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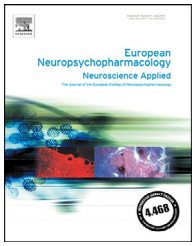

Impact of antidepressant use, discontinuation, and dosage modification on maternal depression during pregnancy

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Abstract
Women tend to discontinue their antidepressants during pregnancy. This study compared the risk of depressive symptoms in the second-half of pregnancy in women who discontinue or continue with or without dosage modification their antidepressant during gestation. Women were eligible if they called MothertoBaby during 2006–2010 and within 14 completed weeks

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Dosage modification; MothertoBaby antidepressants in pregnancy cohort

of pregnancy. A total of 367 pregnant women were included. The Edinburgh Postnatal Depression Scale (EPDS) was used to measure depression during the first and second half of pregnancy. Presence of depressive symptoms was defined as EPDS ≥13. Among participants, 149 did not use antidepressants, 38 used antidepressants at the beginning of pregnancy but discontinued before the end of second-trimester, and 180 used antidepressants continuously throughout pregnancy. Among continued users, 46 modified antidepressant dosage before the end of the second trimester, and 134 did not modify dosage. The majority of antidepressant users (150/218, 68.8%) had mild to moderate depression. Thirteen percent (13%) of women who continued antidepressant use throughout pregnancy without dosage modification remained depressed. Adjusting for potential confounders including maternal depression/anxiety before pregnancy, and compared to non-users, discontinued users were 5.95 times (95%CI: 1.54–23.02), and continued users without dosage modification 4.59 times (95%CI: 1.44–14.64) more at risk of depression in the second-half of pregnancy. Those with dosage modifications were at a similar risk of depression during pregnancy than non-users (adjusted odds ratio 0.58, 95%CI: 0.06–5.52). In conclusion, in a cohort of mild to moderate depressive pregnant women, discontinuing or continuing antidepressant use without dosage modification during pregnancy were associated with an increased risk of depression during the remaining gestational period.

1. Introduction

Antidepressants are frequently prescribed during pregnancy with a 5–15% prevalence (Cooper et al., 2007; Mitchell et al., 2011). Approximately 50% of pregnant women discontinue or reduce their antidepressants during gestation (Marcus et al., 2005; Petersen et al., 2011), even if antidepressant requirements may increase as pregnancy progresses (Hostetter et al., 2000). The discontinuation of antidepressants may cause the re-emergence of the primary psychiatric disorder (Cohen et al., 2006; Kimmel et al., 2015; Swanson et al., 2015; Yonkers et al., 2011). Indeed, in a prospective cohort of pregnant women with a history of recurrent major depression, antidepressant discontinuation during pregnancy was associated with a five-fold increased risk of relapse over the course of pregnancy compared with women who maintained their medication (Cohen et al., 2006). However, in a prospective study of pregnant women with a history of depression, no differences were found in the risk of having another episode of depression during gestation among women who discontinued their antidepressant treatment compared to women who did not (Yonkers et al., 2011). Kimmel et al. (2015) also showed that pregnant women who do not use psychiatric medications during pregnancy were 2.8 times more likely to be depressed than those who do. The differences in the severity of illness may at least partially explain the differences in risks. Indeed, women with more severe forms of the disorders are likely at greatest risk for relapse (Cohen et al., 2006; Kimmel et al., 2015). There is no data thus far on the risk of depression associated with antidepressant discontinuation in pregnant women with mild to moderate depressive disorders, which represents the majority of depressed pregnant women (Lupattelli et al., 2018). Such information is critical for clinicians and their patients. Therefore, the objective of this study was to compare the risk of depressive symptoms in the second half of pregnancy between women who 1) did not use antidepressants during pregnancy, 2) used antidepressants at the beginning of pregnancy but discontinued and did not restart during gestation, 3) maintained antidepressant treatment without dosage modification, and 4) maintained antidepressant treatment with dosage modifications, adjusting for pre-pregnancy history of maternal depression.

2. Experimental procedures

2.1. Study population

This study was conducted using data from the MothertoBaby Antidepressants in Pregnancy Cohort. Details on this cohort have been described elsewhere (Berard et al., 2017; Karam et al., 2012). Briefly, between 2006 and 2010, pregnant women (within 14 completed weeks of gestation) were recruited from participating MothertoBaby teratology information services in the United States (US) and Canada [(a) US - MotherToBaby Texas; Pregnancy Riskline Utah; MotherToBaby New York; MotherToBaby Arizona; MotherToBaby California; MotherToBaby Connecticut; and MotherToBaby Illinois; and (b) in Canada - Info-Médicaments en Allaitement et Grossesse (IMAGe), CHU Sainte-Justine, Montreal, Quebec; and Motherisk, Hospital for Sick Children, Toronto, Ontario]. Teratology information services (TIS) provide free and confidential information to women or their healthcare providers seeking evidence regarding the risks/benefits associated with taking medications or being exposed to chemicals while being pregnant, planning a pregnancy, or breastfeeding. Recruitment was also conducted through the MothertoBaby website, and in the Obstetrics and Gynaecology Clinic of CHU Sainte-Justine.

