Association Between Incident Exposure to Benzodiazepines in Early Pregnancy and Risk of Spontaneous Abortion

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Journal Review

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Contents

I. INTRODUCTION

Background

- Benzodiazepines(BZD) are psychoactive medications that are frequently prescribed during pregnancy for the treatment of anxiety, insomnia, and mood disorders.

- BZD are anxiolytic medications that act as **agonists at the GABA** receptors, with inhibitory postsynaptic signaling.
- BZD also bind to peripheral tissues through peripheral benzodiazepine receptors and may play a role in **steroidogenesis** and **cell proliferation**.

Background

- BZD cross the placental barrier and accumulate in the fetal circulation at levels that are **1 to 3 times higher** than the maternal serum levels and may accumulate substantially in the embryo and fetal tissues, **causing adverse effects**.
- BZD were classified as **FDA category D** based on findings suggesting an increased risk of cleft lip or palate, urogenital, and neurologic congenital malformations.

Importance

- Benzodiazepine use in early pregnancy is associated with spontaneous abortion(SA)[1),2)].
  - A population-based study from the UK found **that women exposed to BZD during pregnancy** had a **60%higher risk of SA** compared with women with **unmedicated depression or anxiety** during the first trimester.
  - Higher rates of SA among benzodiazepine users have also been reported in a prospective study from Israel

1) Ban L, Tata LJ,West J, Fiaschi L, Gibson JE. Live and non-live pregnancy outcomes among women with depression and anxiety: a population-based study. *PLoS One*. 2012;7(8)
2) Ornoy A, Arnon J, Shechtman S, Moerman L, Lukashova I. Is benzodiazepine use during pregnancy really teratogenic? *Reprod Toxicol*. 1998;12(5):

Importance

- Previous studies concerning BZD exposures in early pregnancy and the risk of major congenital malformation have shown **considerable differences in the safety profiles** among different benzodiazepines.

- However, to date, the association between **specific benzodiazepine agent exposure** and **the risk of SA** has not been examined.

Objective

- To quantify the risk of SA associated with gestational benzodiazepine incident use by **drug class**, **duration of action**, and **specific benzodiazepine agent**.

Drug Class

Duration of Action

Specific BZD Agent

Which type of benzodiazepine places women in early pregnancy at increased risk of spontaneous abortion?

II. METHODS

Setting and Data Sources

- A nested case-control study within the Quebec Pregnancy Cohort (QPC)
- **Quebec Pregnancy Cohort**
  - an ongoing population-based cohort with prospective data collection on **all pregnancies of women** covered by the Quebec Public Prescription Drug Insurance Plan from January 1, 1998, to December 31, 2015
  - Individual-level information was obtained from province wide databases and linked using the unique health care personal identifiers.
- Data sources
  - The medical service database RAMQ : diagnoses, medical procedures, socioeconomic status of women, and prescribers
  - The Quebec Public Prescription Drug Insurance Plan database : drug name, start date, dose, and duration
  - The Med Echo database : in-hospital diagnoses and procedures, including gestational age for planned abortions, SAs, and deliveries
  - The Quebec Statistics database : patient sociodemographics and birth weight.

Study Population

- Pregnancies of women aged **15 to 45 years** who were continuously insured by the **Quebec Public Prescription Drug Insurance Plan** for at least 12 months before their LMP[1)] and during their pregnancy

- **Exclusion Criteria**
  - ▶Pregnancies among women exposed to known teratogens during the first trimester
  - ▶Epilepsy without pharmacologic treatment
  - ▶A history of epilepsy
  - ▶Previous use of benzodiazepines
  - ▶planned or induced abortions.

1) The first day of the last menstrual period (LMP) was defined using data on gestational age, which was validated against ultrasound measures in patients' medical records.

Cases of SA and Controls

- Spontaneous abortion(SA)
  - Any pregnancy loss between the beginning of the 6th week~ 19th completed week of pregnancy
- The index date : the calendar date of the SA diagnosis.

- **5 controls** for each case at the index date and matched them with the case pregnancy by gestational age and calendar year.

