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ORIGINAL ARTICLE

Prevalence and determinants of attention deficit/hyperactivity disorder (ADHD) medication use during pregnancy: Results from the Quebec Pregnancy/Children Cohort

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Abstract

Aims: The use of attention deficit/hyperactivity disorder (ADHD) medications has grown over the past decade among pregnant women, but these treatments are not without risk. Updated prevalence of ADHD medication use and whether prescribed dosages follow guidelines are needed. The aim of this study is to describe the prevalence of ADHD medication use among pregnant women—dosages and switches—and identify determinants of ADHD medication use.

Method: A population-based longitudinal cohort study within the Quebec Pregnancy/Children Cohort (QPC). Women aged 15–45 years old covered by the RAMQ prescription drug plan for at least 12 months before and during pregnancy from 1998 to 2015. ADHD medication exposure was assessed before and during pregnancy. We estimated odds ratios (ORs) for determinants of ADHD medication use during pregnancy with generalized estimating equations.

Results: Among 428,505 included pregnant women, 1,130 (0.26%) used ADHD medication. A 14-fold increase in the prevalence of ADHD medication use in pregnant women was observed, from 1998 (0.08%) to 2015 (1.2%). Methylphenidate was the most prevalent medication at 70.1%. ADHD medication fillings were at optimal dosage 91.8% of the time based on guidelines and 18.1% of women switched to another ADHD medication class during gestation. Main determinants of ADHD medication use during pregnancy were psychiatric disorders (aOR 2.19; 95% confidence interval [CI] 1.57, 2.96), mood and anxiety disorders (aOR 1.74; 95% CI 1.32, 2.24), and calendar year.

Conclusions: The number of pregnancies exposed to ADHD medications has increased similarly to the increase reported in other countries between 1998 and 2015. In addition to the current literature, the use of ADHD medications during pregnancy is consistent with Canadian guidelines recommendations on dosage.

Principal Investigator statement The authors confirm that the Principal Investigator and Corresponding Author for this study is Anick Bérard and she had full access to all the data in the study and had final responsibility for the decision to submit for publication.

KEYWORDS
attention deficit/hyperactivity disorders (ADHD), dosage, methylphenidate, non-stimulants, pregnancy, prenatal exposure, prevalence, Quebec Pregnancy Cohort, stimulants

What is already known?

Attention deficit/hyperactivity disorder (ADHD) medication use among pregnant women has increased significantly. There is little information on the most recent prevalence of ADHD medication use in pregnancy and its long-term trends. There are no updated data on dosages and characteristics of ADHD medications, while adverse outcomes following their use have been reported in children.

What this study adds?

Previous studies have focused on ADHD medication use in children and adults. This study adds to the literature by reporting on the ADHD medication use in pregnant women according to guideline recommendations, as well as details about determinants of use and dosage.

1 | INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) is a heritable neurodevelopmental childhood disorder that often persists into adulthood, with significant functional and psychosocial impairments and high prevalence of psychiatric comorbidities.[1,2] Guidelines recommend pharmacological treatment as the first-line treatment for adult ADHD to manage symptoms and impairments.[3-5] Treatment may include prescription combination of stimulant and non-stimulant medications.[2,6-9] Untreated ADHD impacts the individual's well-being as well as their psychosocial health, and is associated with important professional and psychosocial outcomes.[10-12] In recent years, there has been a steady increase in ADHD medication use by young adults, including women of childbearing age and during pregnancy.[13-22] This increase has been reported in several countries, including Canada, the UK, and the USA. In Canada, there was more than a fourfold increase in the prevalence of ADHD medication prescriptions in adults, from 0.32% in 2005 to 1.29% in 2015.[18] In 2015–2016, 4.5% (or 16 millions) of adults in the USA used prescription stimulants for the treatment of ADHD.[6,23] Studies indicated that 31%–57.9% of women using stimulants during pregnancy had an ADHD diagnosis,[14,15,24,25] while 30% of women with an ADHD diagnosis used ADHD medication during pregnancy.

A recent study using the U.S. Medicaid data by Huybrechts et al. indicated that major congenital malformation and heart defects may be associated with intrauterine exposure to methylphenidate and amphetamine.[25,26] After adjusting for sociodemographic and psychiatric disorders, the associations lost significance. However, an association between intrauterine methylphenidate exposure and congenital heart defect was still present. Anderson et al. also reported that early pregnancy ADHD medication use was associated with increased risk of specific birth defect.[27] The Centers for Disease Control and Prevention (CDC) reported an increased risk in three types of birth defects, namely gastroschisis, omphalocele, and transverse limb deficiency; however, the absolute risk of birth defects after early pregnancy ADHD medication use was relatively low.

