File and pregnancy-induced hypertension outcomes in the MED-ECHO database overcome limitations with maternal self-report data and allowed for evaluation of antidepressants overall as well as specific classes and types. As the first database to provide exact gestational age, the MED-ECHO database also eliminates potential misclassification of the exact timing (time window) of antidepressant use during pregnancy, which has historically been considered a challenge in perinatal pharmacopiepidemiologic research [21].

A recent study using data from the Swedish Medical Birth Register provides further support for our findings by reporting an association between antidepressant use and pre-eclampsia (OR 1.50, 95% CI 1.33, 1.69) [10]. Of note while our current study specifically evaluated the association between gestational antidepressant use and pregnancy-induced hypertension, the Swedish Medical Birth Register primarily evaluated the impact of antidepressant use on neonatal outcomes, and secondarily reported on maternal outcomes, including pre-eclampsia [10].

The exact mechanism of action explaining the association between gestational antidepressant use and pregnancy-induced hypertension is controversial [9]. Nevertheless, driven by its effect on vasoconstriction [7] as well as its role in amplifying the release of other mediators of vasoconstriction including angiotensin II and norepinephrine [22], serotonin may contribute to the pathophysiology of pre-eclampsia [7]. Alterations of these interactions by pharmacologic agents, in particular antidepressants, may thus contribute to pregnancy-induced hypertension. Specifically, SSRIs modulate peripheral handling of serotonin by reducing the ability of the pulmonary vasculature to clear serotonin [23] and blocking the uptake of serotonin by platelets [24], as well as inhibiting production of nitric oxide, a known vasodilator [25, 26]. SNRIs have also been shown to increase diastolic blood pressure, likely due to their noradrenergic effects [8].

Potential contributions of underlying indications for antidepressants, including depression and anxiety, should also be considered. A Finnish cohort study of 623 nulliparous, healthy women assessed with the Beck Depression Inventory showed that depression was associated with increased risk for pre-eclampsia (adjusted OR 2.5, 95% CI 1.1, 5.4), as was anxiety (adjusted OR 3.2; 95% CI 1.4, 7.4) [27]. However, multivariable models in this study did not account for antidepressant use during pregnancy. A Peruvian study of 339 pre-eclampsia cases and 337 controls reported the association between moderate depression and eclampsia (OR 2.3, 95% CI 1.2, 4.4) and severe depression and eclampsia (OR 3.2, 95% CI 1.1, 9.6) [28]. As with the prior Finnish study, this study did not examine whether the effect of depression was independent of antidepressant use. Of note, the Slone Epidemiology Center study on SSRIs and pregnancy-induced hypertension was also unable to evaluate the contribution of underlying indication, given that mood disorders were not identified among women who did not report drug treatment [9]. In our study however, we accounted for indication for antidepressant use by adjusting for maternal depression and anxiety as well as visits to psychiatrists in multivariable models.

The strengths and limitations of our study deserve comment. The RAMQ Prescription Drug File covers complete and accurate information on medications dispensed throughout pregnancy including drug name, dosage, quantity and treatment duration, eliminating potential maternal recall. We also had prospectively and routinely collected data on physician-based diagnoses for pregnancy-induced hypertension, which limited the potential for detection bias. However, observational studies using administrative data are vulnerable to diagnostic uncertainty. For example, use of administrative diagnostic codes to define pregnancy-induced hypertension may potentially lead to misclassification of diagnosis or underestimation of incidence if codes are not properly used or entered by physicians. Nonetheless, we used a previously validated case definition that is consistent with clinical guidelines for diagnosing pregnancy-induced hypertension [16]. Although we adjusted for risk factors for antidepressant use and pregnancy-induced hypertension, we could not adjust for lifestyle factors, such as smoking and obesity, that were not available in our databases. However, using the Quebec Pregnancy Registry we have previously shown that lack of data on smoking and maternal body mass index had minimal impact on the association between antidepressant use during pregnancy and adverse pregnancy outcomes [29]. While use of pharmacy records are well established in pharmacoepidemiology [30], data are limited to prescriptions dispensed and we did not have information on whether pills were actually taken. However, a study comparing pharmacy records with maternal interviews in the Netherlands showed that most filled prescriptions by pregnant women are taken [31]. Finally, even with our large sample, our analyses of specific

classes and type of antidepressants may have missed significant associations because of lack of statistical power. A further consequence is the inability to evaluate dose effects within each class. Further studies, confirming class effects, particularly non-SSRIs, as well as dose effects, are needed. Finally, we also cannot rule out the possibility that multiple testing may partially explain some of our findings.

In conclusion, using the population-based Quebec Pregnancy Registry, we have shown that women who use antidepressants during pregnancy have an increased risk of pregnancy-induced hypertension with or without preeclampsia above and beyond the risk that could be attributed to their depression or anxiety disorders. The increased risk among SSRI users and more specifically, among paroxetine users, require further confirmation. Overall these findings provide clinically relevant information on the risks of antidepressant use during pregnancy from the mother's perspective and highlight the importance of future research evaluating the impact of gestational medication use on maternal outcomes.

Competing Interests

Dr Bérard was a consultant in the litigation involving antidepressants.

Dr De Vera is a recipient of postdoctoral fellowships from the *Canadian Institutes of Health Research* (CIHR) and the *CHU Sainte-Justine et de la Fondation des Étoiles*.

Dr Bérard is the recipient of a career award from the *Fonds de la Recherche en Santé Québec* (FRSQ) and is on the endowment Research Chair of the Famille Louis-Boivin on Medications, Pregnancy and Lactation at the Faculty of Pharmacy of the University of Montreal.

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