Women were eligible at the time of their call to a participating TIS or at the time of enrolment at the CHU Sainte-Justine clinic, if they were 1) at least 18 years of age; 2) within 14 completed weeks of pregnancy, where beginning of pregnancy was defined as the first day of their last menstrual period, self-reported by women; 3) exposed to an antidepressant (for the exposed group) or having any exposure considered non-teratogenic (for the non-exposed group); 4) able to read and understand French or English; and 5) provide written informed consent. Women were excluded if they were 1) exposed to fetotoxic medications other than the study drugs (Supplementary Table S1) (Kulaga et al., 2009); 2) using antidepressants in the 12 months before pregnancy (for the non-exposed group); or 3) exposed to other psychotropic drugs (e.g. lithium or buspirone, excluding benzodiazepines).

2.2. Data collection

A trained teratology information specialist conducted a telephone interview at the time of subject recruitment (within 14 completed weeks of gestation), and a telephone interviewer-administered questionnaire was used to collect information on: 1) maternal characteristics: age, gestational age, pregnancy due date, pre-pregnancy BMI, and ethnicity; 2) socio-demographic characteristics: education, household annual income, and marital status; 3) lifestyle habits during the first trimester of pregnancy including smoking, multivitamin use, and over-the-counter medication (OCT) use; 4) health status and medication use such as prescribed medication use (excluding antidepressants), comorbidities history (asthma, hypertension, diabetes, hyperthyroidism, hypothyroidism, high cholesterol); 5) pregnancy history including parity; 6) history of physician diagnosed depression and/or anxiety (major depression; situational depression; mild/moderate depression; generalized anxiety disorder; other anxiety disorders such as phobia, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder; others), and 7) antidepressant use. During the interview, those who had taken antidepressants before and during pregnancy were asked to specify which antidepressants, dosage, start and end dates (duration). In order to fully capture antidepressant use, women were given a diary that they had to fill-out in real-time in between telephone interviews; the diary was also used to document physician visits and diagnoses as well as any other medication use (prescribed or OTC). The diary data were collected during the telephone interviews, and all diaries were returned to the coordinating office at the end of the study.

Similar telephone interviews were also performed during each remaining trimester of pregnancy.

2.3. Antidepressant exposure

Mothers reported data on medication use, including type, duration, dosage and number of antidepressants during telephone interviews and in their pregnancy diary. We considered use of selective serotonin reuptake inhibitors (SSRIs); serotonin-norepinephrine reuptake inhibitors (SNRIs); tricyclic antidepressants (TCAs); and atypical antidepressants (bupropion, trazodone, mirtazapine). Five comparator groups were defined based on the antidepressant use status during the first and second half of pregnancy: 1) non-users; 2) discontinued users, where discontinuation was defined as use at the beginning of pregnancy but discontinuation for at least 4 weeks during the first or second trimester without restarting during the remaining of pregnancy; 3) continuous users without dosage modifications throughout pregnancy; 4) continuous users with dose decrease during pregnancy, and 5) continuous users with dose increase during pregnancy. The reason for antidepressant discontinuation or dosage modification was asked if appropriate. More specifically, we asked whether the change or discontinuation were initiated by themselves or their treating physician (general practitioner (GP), psychiatrist, OB/GYN).

2.4. Depressive symptom assessment

The presence of depressive symptoms was evaluated twice during pregnancy, at the first (recruitment) and second trimester of pregnancy, using the telephone interviewer-administered Edinburgh Postnatal Depression Scale (EPDS) (Murray and Carothers, 1990). The EPDS is the most widely used international screening questionnaire for the symptoms of depression during pregnancy and after delivery (Cox et al., 1987). The EPDS has been validated among different populations of pregnant women and used in clinical practice and research globally, with satisfactory reliability (Cronbach's alpha reliability (ranging from 0.80 to 0.87)) (Bergink et al., 2011; Boyce et al., 1993; Cox et al., 1987; Eberhard-Gran et al., 2001; Friesen et al., 2017; Gibson et al., 2009; Murray and Carothers, 1990; Pop et al., 1992). It includes 10 items, and women were asked to rate whether each item reflected how they have felt during the previous week. Each item has four possible answers and is scored from 0 to 3, generating a total EPDS score of 0 to 30, with higher scores indicating greater depressive symptoms. The cut-off score for screening for depression (major and minor depression) is 13 (Murray and Cox, 1990). If a woman had a score of 13 or more, she was considered to have depressive symptoms during pregnancy.

History of maternal depression before pregnancy was self-reported by pregnant women, and was considered as a potential confounder. It was measured at recruitment, and was defined as having a physician-based diagnosis of depression before the beginning of pregnancy.