1) using *ICD-9* diagnosis code 634 or *ICD-10* diagnosis code O03 in the RAMQ or Med Echo databases

Incident Benzodiazepine Exposure

- Incident benzodiazepine exposure
  - if the mother had filled at least 1 prescription for any type of benzodiazepine from the LMP until the index date.

- Mean daily equivalent dose of diazepam
  - ≦5mg, 6-20mg, >20mg

- Categorization of benzodiazepine
  - Short acting (half-life ≦ 24 hours) : alprazolam, bromazepam, lorazepam, oxazepam, temazepam, and triazolam
  - Long acting (half-life >24 hours) : chlordiazepoxide, clonazepam, diazepam, flurazepam hydrochloride, and nitrazepam

Potential Confounders

- **Maternal sociodemographic** variables measured by LMP
- **Maternal chronic conditions** measured by diagnostic codes or prescribed medications in the year before the LMP and during pregnancy
- **Health care resources utilization** in the year before the LMP and during pregnancy in the year before the LMP and during pregnancy
- **Pregnancy-associated variables**

- We adjusted for the presence of **physician-based diagnoses** for these conditions(**mood and anxiety disorders or insomnia**)[1)] in the year before pregnancy until the index date.
- We also adjusted for **concomitant exposure to antidepressant and antipsychotic medications** between the LMP and the index date.

1) ICD-9 diagnosis codes 296, 309, 311, 300.0, and 300.4 and ICD-10diagnosis codes F30-F43 for mood and anxiety disorder and ICD-9 diagnosis codes 307.4, 327.0, 327.3, and780.5 and ICD-10 diagnosis codes G47 and F51 for insomnia

Statistical Analysis

- **Descriptive statistics**
- **Conditional logistic regression models** : The association between benzodiazepine use in early pregnancy and the risk of SA
- Four independent models -> adjusted for the potential confounders
  - (1) overall benzodiazepine exposure between the LMP and index date
  - (2) benzodiazepine exposure by duration of action (short and long acting)
  - (3) specific benzodiazepine agents
  - (4) mean daily diazepam-equivalent

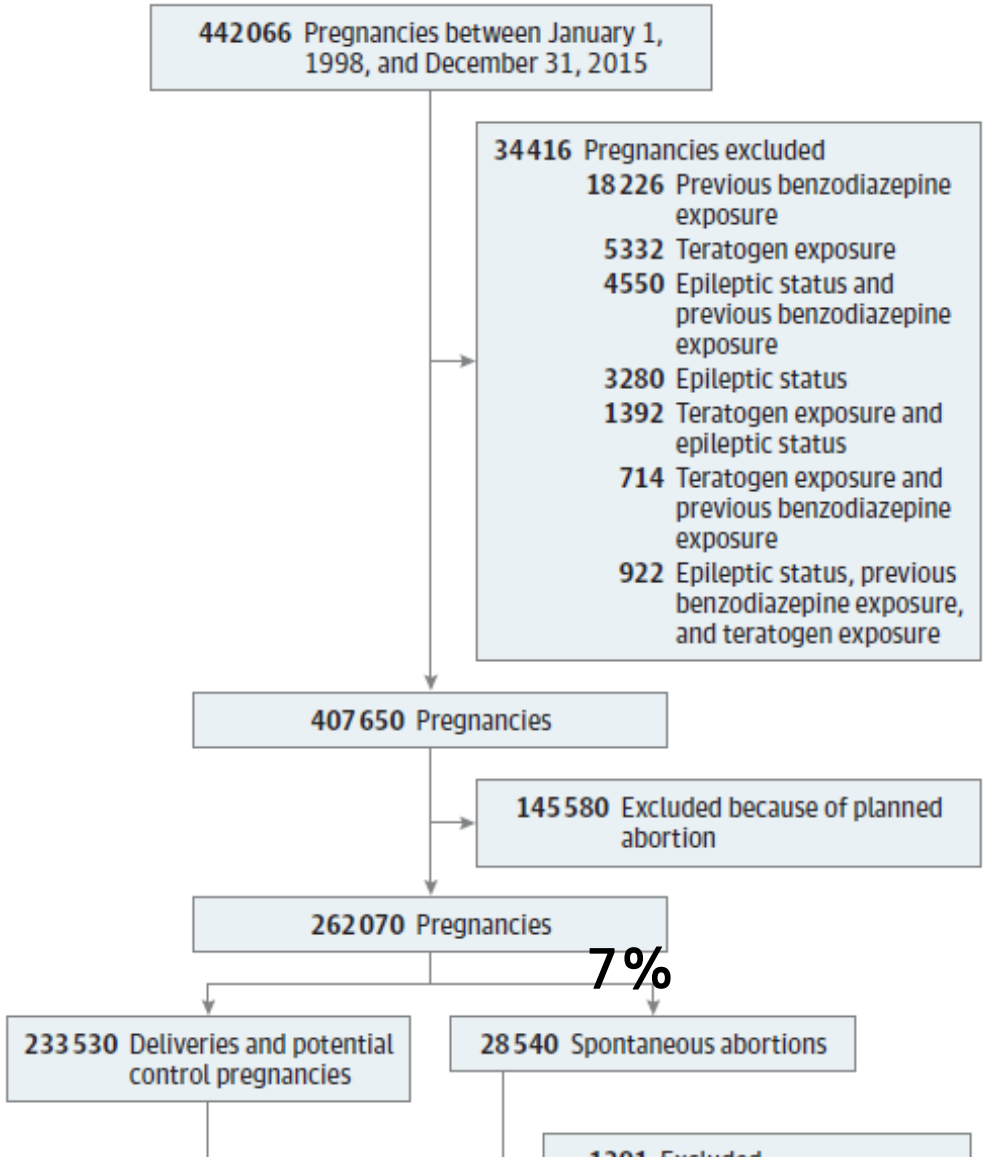
- **Cochran-Armitage trend test** : the dose response trend
- **Sensitivity Analysis** : the robustness of estimates using the overall incident benzodiazepine exposure in early pregnancy model
- **E-value** : the robustness of the association between incident benzodiazepine exposure and SA for unmeasured or unadjusted confounding

