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Risk of Preterm Delivery and Other Adverse Perinatal Outcomes in Relation to Maternal use of Psychotropic Medications during Pregnancy

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Abstract

Objectives—To study the association of maternal psychotropic medication use during pregnancy with preterm delivery and other adverse perinatal outcomes.

Study design—A cohort of 2793 pregnant women in Washington State was interviewed and their medical files were abstracted. Logistic regression models were constructed to assess odds ratios (OR) for perinatal outcomes by use of psychotropic medications.

Results—Maternal use of benzodiazepines during pregnancy was associated with an increased risk of preterm delivery (adjusted OR:6.79, 95% confidence interval: 4.01–11.5) and with increased risks of low birthweight, low Apgar score, neonatal intensive care unit (NICU) admissions, and respiratory distress syndrome (RDS). Selective serotonin receptor inhibitors (SSRIs) were associated with preterm deliveries only among women who started treatment after first trimester.

Conclusion—Benzodiazepines were highly associated with preterm delivery and other adverse perinatal outcomes. Well-conducted cohort studies are warranted to draw conclusions on risks and benefits of psychotropic medication use during pregnancy.

Keywords

benzodiazepines; selective-serotonin-uptake inhibitors (SSRI); preterm birth; cohort; pregnancy

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INTRODUCTION

The prevalence of antidepressant use in pregnancy varies across countries^{1, 2}. In the US, approximately 8% of pregnant women are prescribed antidepressants, with an increasing trend over the last decade that is primarily owed to the increased use of selective serotonin receptor inhibitors (SSRIs)³. Data on prevalence of use of other psychotropic medications in pregnancy is lacking. Although the rate of benzodiazepines (BZD) prescription for depression in the general population has decreased⁴, it remains one of the major treatments for anxiety and panic disorders, as well as one of the treatments for restless leg syndrome⁵ in pregnancy.

An increase in awareness of antenatal and postpartum depression and other psychosomatic conditions⁶, raise concern for possible associations between psychotropic medications and adverse perinatal outcomes; however, available data are insufficient to draw conclusions for most drugs. While there have been numerous studies on adverse effects of psychotropic medications, especially with regards to congenital malformations^{6, 7} and withdrawal symptoms of the newborn (e.g., ‘the floppy-infant syndrome’ following benzodiazepines⁶, and the ‘neonatal behavioral syndrome’ following exposure to SSRIs^{8, 9}), many studies were based on case series and case reports and provided inconsistent results.

Preterm births are the most common adverse outcomes of pregnancy, accounting for approximately 12% of births, with an increasing trend over the last two decades, that was mainly attributed to delivery inductions for maternal or fetal indications¹⁰. Preterm births harbor most devastating sequelae¹¹, including increased perinatal mortality, increased risks of respiratory illnesses, and delayed neurodevelopment among offspring. Only few studies were published on the association of psychotropic medications and preterm deliveries^{12–14}. We aimed to study the risks of preterm delivery and other adverse perinatal outcomes in relation to maternal use of psychotropic medications during pregnancy.

MATERIALS AND METHODS

Study Population and Data Collection

The population for the present analysis was drawn from the participants of the ongoing Omega Study, a prospective cohort study of pregnant mothers who attended prenatal care clinics affiliated with Swedish Medical Center (Seattle, Washington) and Tacoma General Hospital (Tacoma, Washington) since December 1996. Women eligible for inclusion in the Omega study were those who initiated prenatal care before 20 weeks’ gestation, were at least 18 years of age, could speak and read English, planned to carry the pregnancy to term, and planned to deliver at either one of the two study hospitals. Participants were interviewed during a prenatal visit prior to 20 weeks of gestation by trained research personnel using a structured questionnaire. Data collected included information regarding maternal sociodemographic and anthropometric characteristics, lifestyle habits, and medical and reproductive histories. Medical records were reviewed for pre-gestational and antepartum diagnoses as well as use of prescription medications. Data on medications used during pregnancy were retrieved from both questionnaires and medical records. Information on pregnancy outcome was ascertained by reviewing hospital labor and delivery medical records and clinic records after delivery. The study was approved by the Institutional Review Boards of Swedish Medical Center and Tacoma General Hospital. All participants provided written informed consent. The original cohort included 2952 women; 67 women who had either iatrogenic or spontaneous abortion were excluded. Data on preterm births were complete for 2793 (96.6%) births.