2.5. Statistical analyses

Subject characteristics are presented as means and proportions for continuous and categorical variables, respectively. Potential confounders were considered for all analyses, including severity of depression [type of physician-based diagnosis of depression before pregnancy (major depression; situational depression; mild/moderate depression; general anxiety disorder; other anxiety disorders such as phobia, panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder; others; unknown)], maternal age, body mass index (BMI, kg/m^2), parity (1 vs. 0 and 2 vs. 0), marital status (living alone or cohabiting), education level ($\leq$12 or $>$12 years), race (Caucasian vs. others), and smoking status. Maternal anxiety during pregnancy was also measured during each trimester interview using the validated Beck Assessment Inventory (BAI). The BAI consists of 21 items corresponding to symptoms of anxiety, and gives a continuous overall score. Anxiety is categorized in three levels of severity: mild (score of 8–15), moderate (score of 16–25), or severe (score of 26–63) (Creamer et al., 1995). Using univariate and multivariate logistic regression models, crude and adjusted odds ratios (ORs) with 95% confidence intervals (95% CI) were calculated to assess the risk of depressive symptoms during the second half of pregnancy, adjusting for maternal depression level at the beginning of pregnancy (using EPDS baseline score at recruitment). Antidepressant non-users were the reference category.

Additional analyses were performed among antidepressant users to quantify the risk of depression associated with antidepressant discontinuation or dosage modification during pregnancy, taking antidepressant continuous users without dosage modification as the reference category. All statistical analyses were performed using SAS (Version 9.02).

2.6. Ethics statement

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the CHU Sainte-Justine, and the Sick Children's Hospital's Institutional Review Boards. Written informed consent was obtained from all participants.

3. Results

3.1. Participant characteristics

A total of 432 pregnant women were recruited for the participating MothertoBaby centers (Fig. 1). Among the 367