- SAS software, release 9.1 (SAS Institute Inc)

III. RESULTS

Flowchart of Case and Control Selection

Figure 1. Flowchart of Case and Control Selection



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Characteristics of Pregnancies

Table 1. Characteristics of Pregnancies[a]

Characteristic	All Pregnancies (n = 161 454)	Spontaneous Abortion (n = 27 149)	Controls (n = 134 305)	*P* Value
Benzodiazepine exposure from LMP until index date[b]				
Overall	1163 (0.7)	375 (1.4)	788 (0.6)	<.001
Short acting[c]	908 (0.6)	284 (1.1)	624 (0.5)	<.001
Long acting[d]	276 (0.2)	98 (0.4)	178 (0.1)	<.001
Alprazolam	100 (0.1)	33 (0.1)	67 (0.1)	<.001
Bromazepam	39 (0)	13 (0.1)	26 (0)	.006
Chlordiazepoxide	7 (0)	0	7 (0)	NA
Clonazepam	220 (0.1)	82 (0.3)	138 (0.1)	<.001
Diazepam	27 (0)	12 (0)	15 (0)	.001
Flurazepam hydrochloride	22 (0)	5 (0)	17 (0)	.46
Lorazepam	588 (0.4)	180 (0.7)	408 (0.3)	<.001
Nitrazepam	1 (0)	0 (0)	1 (0)	NA
Oxazepam	160 (0.1)	48 (0.2)	112 (0.1)	<.001
Temazepam	29 (0)	14 (0.1)	15 (0)	<.001
Triazolam	5 (0)	1 (0)	4 (0)	NA
Antidepressants				
SSRI alone[e]	2525 (1.6)	628 (2.3)	1897 (1.4)	<.001
SNRI alone[f]	1163 (0.7)	289 (1.1)	874 (0.6)	
Tricyclic alone[g]	442 (0.3)	129 (0.5)	313 (0.2)	
Other alone[h]	402 (0.2)	136 (0.5)	266 (0.2)	
Combined antidepressants	496 (0.3)	146 (0.5)	350 (0.3)	
Antipsychotics				
Typical alone[i]	213 (0.1)	22 (0.1)	191 (0.1)	<.001
Atypical alone[j]	835 (0.5)	251 (0.9)	584 (0.4)	
Combined antipsychotics	26 (0)	4 (0)	22 (0)	