Previous studies have focused on ADHD medication use in children and in adults, but their use in the context of pregnancy is not well documented.[28] The current study adds to the literature by reporting on the ADHD medication use in pregnant women, while fetal consequences of prenatal exposure is still to be determined. Specifically, we aimed to describe the prevalence and trends over time of ADHD medication use before and during pregnancy, ADHD medication mean dosages by class, and prevalence of medication switches, as well as determinants of ADHD medication use during pregnancy.

2 | METHOD

2.1 | Setting

This study was performed within the Quebec Pregnancy/Children Cohort (QPC).[29] The QPC is an ongoing population-based cohort with prospective data collection on all pregnancies of mothers covered by the Quebec Public Prescription Drug Insurance Plan, from January 1998 to December 2015, in the province of Quebec.[29]

The QPC data sources include the *Régie de l'Assurance Maladie du Québec* (RAMQ), MedEcho, *Institut de la Statistique du Québec* (ISQ), and the *Ministère de l'Éducation et de l'Enseignement Supérieur du Québec* (MEES). The medical service database includes (RAMQ: diagnoses, medical procedures, socioeconomic status (SES) of women, and prescribers), the Quebec Public Prescription Drug Insurance Database (drug names, start date, dosage, and duration), the Hospitalization Archive Database (MedEcho: in-hospital diagnoses and procedures), and the Quebec Statistics Database (ISQ: patients' socio-demographic information and birth weight). For each pregnancy, information was obtained from province-wide databases and linked using unique personal identifiers. The first day of the last

menstrual period (first day of gestation: 1DG) was defined using data on gestational age, which was validated against ultrasound measures from patients' charts.[30]

2.2 | Study population

All pregnant women identified in the QPC between January 1, 1998, and December 31, 2015, who met eligibility criteria were included in the study to describe the time trends of ADHD medication use, regardless of receiving ADHD diagnosis. The date of entry into the cohort was the first day of gestation, defined as the first day of the last menstrual period. We included all women who met the following eligibility criteria: (i) aged between 15 and 45 years old on the first day of gestation; and (ii) continuously covered by the RAMQ prescription drug plan for at least 12 months before the first day of gestation and during pregnancy.

2.3 | Exposure

We identified prescription fillings for any ADHD medication dispensed to women in the study cohort from the Quebec Public Prescription Drug Insurance database.

Women were considered ADHD medication users if they had filled at least one prescription during pregnancy or filled a prescription before pregnancy with duration overlapping the first day of gestation. The first trimester was defined as up to 14 completed weeks of gestation and the second/third trimesters from week 15 of gestation to delivery. ADHD class-specific medication considered in this study was stimulants (i.e., methylphenidate, amphetamine mixed salts, lisdexamfetamine, and dexamphetamine) and non-stimulant (i.e., atomoxetine and guanfacine) (see, Table S1 for codes of all ADHD medications studied). Filled prescriptions for medications in the QPC have been validated against maternal reports of taking the prescribed medication with high positive and negative predictive value PPV ≥87% (95% confidence interval [CI] 70%, 100%),and NPV ≥92% (95% CI 86%, 98%).[31]

2.4 | Prevalence of ADHD medication use

The annual prevalence of ADHD medication use was calculated where the numerator corresponds to the number of women with at least one prescription filled of a given type of ADHD medication in a particular year on the 1DG, and the denominator corresponds to the total number of women in that particular year on the 1DG. The same calculation was made to estimate the annual prevalence of ADHD medications stratified by trimesters. Cochran-Armitage trend test was used for trend analyses of overall ADHD medication use in pregnancy, as well as those stratified by trimesters. The annual prevalence rate of ADHD medication use was also stratified by class- and type-specific ADHD medications.

In order to define family history use, we calculated the prevalence of ADHD medication use among women who have had at least one prior live birth with or without ADHD. To determine if having a child diagnosed with ADHD or under treatment has any impact on maternal ADHD medication exposure, we restricted our analyses to women who had singleton children aged at least 4 with at least 1 diagnosis of ADHD according to the 9th and 10th edition of the International Classification of Diseases (ICD 9-10) codes (ICD-9 codes: 314.0, 314.01, 314.8, and 314.9; ICD-10 codes: F90, F90.1, F90.2, F90.8, and F90.9) (see, Table S2) or as having filled one prescription for ADHD medications. The 4-year-old cut-off was chosen as children can be diagnosed as young as age 4 according to guidelines set by the American Academy of Pediatrics.[3] As children under the age of 4 are less likely to have a diagnosis of ADHD or to receive an ADHD medication, this restriction ensured that all children included in the non-previous live birth cohort would have a minimum of 4 years of age, thereby increasing the validity of our results.