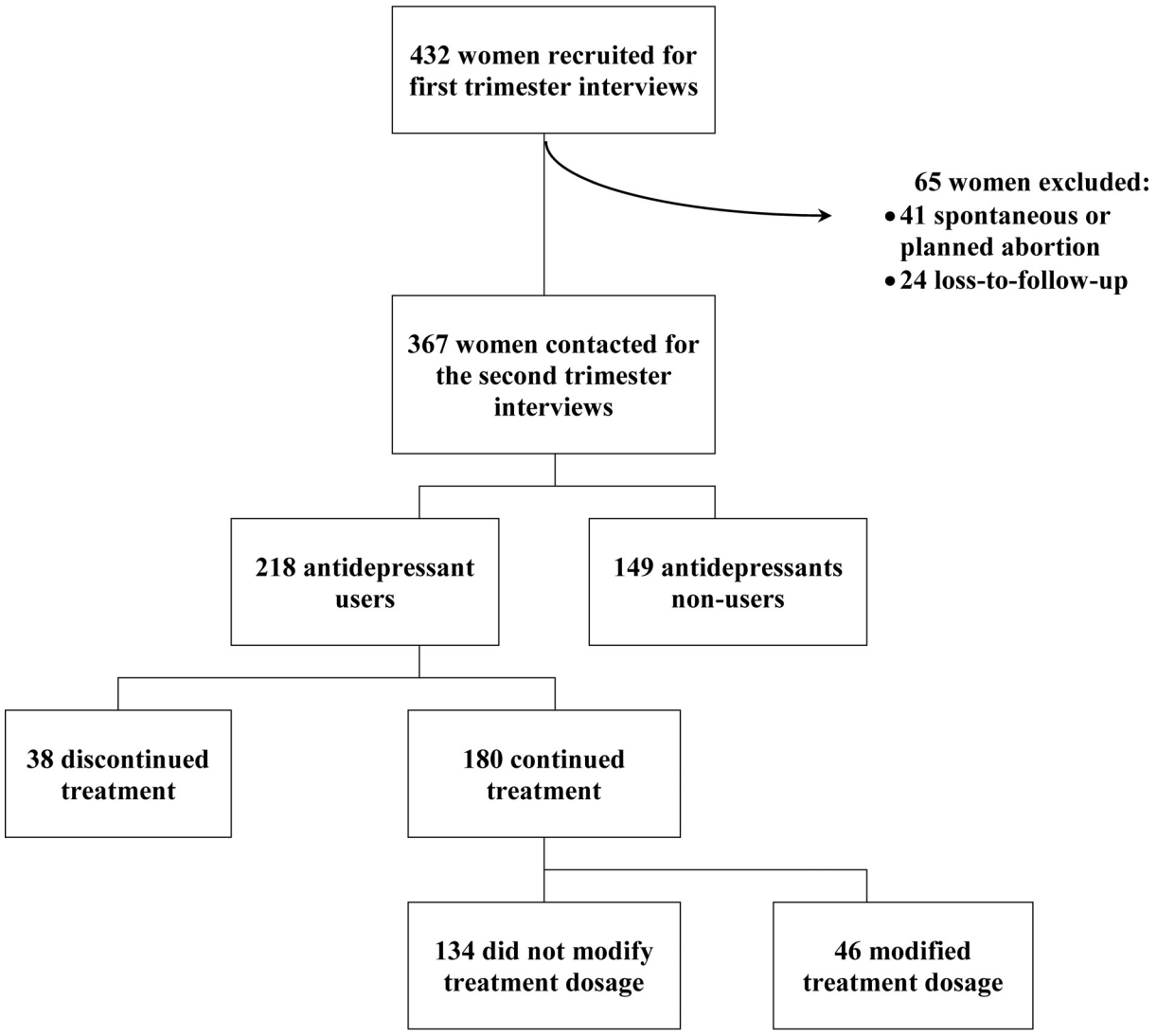

Fig. 1 Flow chart of the selection of the study cohort.

women who participated in the second trimester interview, 149 did not use antidepressants during pregnancy, 218 used antidepressants at recruitment. Among the antidepressant users, 38 used antidepressants at the beginning of pregnancy but discontinued for more than four weeks during the first or second trimester without restarting them during pregnancy (17% discontinuation rate), and 180 used antidepressants continuously throughout the entire first and second half of pregnancy. Among the continued users, 134 did not modify their antidepressant dosage, while 14 increased their dosage, and 32 decreased it before the end of the second trimester and throughout the rest of pregnancy. The reasons for discontinuation included advice from physician (50.0%, 19/38), patient's own decision (42.1%, 16/38), and other reasons (one advice from pharmacist, one advice from family/friends, and one due to severe vomiting). The decision to modify dosages was made by physician (43.5%, 20/46), by patient's own decision (28.3%, 13/46), by common agreement between physician and patient (26.1%, 12/46), or as a family decision (2.2%, 1/46). Overall, among those using antidepressants during pregnancy, 107 (49%) were being treated by general practitioners (GP) (97 GP alone, 10 by GP and psychologists); 56 (26%) were by psychiatrists (48 by psychiatrists alone, 8 by psychiatrists and psychologists); and the remaining were treated by OB/GYN. Hence, the majority of dosage modifications were following the advice of the treating GP. Characteristics of the participants are shown in Table 1. Overall, for all 5 antidepressant exposure groups, the majority of pregnant women were Caucasian, with post-secondary education, and living with their spouse. Antidepressant users called MotherToBaby centers earlier in their pregnancy than non-users (mean gestational age and standard deviation: 8.8 ± 2.9 vs. 11.4 ± 2.8, $P<0.001$). The prevalence of unplanned pregnancy was significantly higher in antidepressant users than non-users (36.0% vs. 19.0%, $P<0.001$; data non-shown).

The majority (150/218, 68.8%) of antidepressant users suffered from mild/moderate depression or anxiety disorders, and 27.5% (62/218) were diagnosed with major depression in the year before pregnancy. Additionally, 3.4%

Table 1 Characteristics of participants at recruitment, according to antidepressant use during the second half of pregnancy.