Characteristics of Pregnancies

Table 1. Characteristics of Pregnancies[a]

Characteristic	All Pregnancies (n = 161 454)	Spontaneous Abortion (n = 27 149)	Controls (n = 134 305)	*P* Value
Maternal age at LMP				
Mean (SD), y	28.58 (5.8)	29.24 (6.5)	28.44 (5.6)	<.001
<35 y	134 150 (83.1)	20 858 (76.8)	113 292 (84.4)	<.001
35-39 y	21 438 (13.3)	4337 (16.0)	17 101 (12.7)	
≥40 y	5866 (3.6)	1954 (7.2)	3912 (2.9)	
Welfare recipient	35 704 (22.1)	6592 (24.3)	29 112 (21.7)	<.001
Urban dweller	133 404 (82.6)	22 426 (82.6)	110 978 (82.6)	.91
Health care utilization within 12 mo before LMP until index date				
Emergency visit and/or hospitalization	86 151 (53.4)	15 279 (56.3)	70 872 (52.8)	<.001
Psychiatrist visit	1575 (1.0)	365 (1.3)	1210 (0.9)	<.001
General practitioner visits, No.				
0	86 198 (53.4)	14 192 (52.3)	72 006 (53.6)	<.001
1-2	26 166 (16.2)	3885 (14.3)	22 281 (16.6)	
≥3	49 090 (30.4)	9072 (33.9)	40 018 (29.3)	
Other specialist visits, No.				
0	104 011 (64.4)	17 239 (63.5)	86 772 (64.6)	<.001
1	14 541 (9.0)	2273 (8.4)	12 268 (9.1)	
≥2	42 902 (26.6)	7637 (28.1)	35 265 (26.3)	
≥1 Diagnosis within 12 mo before LMP until index date				
Mood and anxiety disorders	13 156 (8.2)	2681 (9.9)	10 475 (7.8)	<.001
Insomnia	69 (0.04)	15 (0.1)	54 (0)	.27
Folic acid exposure within 6 mo before LMP until index date	5932 (3.7)	751 (2.8)	5181 (3.9)	<.001

(continued)

Characteristics of Pregnancies

Table 1. Characteristics of Pregnancies[a] (continued)

Characteristic	All Pregnancies (n = 161 454)	Spontaneous Abortion (n = 27 149)	Controls (n = 134 305)	*P* Value
Comorbidities within 12 mo before LMP until index date				
Hypertension	6943 (4.3)	1336 (4.9)	5607 (4.2)	.001
Diabetes	5979 (3.7)	1022 (3.8)	4957 (3.7)	.56
Asthma	25 799 (16.0)	5001 (18.5)	20 788 (15.5)	<.001
Thyroid disorders	9048 (5.6)	1467 (5.4)	7581 (5.6)	.12
Tobacco dependence	3077 (1.9)	696 (2.6)	2381 (1.8)	<.001
Alcohol dependence	985 (0.6)	258 (1.0)	727 (0.5)	<.001
Other drug dependence	1600 (1.0)	373 (1.4)	1227 (0.9)	<.001
Pregnancy follow-up by gynecologist or obstetrician	66 980 (41.5)	8037 (29.6)	58 943 (43.9)	<.001
Pregnancy within 12 mo before LMP	7939 (4.9)	1693 (6.2)	6246 (4.6)	<.001

Abbreviations: LMP, first day of the last menstrual period; NA, not applicable; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Index date defined as the calendar date of the diagnosis of spontaneous abortion.

[c] Short-acting benzodiazepines defined as half-life less than or equal to 24 hours and included alprazolam, bromazepam, lorazepam, oxazepam, temazepam, and triazolam.

[d] Long-acting benzodiazepines defined as half-life greater than 24 hours and included chlordiazepoxide, clonazepam, diazepam, flurazepam hydrochloride, and nitrazepam.

[e] SSRI antidepressants included citalopram hydrobromide, escitalopram oxalate, fluoxetine hydrochloride, fluvoxamine maleate, paroxetine hydrochloride, and sertraline hydrochloride.

[f] SNRI antidepressants included desvenlafaxine, duloxetine hydrochloride, and venlafaxine hydrochoride.