2.5 | Dosage characteristics of ADHD medications

For each dispensed ADHD medication prescription, the daily dosage was calculated by dividing the total number of pills received by the duration of the prescription multiplied by the equivalent methylphenidate dosage. The daily dosage was compared to the recommended range according to published guidelines in Canada.[10] The daily dosage for each ADHD prescription was classified in three categories: optimal dosage, sub-dosage, or over-dosage. Optimal dosage was defined by a dose between the lower and upper limit of the starting dosage recommended by the guidelines; sub-dosage is defined as a dose smaller than the lower dosage bound; and over-dosage is defined as a dose higher than the upper dosage bound. Given that lower dosages are often prescribed at the initiation of medication intake, this clinical practice may lead to a decrease in the overall daily dosage.[32] As such, we used the lower range of what is recommended as the minimum threshold of pharmacotherapy efficacy.[10] For a specified ADHD medication, the percentage of prescriptions with optimal dosage was estimated by dividing the number of all prescriptions optimally prescribed according to guidelines by the total number of prescriptions for that particular ADHD medication. The calculation for prescriptions with sub-dosage and over-dosage for each ADHD medication was calculated in the same manner.

2.6 | Patterns of ADHD medication use

We identified the percentage of women who had at least one switch from one ADHD class-specific medication to another with a maximum of 2 weeks intervals throughout the follow-up. The 2-week period between prescriptions is defined as the grace period, which represents the time between switching from one class of drug for the treatment of ADHD to another (i.e., stimulant and non-stimulant). Along with the medication switch, as some women had

add-on ADHD medication, we identified women who used multiple ADHD medications concomitantly.

2.7 | Determinants of ADHD medication use

In order to assess the potential determinants of ADHD medication use in pregnancy, the following variables were considered: maternal sociodemographic characteristics, maternal psychiatric condition/chronic physical conditions, and health services usage. Maternal sociodemographic characteristics measured on the 1DG included maternal age, area of residence (urban or rural), and health insurance types (adherent or welfare recipients). Maternal psychiatric conditions included the diagnosis of ADHD to control for the indication, mood and anxiety disorders, and other psychiatric conditions. Other psychiatric conditions were defined as schizophrenia, schizotypal and delusional disorders, disorders of adult personality and behavior, dissociative and conversion disorders, phobic disorders, obsessive-compulsive disorder, dysthymic disorder, neurasthenia, somatoform disorder, unspecified non-psychotic mental disorder, and drug dependence (benzodiazepines, antipsychotics, central nervous system stimulants, other psychotropic, anxiolytics, sedatives, and hypnotics). Maternal chronic conditions included chronic diabetes (yes/no), chronic hypertension (yes/no), asthma (yes/no), and smoking dependence (yes/no). Maternal psychiatric conditions and other chronic conditions were defined as a medical service claim or hospitalization with the corresponding diagnosis as per the ICD-9 and ICD-10 codes or one filled prescription of related medications, and were identified in the 12 months before the 1DG (see, Appendix S1).We further considered emergency department visits/hospitalizations, number of other medications, and use of folic acid in the 12 months before the 1DG and calendar year for change in practice.

2.8 | Statistical analyses

Descriptive analyses were performed for study population characteristics. Annual prevalence of maternal ADHD medication use (overall, class specific, and type specific) was calculated from 1998 to 2015. The Cochran-Armitage test was used for linear trends. Since women could contribute to more than one pregnancy during the study period, generalized estimating equations (GEE) models were used to estimate crude and adjusted odds ratios (OR) with 95% CI to identify and quantify determinants of ADHD medication use on the first day of gestation. We used GEE to account for clustering on multiple pregnancies (i.e., a woman could contribute multiple pregnancies to the database in different calendar year). Differences were considered statistically significant if the 95% CIs did not overlap 1.0 and if $p < .05$ for two-tailed analysis. Lastly, we performed a sensitivity analysis to measure the prevalence among pregnant women who filled a prescription for ADHD medication during pregnancy only. We identified prescription fillings for any ADHD medication dispensed to women "during" pregnancy only and considered as non-user those who only filled a prescription for an ADHD medication before pregnancy that overlapped the first day of gestation as some of these women might have stopped the medication when planning their pregnancy. All analyses were performed with SAS software (SAS Institute Inc.) version 9.4.

2.9 | Ethical considerations

This study was approved by the Sainte-Justine's Hospital Ethical Research Committee. The Quebec *"Commission d'Accès à l'Information"* authorized database linkages (January 1, 2020—#1740 and #2976).

3 | RESULTS

Among 428,505 included pregnant women, 1,130 (0.26%) used ADHD medication during pregnancy, of which 30.7% had a diagnosis of ADHD. The mean (SD) age of the cohort was 28.1 (6.3) years. Pregnant women using ADHD medications were more likely to be urban dwellers, and 29.5% of them were welfare recipients. They were also younger and had more comorbidities, namely diabetes, hypertension, and asthma, compared to non-users. Pregnant women using ADHD medications had also a higher prevalence of mood and anxiety disorder, and were more likely to present other psychiatric disorders. Finally, during-pregnancy ADHD medication users were also more likely to use non-ADHD medications compared to non-ADHD medication users and were more likely to use folic acid (Table 1).