Characteristics	Non-exposed ($n=149$)	Discontinued ($n=38$)	Continued		
			Same dosage ($n=134$)	Increased dosage ($n=14$)	Decreased dosage ($n=32$)
Age, mean (SD), y	31.2 (3.8)	30.7 (5.4)	30.7 (4.7)	30.2 (4.6)	31.1 (5.1)
Gestational age at recruitment, mean (SD), weeks**	11.4 (2.8)	8.4 (2.9)	9.1 (2.9)	9.0 (2.6)	9.1 (3.4)
Gestational age at 2nd trimester interview, mean (SD), weeks	24.7 (1.2)	25.0 (1.4)	24.9 (1.5)	24.7 (1.1)	24.9 (1.5)
Pre-pregnancy BMI $\geq$30 (kg/m^2)	14 (9.4)	6 (15.8)	19 (14.2)	3 (21.4)	7 (21.9)
Ethnicity: Caucasian	131 (87.9)	36 (94.7)	125 (93.3)	14 (100.0)	31 (96.9)
Post-secondary education*	134 (89.9)	29 (76.3)	114 (85.1)	11 (78.9)	23 (71.8)
Household annual income (CAN$)					
40 000 - 80 000	46 (31.5)	15 (39.5)	47 (35.9)	8 (57.1)	11 (34.4)
>80 000*	87 (59.6)	15 (39.5)	55 (42.0)	3 (21.4)	14 (43.8)
Marital status: living alone	0 (0.0)	2 (5.3)	5 (3.7)	1 (7.1)	3 (9.4)
Parity: $\geq$ 2*	28 (18.8)	11 (29.0)	19 (14.2)	5 (35.7)	4 (12.5)
Caffeine intake during pregnancy	70 (47.0)	18 (47.7)	71 (52.9)	6 (42.9)	18 (56.3)
Smoking during pregnancy*	4 (2.7)	3 (7.9)	20 (14.9)	2 (14.3)	8 (25.0)
Alcohol intake during pregnancy	4 (2.7)	4 (10.5)	10 (7.5)	0 (0.0)	3 (9.4)
Illicit drug use during pregnancy	0 (0.0)	1 (2.6)	3 (2.2)	0 (0.0)	2 (6.3)
Multivitamin use during pregnancy	143 (96.0)	37 (97.3)	129 (96.3)	13 (92.9)	29 (90.7)
OTC medication use during pregnancy	70 (47.0)	16 (42.1)	57 (42.5)	4 (28.6)	15 (46.9)
Prescribed medication use before pregnancy (excluding antidepressants)	73 (49.0)	18 (47.4)	61 (45.5)	6 (42.9)	17 (53.1)
Medical history (past and present)					
Asthma	25 (16.7)	5 (13.2)	23 (17.6)	6 (42.9)	4 (12.5)
Diabetes	2 (1.3)	0 (0.0)	2 (1.5)	1 (7.1)	0 (0.0)
High cholesterol	8 (5.4)	1 (2.7)	8 (5.9)	1 (7.1)	2 (6.3)
Hypertension	2 (1.3)	1 (2.7)	3 (2.2)	0 (0.0)	1 (3.1)
Hyper- or hypo- thyroidism*	12 (8.1)	4 (10.5)	8 (6.0)	2 (14.3)	9 (28.1)
Depression and/or anxiety physician-based diagnosis before pregnancy	4 (2.7)	38 (100.0)	134 (100.0)	14 (100.0)	32 (100.0)
Type of depression/anxiety before pregnancy					
Major depression	0 (0.0)	8 (21.1)	38 (28.4)	5 (35.7)	11 (34.4)
Situational depression	1 (0.7)	3 (7.9)	11 (8.2)	0 (0)	3 (9.4)
Mild/moderate depression	0 (0.0)	6 (15.8)	17 (12.7)	2 (14.3)	2 (6.3)
General anxiety disorder*	2 (1.3)	6 (15.8)	45 (33.6)	6 (42.9)	7 (21.9)
Other anxiety disorders*	2 (1.3)	15 (39.5)	35 (26.1)	3 (21.4)	6 (18.8)
Others	0 (0.0)	3 (7.9)	10 (7.5)	1 (7.1)	4 (12.5)
Unknown	0 (0.0)	8 (21.1)	25 (18.7)	2 (14.3)	6 (18.8)
Number of antidepressants used before pregnancy					
1	-	35 (92.15)	113 (84.3)	12 (85.7)	29 (90.6)
2	-	3 (7.9)	21 (15.7)	2 (14.3)	3 (9.4)
Duration of antidepressant use before pregnancy, mean (SD), months*	-	26.6 (33.5)	40.2 (36.9)	44.7 (36.9)	24.2 (35.9)
Antidepressant used at recruitment		$n=35$	$n=111$	$n=11$	$n=27$
Type Citalopram	-	6 (17.1)	22 (19.8)	1 (8.3)	6 (22.2)
Escitalopram	-	6 (17.1)	6 (5.4)	1 (8.3)	1 (3.7)
Venlafaxine	-	8 (22.9)	39 (35.1)	6 (54.5)	9 (33.3)
Fluoxetine	-	4 (11.4)	9 (8.1)	0 (0.0)	2 (7.4)
Paroxetine	-	8 (22.9)	5 (4.5)	1 (8.3)	2 (7.4)
Sertraline	-	2 (5.7)	17 (15.3)	1 (16.7)	5 (18.5)
Class SSRI	-	26 (74.3)	60 (54.1)	5 (45.5)	17 (63.0)
SNRI	-	8 (22.9)	41 (36.9)	6 (54.5)	9 (33.3)

* Fisher exact test P-value < 0.05 (compared across all 4 antidepressant groups).
** P-value <0.001(compared across all 4 antidepressant groups).

Table 2 Women with depressive symptoms during pregnancy: Edinburgh postnatal depression scale score ≥13.

	Non-exposed	Discontinued	Continued			p-value
			Same dosage	Increased dosage	Decreased dosage	
At the first trimester interview	$n=147$	$n=38$	$n=134$	$n=14$	$n=32$	
Mean (SD)	3.0 (3.2)	8.2 (5.9)	6.6 (5.0)	6.1 (4.6)	7.5 (6.7)	< 0.001
Depressive symptom (score ≥13), No. (%)	1 (0.7)	10 (26.3)	18 (13.4)	1 (7.1)	6 (18.8)	< 0.001
At the second trimester interview	$n=146$	$n=38$	$n=129$	$n=14$	$n=30$	
Mean (SD)	2.9 (3.4)	7.8 (5.3)	5.8 (5.2)	4.3 (3.4)	4.8 (4.1)	< 0.001
Depressive symptom (score ≥13), No. (%)	4 (2.7)	8 (21.1)	17 (13.2)	0 (0.0)	1 (3.3)	n/a