[g] Tricyclic antidepressants included amitriptyline, clomipramine hydrochloride, desipramine hydrochloride, doxepin, imipramine pamoate, nortriptyline hydrochloride, and trimipramine.

[h] Other antidepressants included bupropion hydrochloride, buspirone, L-tryptophan, maprotiline hydrochloride, mirtazapine, trazodone hydrochloride, moclobemide, and nefazodone.

[i] Typical antipsychotic agents included chlorpromazine, fluphenazine, flupentixol, haloperidol, loxapine succinate, methotrimeprazine hydrochloride, pericyazine, perphenazine, pimozide, prochlorperazine maleate, trifluoperazine, zuclopenthixol acetate, zuclopenthixol decanoate, and zuclopenthixol dichlorhydrate.

[j] Atypical antipsychotic agents included aripiprazole, clozapine, olanzapine, risperidone, quetiapine fumarate, and ziprasidone.

Benzodiazepines Uses in Pregnancy

- Among the 1163 pregnancies exposed to BZD in early pregnancy, 1128 (**97.0%**) women received **only 1 specific BZD agent** and 897 (**77.1%**) had **only 1 prescription filled**.

- The most frequently prescribed BZD were **lorazepam**(768 of 1715; 44.8%) and **clonazepam**(402 of 1715; 23.4%).

- The mean duration of benzodiazepine use was **16.5 days** (median, 15.0 days), and the mean number of pills provided was **24.3** (median, 20.0 pills).

Overall Incident Benzodiazepine Use During Early Pregnancy and the Risk of Spontaneous Abortion

Table 2. Overall Incident Benzodiazepine Use During Early Pregnancy and the Risk of Spontaneous Abortion

Characteristic	No. (%)		Odds Ratio (95% CI)		P Value
	Spontaneous Abortion (n = 27 149)	Controls (n = 134 305)	Crude	Adjusted	
Study medication exposure from LMP until index date					
All benzodiazepines	375 (1.4)	788 (0.6)	2.39 (2.10-2.73)	1.85 (1.61-2.12)	<.001
Antidepressants					
SSRI alone[a]	628 (2.3)	1897 (1.4)	1.64 (1.49-1.81)	1.28 (1.16-1.43)	<.001
SNRI alone[b]	289 (1.1)	874 (0.6)	1.70 (1.47-1.97)	1.29 (1.11-1.51)	.001
Tricyclic alone[c]	129 (0.5)	313 (0.2)	2.06 (1.67-2.57)	1.83 (1.45-2.29)	<.001
Other alone[d]	136 (0.5)	266 (0.2)	2.48 (1.98-3.10)	1.94 (1.54-2.45)	<.001
Combined antidepressants	146 (0.5)	350 (0.3)	2.02 (1.64-2.49)	1.35 (1.08-1.68)	.008
Antipsychotics					
Typical alone[e]	22 (0.1)	191 (0.1)	0.54 (0.34-0.85)	0.47 (0.30-0.75)	.002
Atypical alone[f]	251 (0.9)	584 (0.4)	2.03 (1.73-2.38)	1.26 (1.06-1.50)	.008
Combined antipsychotics	4 (0)	22 (0)	0.96 (0.28-3.28)	0.64 (0.18-2.23)	.48
Demographic characteristic at LMP					
Maternal age, y					
<35	20 858 (76.8)	113 292 (84.4)	1.00	1.00	NA
35-39	4337 (16.0)	17 101 (12.7)	1.38 (1.32-1.43)	1.55 (1.49-1.61)	<.001
≥40	1954 (7.2)	3912 (2.9)	2.73 (2.57-2.90)	3.11 (2.92-3.31)	<.001
Welfare recipient	6592 (24.3)	29 112 (21.7)	1.16 (1.12-1.19)	1.07 (1.03-1.10)	<.001
Urban dweller	22 426 (82.6)	110 978 (82.6)	1.00 (0.96-1.03)	1.02 (0.98-1.05)	.45
Health care utilization within 12 mo before LMP until index date					
Emergency visit and/or hospitalization	15 279 (56.3)	70 872 (52.8)	1.15 (1.11-1.18)	1.17 (1.13-1.21)	<.001
Psychiatrist visit	365 (1.3)	1210 (0.9)	1.52 (1.34-1.73)	1.07 (0.93-1.22)	.34
General practitioner visits, No.					
0	14 192 (52.3)	72 006 (53.6)	1.00	1.00	NA
1-2	3885 (14.3)	22 281 (16.6)	1.05 (0.99-1.11)	1.03 (0.97-1.09)	.39
≥3	9072 (33.9)	40 018 (29.3)	1.36 (1.29-1.43)	1.17 (1.11-1.23)	<.001
Other specialist visits, No.					
0	17 239 (63.5)	86 772 (64.6)	1.00	1.00	NA
1	2273 (8.4)	12 268 (9.1)	0.98 (0.93-1.04)	0.96 (0.91-1.02)	.16
≥2	7637 (28.1)	35 265 (26.3)	1.16 (1.11-1.20)	1.05 (1.01-1.10)	.03