3.1 | Trends in prevalence of ADHD medication use in pregnancy

There was a 14-fold increase in the rate of ADHD medication use from 0.08% in 1998 to 1.2% in 2015 ($p < .01$) (Figure 1). Similarly, there was a 29-fold increase in the rate of ADHD diagnosis from 0.02% in 2000 to 0.6% in 2015 ($p < .01$) (Figure 1). Figure 2 shows the annual prevalence of ADHD medications stratified by type. Methylphenidate was the most used ADHD medication among all type-specific medication (70.1%). The use of all stimulants (amphetamine, dexamphetamine, lisdexamfetamine, and methylphenidate) and non-stimulants (atomoxetine) ADHD medications during gestation increased over time. On the other hand, the prevalence of ADHD medication use 12 months before pregnancy compared to during pregnancy was higher. Trimester-specific ADHD medication use in women ranged from 0.26 per 100 pregnancies in the first trimester compared to 0.14 per 100 pregnancies in the second/third trimesters ($p < .01$) (Figure 3).When considering stimulant versus non-stimulant ADHD medications, 91.6% of the prescriptions in the 12 months before pregnancy

TABLE 1 Determinants of ADHD medication use on the first day of gestation

Variables	Users of ADHD medication (*n* = 1130)	Non-users of ADHD medication (*n* = 427,375)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Characteristics—on the first day of gestation				
Maternal age, *n* (%)				
<18	110 (9.7)	11,118 (2.6)	3.40 (2.62, 4.41)	2.73 (2.52, 5.27)
18–24	384 (34.0)	126,936 (29.6)	Ref.	Ref.
25–34	503 (44.5)	221,356 (51.8)	1.00 (0.85, 1.17)	0.72 (0.62, 0.84)
≥35	133 (11.8)	68,505 (16.9)	0.93 (0.75, 1.16)	0.52 (0.41, 0.66)
Welfare recipient, *n* (%)	471 (41.7)	111,675 (26.1)	1.82 (1.59, 2.10)	1.28 (1.11, 1.48)
Urban dwellers, *n* (%)	942 (83.4)	361,205 (84.5)	1.09 (0.91, 1.30)	1.02 (0.85, 1.23)
Maternal comorbidities in the year before the first day of gestation				
Attention deficit hyperactivity disorder (ADHD)[b], *n* (%)	347 (30.7)	4278 (1.1)	1.54 (1.39, 1.74)	1.49 (1.32, 1.68)
Mood and anxiety disorder[c], *n* (%)	432 (38.2)	45,662 (10.7)	2.95 (2.41, 3.57)	1.74 (1.32, 2.24)
Other psychiatric disorder[d,e], *n* (%)	221 (19.6)	11,143 (2.6)	2.45 (1.20, 3.98)	2.19 (1.57, 2.96)
Diabetes[f], *n* (%)	35 (3.1)	11,463 (2.7)	1.32 (0.95, 1.83)	0.76 (0.53, 1.09)
Hypertension[f], *n* (%)	63 (5.6)	10,677 (2.5)	2.17 (1.63, 2.88)	1.54 (1.14, 2.08)
Asthma[f], *n* (%)	244 (21.6)	46,570 (10.9)	2.00 (1.70, 2.35)	1.27 (1.07, 1.50)
Tobacco dependence, *n* (%)	16 (1.4)	834 (0.2)	4.97 (2.54, 9.74)	1.12 (0.66, 1.92)
Folic acid use in the year before the first day of gestation and in first trimester				
Folic acid, *n* (%)	21 (1.9)	6455 (1.6)	0.98 (0.57, 1.63)	0.47 (0.30, 0.74)
Health services usage in the year before the first day of gestation				
Number medications used other than use for maternal comorbidities, *n* (%)				
0	76 (6.7)	126,485 (29.6)	Ref.	Ref.
1, 2	313 (27.7)	150,432 (35.2)	2.99 (2.39, 3.74)	2.46 (1.72, 3.39)
3–5	356 (31.5)	105,868 (24.8)	4.62 (3.69, 5.78)	4.47 (3.49, 5.73)
≥6	385 (34.1)	44,590 (10.4)	10.4 (8.30, 13.2)	7.14 (5.48, 9.31)
Emergency department visit/ hospitalization, *n* (%)	616 (54.5)	147,956 (34.6)	1.96 (1.75, 2.20)	0.89 (0.78, 1.02)
Calendar year on the first day of gestation, *n* (%)				
Calendar time (year)	NA	NA	1.30 (1.28, 1.33)	1.35 (1.32, 1.37)

Abbreviations: ADHD, Attention Deficit Disorder with or without Hyperactivity; OR, odds ratio.