Study Outcomes

Our primary outcome, preterm delivery (PTD), defined as a delivery that occurred at gestational age of more than 20 and before the completion of 37 weeks of gestation. Secondary outcomes included low birth weight (LBW - a birth weight below 2500gr), small for gestational age (SGA - birth weight 2 standard deviations below the mean for the newborn's gestational age at birth), low Apgar score (5-minute Apgar score below 7), admissions to the neonatal intensive care unit (NICU), and diagnosis of respiratory distress syndrome (RDS).

Statistical Analysis

The characteristics of the study population were described by type of psychotropic medication used during pregnancy. Logistic regression models were constructed to assess the odds ratios (OR) for the outcomes according to medication use. Unadjusted models were followed with adjustments for maternal age, race, years of education, marital status, smoking during pregnancy, preeclampsia, parity, and singleton/multiple pregnancy. Analyses were conducted for any psychotropic medication use (yes vs. no), for specific groups of medications (e.g., SSRIs vs. no medication) and for specific formulations (e.g., *Fluoxetine* vs. No medication). We also conducted analyses by time of initiation of medication use (categorized into trimesters of pregnancy), and by number of medications used. Sensitivity analyses were performed to estimate ORs for preterm delivery by time interval from onset of medication use to delivery. We report OR, 95% confidence intervals (CI) and two-sided p values.

RESULTS

Overall, 300 women (10.7%) used a psychotropic medication during pregnancy. Table 1 describes medications used. Of the women who were taking psychotropic medications, 235 (78%) took only one medication, 51 (17%) used two medications, and 14 (5%) used three or more medications. The characteristics of the study population and the incidence of adverse outcomes by categories of psychotropic medications used during pregnancy are depicted in Table 2. Women who used any medication differed from those who did not use medications in years of education, pre-pregnancy BMI, and rate of multiple pregnancy. Women who used SSRIs, selective norepinephrine receptor inhibitors (SNRI), or BZD were more likely to be multiparous than their counterparts who did not use psychotropic medications during pregnancy.

Medications and Preterm Delivery

Among women who used any psychotropic medication, 23.3% (n=70) had a preterm delivery, compared with 9.4% of women who did not use psychotropic medications (Table 1). Compared with non-users, women who used any psychotropic medication during pregnancy had an increased risk of preterm delivery (unadjusted OR=2.94; 95% CI: 2.18–3.96). Adjustments for maternal age, race, marital status, education, smoking, parity, preeclampsia and singleton pregnancy, resulted in an attenuation of the association (adjusted OR=2.08; 95% CI: 1.46–2.96), though the association remained statistically significant. As shown in Table 3, there was evidence of an increasing trend of preterm delivery risk with the number of medications taken during pregnancy.

Maternal use of any SSRI or SNRI was associated with a small non-significant increased risk of preterm delivery (adjusted OR=1.34, 95% CI: 0.76–2.36). There was a suggestion for differential risk of preterm delivery when specific medications within this class of therapeutic agents were evaluated. For example, maternal use of the SSRI, *Paroxetine* was associated with an adjusted OR of 2.30 for preterm delivery, though the association did not reach statistical significance (95% CI: 0.90–5.83; p=0.081). Maternal use of *Venlafaxine*, an SNRI, was

associated with an adjusted OR of 3.78, though again this association did not reach statistical significance (95% CI: 0.81–17.6; $p=0.091$).

Information regarding the time of initiation of medication use was available for 121 (91.7%) of women who were taking SSRIs. Most (83%) mothers who have used SSRIs started treatment either before pregnancy or during the first trimester (i.e., before completion of 14 weeks) of pregnancy. Mothers who initiated use of SSRIs in second or third trimester tended to report use of multiple drugs compared with mothers who initiated medication use in early pregnancy, with additional medications in 47.6% vs. 18.8% of women who were taking SSRIs, respectively. An increased risk of preterm delivery was found only among mothers who began taking SSRIs in the second or third trimester with an adjusted OR of 4.79 (1.66–13.9; $p=0.004$), whereas no association was found among mothers who started using SSRIs before or during the first trimester (OR=0.88, 95% CI: 0.42–1.85; $p=0.739$) (Table 3).

Benzodiazepines (BZD)

Maternal use of BZD during pregnancy was associated with an adjusted OR of 6.79 for preterm delivery (95% CI=4.01–11.5; $p<0.001$). Among women who took BZD, those who used one medication had an adjusted OR of 5.56 for preterm delivery (95% CI: 2.71–11.4); those who used multiple BZD formulations or use used BZD in combination with another psychotropic medication had an OR of 8.48 for preterm delivery (95% CI: 4.03–17.8; p for trend<0.001). Lorazepam, the most frequently used BZD in the cohort, was associated with an OR of 7.94 for preterm delivery (95% CI: 4.47–14.1; $p<0.001$). Information regarding the onset of BZD use was available for 93% ($n=80$) of patients who used BZD. Of those, 11 started treatment either before pregnancy ($n=4$) or during first trimester ($n=7$), 19 had started treatment during the second trimester, and 50 had started treatment during the third trimester. Initiations of treatment before or during the first trimester, in second, or in third trimester of pregnancy were associated with adjusted ORs of 5.15 (95% CI: 1.34–19.8; $p=0.017$), 7.39 (95% CI: 2.35–23.2; $p=0.001$), and 10.1 (95% CI: 4.84–21.1; $p<0.001$), respectively.