Overall Incident Benzodiazepine Use During Early Pregnancy and the Risk of Spontaneous Abortion

Table 2. Overall Incident Benzodiazepine Use During Early Pregnancy and the Risk of Spontaneous Abortion

Characteristic	No. (%)		Odds Ratio (95% CI)		*P* Value
	Spontaneous Abortion (n = 27 149)	Controls (n = 134 305)	Crude	Adjusted	
≥1 Diagnosis within 12 mo before LMP until index date					
Mood and anxiety disorders	2681 (9.9)	10 475 (7.8)	1.38 (1.32-1.44)	1.17 (1.11-1.22)	<.001
Insomnia	15 (0.1)	54 (0)	1.46 (0.79-2.71)	1.22 (0.64-2.32)	.55
Folic acid exposure within 6 mo before LMP until index date	751 (2.8)	5181 (3.9)	0.71 (0.66-0.78)	0.69 (0.64-0.76)	<.001
Comorbidities within 12 mo before LMP until index date					
Hypertension	1336 (4.9)	5607 (4.2)	1.20 (1.13-1.28)	1.18 (1.10-1.27)	<.001
Diabetes	1022 (3.8)	4957 (3.7)	0.99 (0.92-1.06)	1.05 (0.97-1.13)	.23
Asthma	5001 (18.5)	20 788 (15.5)	1.22 (1.18-1.27)	1.18 (1.13-1.22)	<.001
Thyroid disorders	1467 (5.4)	7581 (5.6)	0.92 (0.87-0.98)	0.91 (0.85-0.97)	.003
Tobacco dependence	696 (2.6)	2381 (1.8)	1.44 (1.31-1.57)	1.28 (1.16-1.42)	<.001
Alcohol dependence	258 (1.0)	727 (0.5)	1.73 (1.48-2.01)	1.22 (1.03-1.45)	.02
Other drug dependence	373 (1.4)	1227 (0.9)	1.47 (1.30-1.67)	1.15 (1.01-1.32)	.04
Pregnancy follow-up by gynecologist or obstetrician	8037 (30.0)	58 943 (43.9)	0.52 (0.50-0.54)	0.47 (0.45-0.48)	<.001
Pregnancy within 12 mo before LMP	1693 (6.2)	6246 (4.6)	1.39 (1.31-1.48)	1.22 (1.14-1.30)	<.001

Abbreviations: LMP, first day of the last menstrual period; NA, not applicable; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

[a] SSRI antidepressants included citalopram, escitalopram oxalate, fluoxetine hydrochloride, fluvoxamine maleate, paroxetine hydrochloride, and sertraline hydrochloride.

[b] SNRI antidepressants included desvenlafaxine, duloxetine hydrochloride, and venlafaxine hydrochloride.

[c] Tricyclic antidepressants included amitriptyline, clomipramine hydrochloride, desipramine hydrochloride, doxepin, imipramine pamoate, nortriptyline hydrochloride, and trimipramine.

[d] Other antidepressants included bupropion, buspirone, L-tryptophan, maprotiline, mirtazapine, trazodone, moclobemide, and nefazodone.

[e] Typical antipsychotic agents included chlorpromazine, fluphenazine, flupentixol, haloperidol, loxapine, methotrimeprazine, pericyazine, perphenazine, pimozide, prochlorperazine, trifluoperazine, zuclopenthixol acetate, zuclopenthixol decanoate, and zuclopenthixol dichlorhydrate.