[a]Adjusted for all variables included in the table.

[b]Based on ICD-9 and ICD-10 diagnostic codes or prescription filled for ADHD.

[c]Based on ICD-9 and ICD-10 diagnostic codes ICD-9296.0, 300.4, 309, and 311.0.

[d]Schizophrenia, schizotypal and delusional disorders, disorders of adult personality and behavior, dissociative and conversion disorders, phobic disorders, obsessive-compulsive disorder, dysthymic disorder, neurasthenia, somatoform disorder, unspecified non-psychotic mental disorder, and drug dependence (benzodiazepines, antipsychotics, central nervous system stimulants, other psychotropic, anxiolytics, sedatives and hypnotics, and other central nervous system stimulants).

[e]Based on ICD-9 and ICD-10 diagnostic codes and prescription filled for medications.

[f]Based on ICD-9 and ICD-10 diagnostic codes and prescription filled for diabetes, hypertension, and asthma medications.

were for stimulants versus 8.4% for non-stimulants, while 91.1% versus 8.9% in the first-trimester and 88.3% versus 11.7% in the second/third trimesters, respectively (Figure 3).

In the sensitivity analysis measuring the prevalence among pregnant women who filled a prescription for an ADHD medication during pregnancy only, 1,009 (0.23%) were considered ADHD medication users. Therefore, prevalence of ADHD medication use during pregnancy was consistent with our main analysis.

In women with at least one prior live birth aged ≥4 years old, 59.2% of mothers with a child with ADHD diagnosis/treatment were using ADHD medications 12 months before or during pregnancy as compared to 40.8% of mothers whose children had no

ADHD diagnosis/treatment from 2002 to 2015 ($p < .01$) (see, Table S3).

3.2 | Dosage characteristics and switches

A total of 4,231 filled ADHD medication prescriptions were identified. As shown in Table 2, 91.8% of overall ADHD medication prescriptions were at optimal dosage (i.e., prescribed between the lower and upper limit range of dose recommendations according to treatment guidelines), compared to 4.7% and 3.5% for sub-dosage and over-dosage, respectively.

Among all filled ADHD medication prescriptions, non-stimulant atomoxetine had the highest percentage of optimal dosage prescriptions (96.8%), followed by dexamphetamine and methylphenidate at 90.8% and 91.2%, respectively (Table 2). Non-stimulant atomoxetine had the lowest over-dosage prescriptions (1.1%), while stimulant methylphenidate (Ritalin®) had the highest percentage of over-dosage prescriptions (7.2%) (Table 2).

Among ADHD medication users, 81.9% of women had used only one class of ADHD medications, whereas 18.1% of women switched from one class of ADHD medications to another or had concomitant use of another ADHD medication class. Among those women who switched, 84.3% switched from a stimulant to a non-stimulant, 14.5% from non-stimulant to a stimulant, and 1.2% had concomitant use.

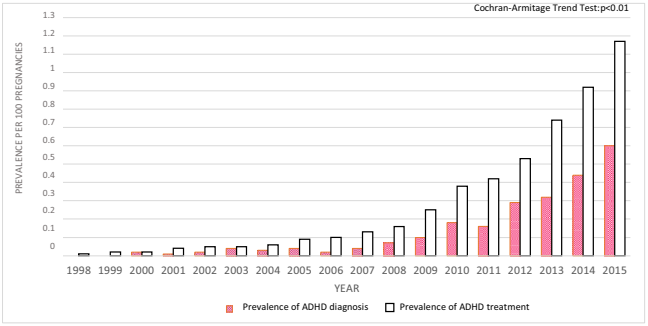

FIGURE 1 Annual prevalence of gestational attention deficit/hyperactivity disorder (ADHD) medication use and ADHD diagnoses in Quebec Pregnancy/Children Cohort from 1998 to 2015

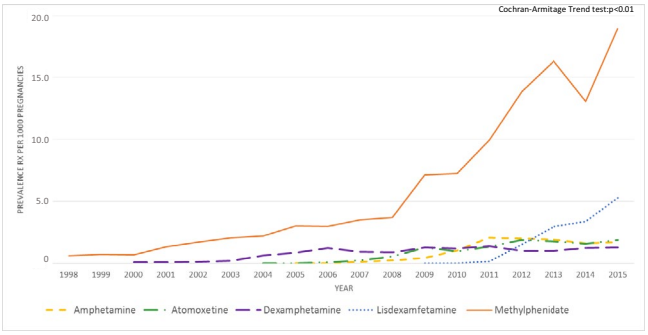

FIGURE 2 Annual prevalence of use of attention deficit/hyperactivity disorder (ADHD) medications by class in women in Quebec Pregnancy/Children Cohort from 1998 to 2015