We next sought to assess whether there was a differential association between maternal use of BZD and preterm delivery by the documented obstetric precursors of preterm delivery. Maternal use of BZD was associated with an adjusted OR of 5.40 for medically induced preterm delivery (95% CI: 2.18–13.3), and with an OR of 7.32 (95% CI: 4.11–13.0; $p<0.001$) for non-medically induced preterm delivery (either preterm premature rupture of the membranes (PPROM), or spontaneous preterm labor (SPTL) with intact membranes) (data not shown).

We further conducted a sensitivity analysis of the multivariate association between BZD and preterm delivery by the time interval from onset of BZD use to delivery (Figure 1). With the exclusion of women who started treatment within a week, two weeks, and three weeks before delivery, the association weakened, however, it remained highly significant when only women who started treatment more than four weeks before delivery were included (OR=3.57, 95% CI: 1.71–7.47; $p=0.001$).

Hydroxyzine

Overall, hydroxyzine use during pregnancy appeared to be associated with an increased risk of preterm delivery (adjusted OR=2.45, 95% CI: 1.44–4.15; $p=0.001$). However, further analyses revealed that women who used hydroxyzine alone ($n=76$) had no substantially increased risk for preterm delivery (adjusted OR=1.19; 95% CI: 0.57–2.50) (Table 3).

LBW, SGA, low Apgar score, NICU admissions, and RDS

Maternal use of any psychotropic medication during pregnancy was associated with an increased risk of delivering LBW newborns (OR=2.12, 95% CI 1.37–3.27; $p=0.001$). Maternal

use of any psychotropic medication was associated with low 5-minute Apgar scores (OR=2.46, 95% CI: 1.26–4.78), increased risk of admission to NICU, and increased risk of RDS (Table 4). Medication use was not associated with delivery of small for gestational age newborns (OR=1.36, 0.72–2.57). Associations of each perinatal outcomes with specific classes of psychotropic medications are shown in the bottom panels of Table 4.

Overall, SSRIs were not associated with LBW, SGA, or low Apgar score (Table 4), neither were they associated with NICU admissions (OR=1.36, 95% CI: 0.70–2.67; $p=0.369$) or RDS (95% CI: 1.39, 0.56–3.44; $p=0.480$). However, an association for SSRIs with LBW was shown among women who started treatment with SSRIs in second or third trimester (OR=5.01, 95% CI: 1.37–18.4; $p=0.015$). No association was found with timing of treatment and SGA, low Apgar score, NICU admissions or RDS (data not shown). The SNRI, *Venlafaxine*, was associated with low 5-minute Apgar score (OR=11.6, 95% CI: 1.85–72.6; $p=0.009$), and there was a suggested association with NICU admissions (3.68, 0.76–17.8; $p=0.104$), and with RDS (5.23, 0.91–30.2; $p=0.064$). BZD were associated with increased risk of low birth weight (adjusted OR=7.43, 95% CI: 4.15–13.3; $p<0.001$), but not with SGA. BZD were associated with low 5-minutes Apgar score (OR=3.87, 95% CI: 1.53–9.76; $p=0.004$), with admission to NICU, (OR=4.33, 95% CI: 2.45–7.63; $p<0.001$), and with a diagnosis of RDS (OR=3.74, 95% CI: 1.86–7.54; $p<0.001$). There were too few subjects taking hydroxyzine as a single treatment to complete similar analyses.

COMMENT

In this study, maternal use of benzodiazepines during pregnancy was associated with a significantly increased risk of preterm delivery (adjusted OR=6.79) and increased risks of low birth weight, low Apgar score, admission to NICU, and RDS. Selective serotonin receptor inhibitors (SSRIs) were associated with preterm deliveries and low birth weight, but not with other adverse outcomes, only among women who started taking these medications during the second or third trimesters.