**Fisher exact test P-value < 0.001 (compared across all 5 exposure groups).

(5/149) of pregnant women with depression and/or anxiety before gestation did not use any antidepressants during pregnancy. SSRIs were the most used antidepressant class at recruitment (first trimester) (58.7%, 108/184; the majority either continued without dosage modification (60 (/108 (55.6%)), or discontinued (26, (/108 (24.1%))), followed by SNRI (34.8%, 64/184; the majority continued without dosage modification (41 (/64 (64.1%), or decreased dosage (9 (/64 (14.1%))) (Table 1). Venlafaxine (an SNRI) was the most prevalent antidepressant at recruitment (33.7%, 62/184), followed by citalopram (an SSRI) (19.0%, 35/184) (Table 1).

3.2. Edinburgh postnatal depression scale

Among the five studied exposure groups, those who discontinued their antidepressants during pregnancy had the highest prevalence of depressive symptoms in both the first (10/38, 26.3%), and second (8/38, 21.1%) trimesters. (Table 2) Among non-users, one (0.7%) woman in the first trimester, and four (2.7%) in the second trimester had depressive symptoms (Table 2). Dosage modification had an impact on reducing depressive symptoms during pregnancy; 13.2% of women who used antidepressants without dosage modification during pregnancy remained depressed (Table 2).

Maternal anxiety was minimal and remained stable throughout pregnancy (average of 8.7 on the BAI (standard-deviation (SD) 7.1 among exposed) regardless of exposure group, and 7.9 (SD 7.7) among non-exposed, $p=0.29$). Although it is true that pregnant women on antidepressants had a history of general anxiety or other anxiety disorders before pregnancy (Table 1), it did not have an impact of their anxiety level during pregnancy.

Adjusting for potential confounders, and compared to non-users, discontinued users were 5.95 times more at risk of depression during pregnancy (95% CI: 1.54 to 23.02); users without dosage modification were 4.59 times more at risk of depression (95% CI: 1.44 to 14.64) during gestation (Table 3). Although the sample size was small, pregnant women with antidepressant dosage modifications were at a similar risk of depression during pregnancy compared to non-users, when adjusting for depressive status at the beginning of gestation (aOR 0.58, 95% CI: 0.06 to 5.52) (Table 3).

When restricting the analyses to those who were using antidepressants at the beginning of pregnancy (at recruitment), and adjusting for depressive symptoms at the beginning of gestation as well as other potential confounders, Table 4 shows that those who discontinued antidepressants during the second half of pregnancy were more likely to be depressed during the remaining of their pregnancy (aOR 1.34, 95% CI 0.49 to 3.65) when compared to those who continued using antidepressants, although no statistically significant association was found; continuous users who had modified their dosage during gestation were less likely to be depressed when compared to those who did not modify their dosage (aOR 0.12, 95% CI 0.02 to 0.94).

4. Discussion

In this prospective study of pregnant women with mild to moderate depression or anxiety disorder, the prevalence of depressive symptoms among those who modified their dosage during pregnancy was lower in the second half of pregnancy than in the first trimester (1/46=2.1% vs. 7/46=15.2%, $P<0.001$). Adjusting for potential confounders, and compared with non-users, discontinued users were 5.95 times more at risk of depression during pregnancy (95%CI: 1.54-23.02). Those who continued using antidepressants but did not modify their dosage were 4.59 times more at risk of depression (95%CI: 1.44-14.64) during the second half of pregnancy. Among users of antidepressants during pregnancy, those who modified their dosage were less likely to be depressed during the gestational period, suggesting that personalized treatment is key. Although individualized treatment has been emphasized in the new treatment guidelines from the American College of Obstetricians and Gynaecologists (Yonkers et al., 2009), this is the first study that directly provides data on the personalized treatment of maternal depression or anxiety during gestation. Another important finding from this study highlights the fact that over 13% of those without dosage modification remained depressed during pregnancy, indicating that the treatment was

Table 3 Risk of depressive symptoms in the second half of pregnancy between users and non-users of antidepressants.