3.3 | Determinants of ADHD medication use in pregnancy

Maternal sociodemographic determinants significantly associated with ADHD medication use during pregnancy were maternal age <18 years old (aOR 2.73; 95% CI 2.52, 5.27) and being a recipient of social assistance (aOR 1.28; 95% CI 1.11, 1.48). Determinants related to maternal comorbidities were the indication for the condition, that is, ADHD, hypertension, and mood and anxiety disorder. Pregnant women with an ADHD diagnosis were also at increased risk of using ADHD medications during pregnancy (aOR 1.49; 95% CI 1.32, 1.68). Hypertension was significantly associated with ADHD medication use in pregnancy (aOR 1.54; 95% CI 1.14, 2.08). Mood and anxiety disorders, as well as other psychiatric disorders were strong determinants of ADHD medication use during pregnancy, with aOR 1.74 (95% CI 1.32, 2.24) and aOR 2.19 (95% CI 1.57, 2.96), respectively.

The number of other medication use in the 12 months before pregnancy was also associated with ADHD medication use in

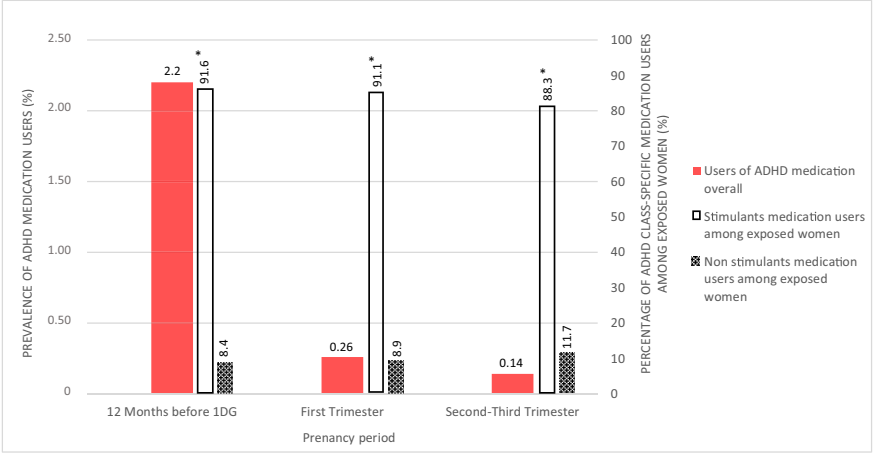

FIGURE 3 Prevalence of gestational attention deficit/hyperactivity disorder (ADHD) medication use by trimesters in Quebec Pregnancy/Children Cohort from 1998 to 2015

TABLE 2 Dosage characteristics of ADHD medications during the gestational period

ADHD medication[a]	Range per day according to published guidelines[b]	Optimal dosage[c] *n* (%)	Sub-dosage[d] *n* (%)	Over-dosage[e] *n* (%)
Overall ADHD medication		3884 (91.8)	199 (4.7)	148 (3.5)
ADHD stimulants				
Amphetamine salts	5–40 mg	211 (91.5)	3 (4.1)	5 (4.4)
Dexamphetamine	Tablet: 5–40 mg; Spansule:10–40 mg	337 (90.8)	14 (6.1)	19 (3.1)
Lisdexamfetamine	20–60 mg	169 (91.7)	11 (6.5)	3 (1.8)
Overall methylphenidate	5–90 mg	2723 (91.2)	139 (2.8)	104 (4.0)
Methylphenidate HCL (Concerta®)	10–80 mg	915 (92.1)	61 (3.9)	37 (4.1)
Methylphenidate HCL (Biphentin®)		854 (94.3)	53 (1.8)	28 (3.9)
Ritalin®	20–60 mg	740 (87.3)	16 (5.5)	21 (7.2)
Generic medication				
PMS-methylphenidate®	5–60 mg	132 (93.6)	4 (3.8)	10 (2.6)
Novo-methylphenidate®	18–72 mg; 18–90 mg	82 (96.2)	5 (1.1)	8 (2.7)
ADHD Non-stimulants				
Atomoxetine	40–100 mg	346 (96.8)	12 (2.1)	17 (1.1)

Abbreviations: ADHD, attention deficit with or without hyperactivity; HCL, chlorhydrate.

[a]Doses are from product monographs. CADDRA recommendation.

[b]Canadian attention deficit hyperactivity disorder resource alliance (CADDRA): Canadian ADHD practice guidelines [Internet]. 3rd ed. Toronto: CADDRA, 2011. Available from: http://www.caddra.ca/cms4/pdfs/caddraGuidelines2011.pdf, https://caddra.ca/pdfs/Medication_Chart_English_QUEBEC.pdf; National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion http://www.cdc.gov/growthcharts.