[f] Atypical antipsychotic agents included aripiprazole, clozapine, olanzapine, risperidone, quetiapine, and ziprasidone.

- The use of **short-acting** (284 exposed cases; aOR, **1.81**; 95%CI, 1.55-2.12) and **long-acting** (98 exposed cases; aOR, **1.73**; 95%CI, 1.31-2.28) benzodiazepines was associated with an increased risk of SA.

Specific Benzodiazepine Incident Exposures During Early Pregnancy and the Risk of Spontaneous Abortion

Table 3. Specific Benzodiazepine Incident Exposures During Early Pregnancy and the Risk of Spontaneous Abortion

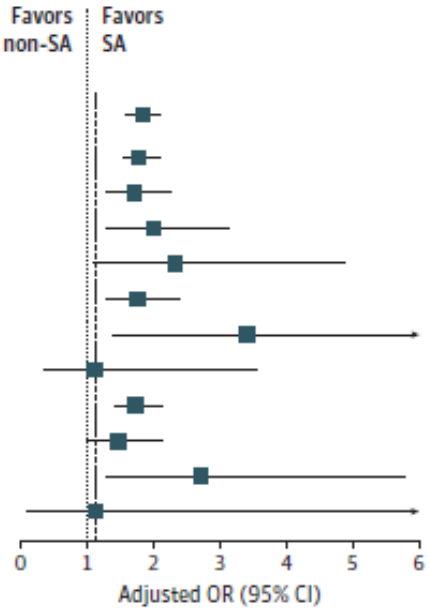
Characteristic	No. (%)		Odds Ratio (95% CI)		*P* Value
	Spontaneous Abortion (n = 27 149)	Controls (n = 134 305)	Crude	Adjusted	
Study medication exposure from LMP until index date					
Benzodiazepine					
Alprazolam	33 (0.1)	67 (0.1)	2.57 (1.67-3.95)	2.02 (1.30-3.15)	.002
Bromazepam	13 (0.1)	26 (0)	2.52 (1.24-5.11)	2.34 (1.11-4.93)	.03
Chlordiazepoxide	0	7 (0)	NA	NA	NA
Clonazepam	82 (0.3)	138 (0.1)	2.83 (2.12-3.79)	1.77 (1.31-2.41)	<.001
Diazepam	12 (0)	15 (0)	4.21 (1.81-9.76)	3.43 (1.42-8.32)	.006
Flurazepam hydrochloride	5 (0)	17 (0)	1.53 (0.53-4.43)	1.13 (0.36-3.60)	.83
Lorazepam	180 (0.7)	408 (0.3)	2.21 (1.83-2.67)	1.75 (1.44-2.14)	<.001
Nitrazepam	0	1 (0)	NA	NA	NA
Oxazepam	48 (0.2)	112 (0.1)	2.09 (1.47-2.97)	1.48 (1.02-2.14)	.04
Temazepam	14 (0.1)	15 (0)	4.72 (2.25-9.94)	2.74 (1.29-5.84)	.01
Triazolam	1 (0)	4 (0)	1.22 (0.12-12.12)	1.14 (0.11-11.83)	.91

- The association between benzodiazepines and SA was **strengthened with increasing diazepam-equivalent daily dose**.

Incident Benzodiazepine Exposure During Early Pregnancy

Figure 2. Incident Benzodiazepine Exposure During Early Pregnancy and the Risk of Spontaneous Abortion (SA)

Factor	Adjusted OR (95% CI)
Benzodiazepine	
Any	1.85 (1.61-2.12)
Short acting	1.81 (1.55-2.12)
Long acting	1.73 (1.31-2.28)
Alprazolam	2.02 (1.30-3.15)
Bromazepam	2.34 (1.11-4.93)
Clonazepam	1.77 (1.31-2.41)
Diazepam	3.43 (1.42-8.32)
Flurazepam	1.13 (0.36-3.60)
Lorazepam	1.75 (1.44-2.14)
Oxazepam	1.48 (1.02-2.14)
Temazepam	2.74 (1.29-5.84)
Triazolam	1.14 (0.11-11.83)



Sensitivity analyses were performed using all pregnancies (161 454 cases and controls) with the categorical previous pregnancy variable (childbirth, planned or induced abortion, and SA); with analysis restricted among the 15 952 pregnancies with mood and anxiety disorders before the first day of the last menstrual period (LMP) until index date; and with prescription filled before overlap of the LMP considered as zero. OR indicates odds ratio.