	Depressive symptoms (Edinburgh Postnatal Depression Scale score ≥13)	
	Crude OR (95% CI)	Adjusted OR (95% CI)
Non-exposed ($n = 144$)	Reference	Reference
Discontinued ($n = 38$)	6.56 (1.75 to 24.56)	5.95 (1.54 to 23.02)
Continued with same dosage ($n = 129$)	4.33 (1.38 to 13.56)	4.59 (1.44 to 14.64)
Continued with dosage modification ($n = 44$)	0.62 (0.07 to 5.90)	0.58 (0.06 to 5.52)
Depressive symptoms at first trimester	4.73 (1.97 to 11.34)	2.91 (1.11 to 7.60)
Age	1.00 (0.92 to 1.09)	1.00 (0.92 to 1.09)
Pre-pregnancy BMI ≥30 (kg/m^2)	1.65 (0.64 to 4.27)	1.42 (0.51 to 3.96)
Parity 1 vs. 0	0.84 (0.34 to 2.10)	1.27 (0.48 to 3.38)
Parity 2 vs. 0	1.90 (0.77 to 4.67)	2.04 (0.74 to 5.60)
Living alone	1.22 (0.15 to 9.96)	0.87 (0.10 to 7.72)
Post-secondary education	0.54 (0.22 to 1.33)	0.67 (0.24 to 1.89)

Note: This analysis was done on 355 women (5 women from the non-user group, 5 women from the continuous user group without dosage modification, and 2 women from the continuous user with dosage modification group were excluded due to missing data on covariates).

Table 4 Risk of depressive symptoms in the second half of pregnancy only among antidepressant users at the beginning of pregnancy, using continuous users without dosage modification as the reference category.

	Depressive symptoms (Edinburgh Postnatal Depression Scale score ≥13)	
	Crude OR (95% CI)	Adjusted OR (95% CI)
Continuous users without dosage modification ($n = 129$)	Reference	Reference
Discontinuous users ($n = 38$)	1.51 (0.58 to 3.95)	1.34 (0.49 to 3.65)
Continuous users with dosage modification ($n = 44$)	0.14 (0.02 to 1.13)	0.12 (0.02 to 0.94)
Depressive symptoms at first trimester	3.24 (1.31 to 8.03)	3.05 (1.16 to 8.03)
Age	0.99 (0.91 to 1.08)	0.98 (0.90 to 1.08)
Living alone	0.78 (0.10 to 6.44)	0.86 (0.10 to 7.83)
Obesity	1.61 (0.60 to 4.36)	1.83 (0.63 to 5.36)
Parity 1 vs. 0	1.24 (0.47 to 3.26)	1.80 (0.63 to 5.15)
Parity 2 vs. 0	1.99 (0.71 to 5.56)	2.01 (0.64 to 6.29)
Post-secondary education level	0.72 (0.27 to 1.94)	0.76 (0.25 to 2.36)

Note: This analysis was done on 211 women (5 women from the non-user group, 5 women from the continuous user group without dosage modification, and 2 women from the continuous user with dosage modification group were excluded due to missing data on covariates).

not optimal in this subgroup, again highlighting the importance of personalized treatment of maternal mental health during gestation (Devane et al., 2006).

Physicians were the driving force behind the majority of discontinuations and dosage modifications (discontinuation of antidepressants was the result of physician advice in 50.0% of cases, and dosage modifications were the result of physician advice in 69.6% of cases). Hence, women should discuss with their physician the risks and benefits of medication use, including antidepressants, during pregnancy.

Few studies (Cohen et al., 2006, 2004; Kimmel et al., 2015; Marcus et al., 2005; Roca et al., 2013; Swanson et al., 2015; Yonkers et al., 2011) have assessed the risk of depressive relapse in pregnancy associated with discontinuation of antidepressants. Cohen et al. (2006) demonstrated that women discontinuing antidepressants in pregnancy had a fivefold increased risk of major depression relapse during pregnancy compared to continuers. Another study from the John Hopkins School of Medicine, performed in a similar setting, also showed a protective effect of psychotropic medication use on maternal depression during pregnancy (Kimmel et al., 2015). However, Yonkers et al. (2011) failed to replicate this association when performing a field community study in a low to moderate risk population; this was further replicated by Swanson et al. (2015) when analysing data from the Medicaid Analytic eXtract databases. Our study differentiated women who continued with and without dosage modification, which could explain part of the discrepancies between Cohen et al. (2006) and Yonkers et al. (2011). Furthermore, the conflicting results are likely attributable in part to divergent populations under investigation (Guille and Epperson, 2013). Individuals in Cohen et al. (2006) and Kimmel et al. (2015) studies were recruited from psychiatric treatment centers and had more severe forms of depression, including earlier age at onset and comorbid psychiatric illnesses. Yonkers et al. (2011) as well as our study population were recruited from community- and hospital-based obstetrical clinics. Indeed, the majority of antidepressant users in our study (150/218, 68.8%) had been previously diagnosed with mild/moderate depression or anxiety disorder, and only 27.5% (62/218) were diagnosed with major depression.