Our results regarding BZD are supported by Wikner et al¹⁴, who demonstrated increased risks of preterm births, LBW and low Apgar scores among Swedish women who used BZD in pregnancy. The associations shown in this latter report were somewhat weaker than those of our study, with ORs for preterm births that ranged between 1.48 (95% CI: 1.26–1.75) and 2.57 (95% CI: 1.92–3.43) for ‘early’ and ‘late’ exposure, respectively¹⁴. Differences in the magnitude of associations may be attributed to variations in population characteristics including different clinical practices of BZD treatment during pregnancy. We noted that the prevalence of BZD use among women in our cohort was approximately 10 times higher than in the cohort studied by Wikner et al¹⁴. Moreover, we noted that *Lorazepam* was the most frequently prescribed BZD regimen in our cohort, however, only 1.4% of women taking BZD used this medication in the Wikner et al cohort¹⁴. Our results are dissimilar with those of Ornoy et al.¹⁵ who did not find differences in gestational age at delivery and infant birthweight among newborns of mothers who used BZD compared with mothers who did not use these medications during pregnancy.

We noted weak and statistically non-significant associations between maternal use of SSRI and preterm delivery overall. Consistent with our results, Lennestall et al.¹⁶ demonstrated a weak association of similar magnitude (unadjusted OR=1.24), and no increased risks of LBW or SGA following treatment with SSRIs/SNRIs. Similarly, Wen et al¹⁷ demonstrated an OR of 1.57 (95% CI: 1.28–1.92) for preterm delivery among women who were prescribed with SSRIs at least once within a year before delivery. Our study suggests an increased risk of preterm birth among women who started taking SSRIs in the second or third trimester, supporting others^{12, 13}. However, this association might be a consequence of concomitant use

of other psychoactive drugs. Contradicting results were shown by other studies, where associations were demonstrated between long-term exposure to SSRIs and reduced gestational age, reduced birthweight, preterm delivery, low Apgar scores and RDS 18–20. Although it was shown that women treated with SSRIs or SNRIs were 7 to 30 times more likely than other women to be treated with sedatives, hypnotics and neuroleptics^{15,21}, none of these studies controlled for additional psychotropic medications.

Our study which relied on medical records documentation of maternal use of psychotropic medications has several advantages over other studies of this topic. Medical records provided detailed information concerning the type and timing of medication use relative to preterm delivery. By so doing, we avoided misclassification of maternal exposure to the medications. The high follow-up rate of enrolled participants (> 95%) also served to attenuate concerns about possible selection bias. Despite these strengths, a number of important limitations should be considered when interpreting results from our study. First, we did not have information concerning the indications for medication use. Hence, we cannot rule out that the association between BZD and preterm birth was confounded by common indications such as maternal anxiety. The few reports on the association of anxiety and perinatal outcomes yielded mixed results. One study²² suggested an increased risk of preterm deliveries only among women who had had previous preterm deliveries. Another study²³ suggested an increased risk of low Apgar score, but not preterm deliveries, for women with anxiety disorder, whereas a recent study²⁴ has suggested that not the level of anxiety itself, but the pattern of change during pregnancy, is related to preterm delivery. None of these studies approached the issue of maternal use of psychotropic medications during pregnancy.

Second, we cannot rule out the possibility that some women with symptoms of preterm labor may have been prescribed psychotropic medications to manage anxiety around the pregnancy. Results from our sensitivity analyses, however, suggest that concerns about “reverse causality” or confounding by indication of use of medications^{25–26} do not fully explain our observations. Our sensitivity analyses suggest that findings are robust and associations were found both among women who started medications more than four weeks before delivery (Figure 1), as well as among women who started using BZD in first trimester of pregnancy. Third, although we had detailed information about medication use, we cannot be certain that women receiving prescriptions during pregnancy actually took the medications as prescribed; nor can we estimate risk of preterm delivery and other adverse outcomes in relation to dosages and the exact duration of use of medications during pregnancy. Fourth, inferences from many of our analyses are hindered by our relatively small sample size. Much larger prospective studies are needed to disentangle the independent effect of specific psychiatric diagnoses and medications used (including dose and timing of use) on risk of adverse perinatal outcome. Lastly, although we adjusted for multiple confounding factors, as with all observational studies, we cannot exclude the possibility of some residual confounding from unmeasured factors such as maternal illicit drug use.

In view of the strong association between BZD and adverse outcomes of pregnancy, as well as the suggested associations of *Venlafaxine* and SSRIs, there is a pressing need to pursue with large well-conducted cohort studies to confirm our results. Finding from additional studies are needed to provide data for decision making on treatment during pregnancies and to promote knowledge on the possible mechanisms in which psychotropic drugs affect perinatal outcomes.

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Figure 1.