[c]Optimal dosage was defined by a dose between the lower and upper limit of the starting dosage recommended by the guidelines.

[d]Sub-dosage is defined as a dose smaller than the lower dosage bound.

[e]Over-dosage is defined as a dose higher than the upper dosage bound

pregnancy (aOR 2.46; 95% CI 1.72, 3.39). Pregnant women were also at increased risk of using ADHD medications during gestation with increasing calendar year (aOR 1.35; 95% CI 1.32, 1.37) (Table 1). On the other hand, folic acid intake is associated with lower use of ADHD drugs during pregnancy (aOR 0.47; 95% CI 0.30, 0.74) (Table 1).

4 | DISCUSSION

4.1 | Main findings

Our findings show an increased trend in ADHD medication use during pregnancy from 1998 to 2015. The prevalence of ADHD medication use in pregnant women was 1.2% in 2015, with stimulants being the most widely used class of ADHD medications. Moreover, ADHD diagnoses tended to increase from 1998 and 2015, which is in line with findings from a number of epidemiological studies: recent studies on ADHD medication prescribing trends in the UK and Canada have reported significant increases in ADHD medication prescriptions.[18,22,28] Similarly, the CDC found that the number of women taking ADHD medications during pregnancy more than doubled from 1998 to 2011.[27] The increase in ADHD medication use in pregnancy could be partially explained by the increase in physician's awareness and better detection of ADHD, but also the persistence of the condition in adulthood.[33] Further, as impairments due to ADHD affect the individual's well-being throughout their lifetime, there is a consequential augmentation in the pharmacological treatment duration.[34,35] Ultimately, this marked growth in the number of prescriptions are raising substantial concerns, as they translate to high prevalence of use during the gestational period.[1,36,37] Hence, it is important to better understand their safety, especially in pregnancy.

Our results highlight that ADHD medications were prescribed according to guidelines in 91.8% of the prescriptions, confirming that prescribers are mainly following recommended guidelines for ADHD.[10,38] Although 4.7% of prescription fillings were sub-dosed, this may be related to a lack of data on safety and efficacy for these medications in pregnancy. Indeed, physicians could be more conservative when it comes to prescribing ADHD medications in pregnant women as prescribing guidelines for over-dosage are inexistent. Moreover, potential side effects of these medications remain unknown. We observed that 18.1% of ADHD medications users switched to another class, of which 85.3% switched from a stimulant to a non-stimulant medication. Based on the prescribing patterns recommendations, these switches are

in concordance with the recommended course of therapy[39]: while stimulants are the recommended first-line therapy, they tend to have more side effects compared to non-stimulants. Additionally, most women treated with ADHD medication during pregnancy used only one class of ADHD medication, predominantly the stimulant class, which aligns with other studies reporting stimulants to be the most prescribed medications for ADHD due to a higher pharmacological response than that of non-stimulants.[40] Furthermore, we report that methylphenidate was the most widely used ADHD medication among our women, which was observed in several studies in non-pregnant women.[41-43] This result is also in line with the current Canadian guidelines for ADHD treatment. Specifically, stimulants, including methylphenidate, are recommended as the first-line pharmacological treatment, whereas non-stimulants such as atomoxetine should be considered as second-line treatments.

The prevalence of ADHD medication use in mothers with a child previously diagnosed with ADHD or treated with ADHD medications was significantly higher compared to mothers with a non-ADHD medication/treatment child, and increased trend in ADHD medication prescribing patterns that is consistent with the literature.[44] In families with history of ADHD, individuals with ADHD are more likely to be under pharmacological therapy, as family and medical history of ADHD are part of the diagnosis procedures.[1] More than half of the women with at least one child with ADHD was using ADHD medications.

Several determinants of ADHD medication use in pregnancy were identified, such as the condition, that is, ADHD, maternal young age (<18 years old), receipt of social assistance, urban dwellers, emergency department visits/hospitalizations, number of other medications use, and maternal comorbidities, namely hypertension, asthma, mood and anxiety disorders, and other psychiatric disorders. One thirds of pregnancies with ADHD medication fills were among women diagnosed with ADHD, which is in concordance with the literature, where studies indicated that approximately 30% of women using stimulants for ADHD during pregnancy had an ADHD diagnosis. Women with mood and anxiety disorders and psychiatric disorders were strong determinants of receiving ADHD medication during pregnancy. As reported in the literature, this result is reassuring as the most frequently reported comorbid psychiatric disorders in patients with ADHD are mood and anxiety, substance use disorders, and personality disorders.[45] Not less than 80% of adults with ADHD condition would have at least one comorbid psychiatric disorder.[46,47] This could also be explained by the fact that mothers with ADHD or psychiatric disorders had a more positive attitude towards ADHD pharmacotherapy compared to women with untreated disorders.[48] Physicians were subsequently more likely to prescribe ADHD medication to these women. Inversely, folic acid was a protective determinant of ADHD medication use. This may be because folic acid use could be an indicator of planned pregnancy, which would also be associated with a better planning of ADHD treatment during pregnancy.[49] Data showing a decrease in ADHD medication use during the second/third trimesters compared to the first trimester support this hypothesis.