Guidelines for treatment of depression in pregnancy have been published (Yonkers et al., 2009). Based on the evidence from the prospective studies (Cohen et al., 2006; Yonkers et al., 2011), the guidelines suggest that women who have a history of recurrent depression, even if currently asymptomatic or minimally symptomatic, are at high risk of relapse if medications are discontinued; they are thus not the candidates for antidepressant discontinuation before or during pregnancy. The guidelines also suggest that patients with mild or no symptoms for 6 months or longer may be good candidates for medication taper and discontinuation prior to conception before or during pregnancy (Yonkers et al., 2009). However, there were no data thus far on the risk of depression associated with antidepressant discontinuation in pregnant women with mild to moderate depression or anxiety disorders. In our study, the decision to discontinue or modify antidepressant dosage was made following the advice of health care professionals including psychiatrists or family physicians, in the vast majority of instances, which is consistent with Einarson et al. (2001). This highlights the importance of individualized treatment of depression during pregnancy.

The prospective design, and centralized follow-up including pregnant women in nine participating teratology information services in the US and Canada is the major strength of this study. Information from patients was collected in real-time using standardized questionnaires and instruments at various stages during pregnancy, which minimized potential recall bias. Although the study participants were recruited from nine participating teratology information services in the US and Canada, the potential effect of center of recruitment has been minimized by centralized follow-ups as all of the interviews were handled by the same research coordinator. In addition, data included various determinants of antidepressant discontinuation during pregnancies, which were used for adjustments in the analyses (Grzeskowiak et al., 2011). Well-established and validated instruments such as the EPDS were used to measure depressive symptoms (Eberhard-Gran et al., 2001; Field, 2010; Murray and Carothers, 1990). Finally, we choose the recommended score of 13 as the cut-off score for depression (major and minor depression) during pregnancy (Matthey et al., 2006), which has been validated in both the US (Beck and Gable, 2001) and Canadian (Clarke, 2008) populations.

4.1. Limitation

The main limitation of the study is that the population consisted only of those who called participating information centres or healthcare professionals with queries. Women contacting teratogen counselling services such as MotherToBaby may have higher education levels and come from higher socioeconomic families. Although this might somewhat impact generalizability of findings, it does not have an effect on internal validity given that a group of non-exposed pregnant women were recruited from the same sites.

Our study relied on maternal self-reports of antidepressant exposures and dosage changes. Although comprehensive data collection have been applied, including a diary that women had to fill-out in real time between calls, and the study population consisted only of those who called participating TISs or healthcare professionals with gestational exposures to medications, we cannot completely rule out exposure misclassification. Given that we used a standardized and validated scale to assess depression, outcome misclassification is unlikely.

To address confounding by indication, we have adjusted for various determinants of antidepressant use or discontinuation during pregnancies in the analyses, including maternal history of depression or anxiety, prior antidepressant use as well as prior overall medication use. Additional analyses were performed only considering antidepressant users, and taking antidepressant continuous users without dosage modification as the reference category, hence adjusting for depression by design. Nevertheless, it remains that unobserved or unquantifiable differences may still be present, and thus we cannot completely rule-out confounding by indication. Although our sample size is limited, we were able to obtain validated measures on exposure and outcome as well as on many important covariates; our sample size is comparable to similar studies (Cohen et al., 2006; Kimmel et al., 2015; Yonkers et al., 2011). Finally, although we do not know the reasons why physicians or women decided to discontinue or modify antidepressant dosages, literature shows that both discontinuation and dosage modifications are mostly the result of fear of teratogenicity (Widnes and Schjott, 2017).

5. Conclusion

For pregnant women with mild to moderate depression, antidepressant dosage modification during pregnancy significantly decreased the risk of relapse of depression during gestation, demonstrating the importance of personalized treatment of depression during pregnancy. It remains however that pregnant women should discuss the risks and benefits of antidepressant use during pregnancy with their physician.

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Conflict of interest

All authors have completed the ICMJE Conflicts of Interest form at http://www.icmje.org/coi_disclosure.pdf and declare: AB is a consultant for plaintiffs in litigations involving

antidepressants and birth defects. All other authors declare that they have no conflicts of interest.

CRediT authorship contribution statement

Anick Bérard: Writing - review & editing, Supervision, Resources, Methodology, Investigation, Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Software, Validation, Writing - original draft. **Odile Sheehy:** Writing - review & editing, Resources, Methodology, Investigation, Conceptualization, Formal analysis, Software, Validation. **Jin-Ping Zhao:** Writing - review & editing, Resources, Methodology, Investigation, Writing - original draft. **Christina Chambers:** Writing - review & editing, Resources, Methodology, Investigation. **Mark Roth:** Writing - review & editing, Resources, Methodology, Investigation. **Pina Bozzo:** Writing - review & editing, Resources, Methodology, Investigation. **Diana Johnson:** Writing - review & editing, Resources, Methodology, Investigation. **Kelly Kao:** Writing - review & editing, Resources, Methodology, Investigation. **Sharon Lavigne:** Writing - review & editing, Resources, Methodology, Investigation. **Lori Wolfe:** Writing - review & editing, Resources, Methodology, Investigation. **Dee Quinn:** Writing - review & editing, Resources, Methodology, Investigation. **Kristen Dieter:** Writing - review & editing, Resources, Methodology, Investigation.

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Supplementary materials

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