- **The E-value** obtained for the association between incident benzodiazepine exposure and SA was **3.1** with a lower limit of 2.6, suggesting that unmeasured confounding was unlikely to explain the findings.

Summary of the Results

- Among pregnancies ending with SA, 375 **(1.4%)** were among women exposed to benzodiazepines in early pregnancy compared with 788 **(0.6%)** of the 134 305 matched control pregnancies (**crude OR, 2.39**).
- Adjusting for potential confounders, including maternal mood and anxiety disorders before pregnancy, and compared with nonuse, benzodiazepine exposure in early pregnancy was associated with an increased risk of SA (**adjusted OR, 1.85**).
- The risk was similar among pregnancies exposed to short-acting(284 exposed cases; **adjusted OR, 1.81**) and long-acting (98 exposed cases; **adjusted OR, 1.73**) benzodiazepines during early pregnancy.
- All benzodiazepine agents were independently associated with an increased risk of SA(**range of adjusted ORs, 1.13-3.43**).

IV. DISCUSSION

Discussion

- The first study to investigate the risk of SA associated with **specific benzodiazepine agent** exposures during early pregnancy as well as the first study considering the association of **duration of action** with SA during early pregnancy
- Early pregnancy incident exposure to **any benzodiazepine agent** was associated with an increased risk of SA; the risk of SA increased with increasing daily dose of benzodiazepines, which may suggest a **dose-response effect**

Discussion

- In our study, we adjusted for diagnoses of **mood and anxiety disorders and insomnia** as well as for several documented proxies of these diseases, such as **concomitant exposure to antidepressants or antipsychotics, visits to a psychiatrist, comorbidities, and hospitalizations**.
- The **large E-value** obtained for the strength of potential residual confounding reinforced the validity of the observed association.
- In our study, data on **filled prescriptions** were used to define exposure, and within the Quebec Drug Plan, pregnant women made a copayment for their medication, which increased the likelihood of taking at least 1 dose.

Strengths and Limitations

Strengths

- They were able to obtain **accurate information on filled prescriptions** rather than rely on maternal recall for a large number of pregnancies.
- **Validated gestational age** allowed us to calculate the exact timing of the beginning of pregnancy and exact date of benzodiazepine prescription fills.
- We only included **incident users of benzodiazepines** during pregnancy because they were more likely to take at least 1 pill during early pregnancy and thus be considered exposed, decreasing exposure misclassification bias.
- We also used prospectively and routinely collected **physician-based diagnoses and records** of procedures related to pregnancy outcomes, which limited the potential for detection and misclassification biases on outcome status.
- The association between benzodiazepines and SA was also adjusted for the **most important potential confounders** (ie, concomitant exposure to antidepressants and/or antipsychotic medications).

Strengths and Limitations

Limitations

- Limitations include **missing information** about potentially important confounders such as smoking and alcohol intake.
- The data on **assisted reproduction** were not available in the cohort.
- Although the main study cohort included a large sample size, **subgroup analyses on specific BZD** agents were performed on a smaller sample, which resulted in lo wer statistical power
- Because we only considered pregnant women insured by the prescription drug i nsurance program, **generalizability** of results to those insured by private drug ins urance could be affected.

- **Large, well conducted cohort studies are needed** to confirm our results.

V. CONCLUSION

Conclusion

- An association between any benzodiazepine exposure during early pregnancy and the risk of SA was observed in all 4 independent models that quantified benzodiazepine exposure as a **class**, by **duration of action**, for **specific benzodiazepine agents**, and by **cumulative diazepam-equivalent dose**.

- The findings suggest that health care clinicians should carefully evaluate **the risk-benefit ratio of benzodiazepines** for the treatment of insomnia and mood or anxiety disorders in early pregnancy.

- Alternative non-pharmacologic treatments exist and are recommended, but if benzodiazepines are needed, they should be prescribed for short durations.

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