4.2 | Strengths and limitations

This study was conducted in a large longitudinal population-based cohort, the QPC, which allowed us to have a substantial sample size of pregnant women exposed to ADHD medications. It is the first study to examine temporal time trends for overall, class-specific, and type-specific ADHD medication use and dosage characteristics. Data in the QPC are prospectively recorded with valid and accurate information obtained from prescriptions filled in pharmacy and based on physician diagnoses rather than based on maternal self-reports, therefore, limiting recall bias. Gestational age was defined using the first day of the last menstrual period, which was validated with patients' charts and ultrasound measures. Accurate and validated information on the exact 1DG and prescription filling duration during gestation was calculated. Thus, we could precisely estimate prevalence rates of ADHD medication use in pregnancy.

Despite these strengths, our study has some limitations. It may be argued that prescription filling data do not reflect actual use of these medications. However, a study previously performed by our research team showed a high validity between medication use in pregnancy and dispensation data within the QPC (PPVs and NPVs were high for all drug classes during pregnancy ≥80%).[31] The validation of prescriptions against maternal declarations of taking the medication prescribed in the QPC was strong. It has also been reported previously that prescription claims database in the Quebec Province may represent one of the most accurate source of medications dispensed to individuals.[31,50,51] As some of these women might have filled their prescription when planning their pregnancy, we performed a sensitivity analysis defining as non-users those who had only filled an ADHD medication prescription before pregnancy with duration overlapping the first day of pregnancy. Hence, all ADHD prescription fillings were filled during pregnancy. Prescribed folic acid intake during pregnancy is based on prescription claims corresponding to a 5 mg dose; however, folic acid is also available over-the-counter below 5 mg. In fact, folic acid users may have been misclassified; however, considering the protective effect of the folic acid, misclassification may have resulted in a more protective estimate. As the information about lifestyles in the Quebec administrative databases is lacking, we used diagnosis of tobacco dependence to take this determinant into consideration for smoking status. The QPC exclusively includes data on all pregnancies of women covered by the public drug insurance plan in Quebec (RAMQ), which may consist of women of lower SES insured for their medications. Pregnant women with private drug insurance may have different prevalence and time trends as ADHD is more prevalent among adults of low SES. However, this is not a reason for a higher representation of the low SES as Berard and Lacasse have previously shown that these women

were comparable to the general population of Quebec in terms of health status and medication use, which is reassuring.[52]

5 | CONCLUSIONS

In this large population-based cohort study among pregnant women, the estimated prevalence of ADHD medication use in pregnancy was 1.2% in 2015, representing a significant increase in prevalence from 1998. Stimulants were also shown to be the most widely used class of ADHD medications. Specifically, this increase is mainly driven by methylphenidate. Independently from the main indication, several determinants such as mood and anxiety disorder, and other psychiatric disorders were associated with ADHD medication use in pregnancy. While fetal consequences of prenatal exposure are still to be determined, an increasing number of pregnant women are taking ADHD medications. Furthermore, the consequences of untreated ADHD on mother and newborn need to be considered.

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DISCLOSURE OF INTERESTS

The authors have no conflicts of interest to declare that are directly or relevant to the content of this study.

ROLE OF THE FUNDER/SPONSOR

The funding sources had no role in the design or conduct of the study; in the collection, management, analysis, and interpretation of the data; in the preparation, review, or approval of the manuscript; and in the decision to submit the manuscript for publication.

AUTHOR CONTRIBUTION

Maxim Lemelin (ML), Takoua Boukrhis (TB), Jin-Ping Zhao (JPZ), Odile Sheehy (OS), and Anick Bérard (AB). Study concept and planning: ML, TB, JPZ, OS, and AB. Acquisition of data: AB and OS. Statistical analyses: ML. Interpretation of data: ML, TB, JPZ, OS, and AB. Drafting of manuscript: ML, JPZ, OS, and AB. Critical revision and approval of the final manuscript: ML, TB, JPZ, OS, and AB.

DATA AVAILABILITY STATEMENT

No additional data are available. The linkages between administrative databases were approved by the Ethics Committee of Ste-Justine's Hospital. The Commission d'accès à l'information (CAI) of Quebec gave the authorization for the acquisition of the data necessary for the creation of the QPC.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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