Sensitivity analysis of the association between benzodiazepines (BZD) and preterm delivery (PTD), according to the interval between initiation of BZD treatment and delivery (weeks). Odds ratios (AOR) and 95% confidence intervals (95% CIs) are adjusted for maternal age, race/ethnicity, marital status, education, smoking during pregnancy, preeclampsia, parity, and singleton pregnancy.

Table 1

Distribution of psychotropic medications used by the Omega cohort members.

Group	Drug	N
SSRIs		132
	Paroxetine (e.g. Paxil)	31
	Fluvoxamine (e.g. Luvox)	3
	Fluoxetine (e.g. Prozac)	36
	Sertaline (e.g. Zoloft)	56
	Citalopram (e.g. Celexa)	16
	Escitalopram (e.g. Lexapro)	6
SNRI	Venlafaxine (e.g. Effexor)	9
BZD		85
	Lorazepam (e.g. Ativan)	73
	Diazepam (e.g. Valium)	2
	Alprazolam (e.g. Xanax)	7
	Clonazepam (e.g. Klonopin)	4
Other anti-depressants	Tricyclics: Amitrypyline (e.g. Elatrol)	4
	Nortriptyline (e.g. Aventyl)	2
	Trazodone (e.g. Desyrel)	1
	Nefazodone (e.g. Serzone)	1
	Bupropion (e.g. Wellbutrin)	13
Other medications		
Antipsychotics	Olanzapine (e.g. Zyprexa)	1
Anticonvulsants	Carbamazepine (e.g. Tegretol),	5
	Gabapentin (e.g. Neurontin)	2
Mood stabilizers	Lithium	1
Other anxiolytics	Hydroxyzine (e.g. Vistaril)	107
	Buspirone (e.g. BuSpar)	1
	Propranolol (e.g. Inderal)	6

SSRI: Selective Serotonin Uptake Inhibitors;

SNRI: Selective Serotonin and Norepinephrine Reuptake Inhibitors

BZD: Benzodiazepines.

Table 2

Characteristics of the study population according to psychotropic medications used during pregnancy.

Characteristics	No Medication (N=2493) %	Any Medication (N=300) %	SSRI/SNRI (N=138) %	BZD (N=85) %
Maternal Age	32.3 ± 4.5*	33.1 ± 4.9	33.0 ± 5.0	33.1 ± 5.3
Married	90.9	87.3	87.7	92.9
Nulliparous	60.4	60.3	50.7	54.1
≤High School Education	4.0	4.7	5.1	5.9
Non-Hispanic White	84.7	91.3	94.2	90.6
Smoked During Pregnancy	5.8	10.7	13.1	7.1
Pre-pregnancy BMI (Kg/m ²)				
<20	17.6	19.1	17.5	16.5
20–24.99	57.5	46.8	43.8	47.1
25–29.99	16.0	17.7	19.7	17.6
≥30	8.9	16.4	19.0	18.8
Singleton Pregnancy	97.0	89.3	94.9	78.8
Gestational Age at Delivery (week)	38.8 ± 2.0*	37.8 ± 2.8	38.3 ± 1.9	36.1 ± 3.6
Birth weight (grams)	3437 ± 581*	3216 ± 732	3314 ± 542	2875 ± 960
Preterm Delivery.(PTD)	9.4	23.3	13.8	49.4
Non-medically induced (spontaneous and PPROM)	6.8	18.0	9.4	38.8
Medically induced	2.6	5.3	4.3	10.6
Low Birth-Weight (LBW)	5.5	15.6	7.2	38.4
Small-for-Gestational Age Infant (SGA)	2.8	4.7	4.3	3.5
APGAR Score@5 minute < 7	1.5	5.0	5.1	8.1
Neonatal Intensive Care Unit (NICU)	6.3	15.4	10.9	32.6
Respiratory Distress Syndrome (RDS)	2.8	7.0	5.8	17.4

* indicating mean ± standard deviation (SD)

SSRI: Selective Serotonin Uptake Inhibitors;

SNRI: Selective Serotonin and Norepinephrine Reuptake Inhibitors

BZD: Benzodiazepines.

Table 3

The Odds Ratio (ORs) and 95% Confidence Intervals (CI) for preterm delivery by type of treatment according to the logistic regression models.

Type of treatment	Preterm Delivery		Unadjusted OR (95%CI)	Adjusted OR* (95%CI)
	Yes (n)	No (n)		
Overall				
No medication	234	2259	1.00 (referent)	1.00 (referent)
Any medication	70	230	2.94 (2.18–3.96)	2.08 (1.46–2.96)
<i>One regimen</i>	43	192	2.16 (1.51–3.09)	1.49 (0.97–2.27)
<i>≥ 2 regimens</i>	27	38	6.86 (4.11–11.4)	5.24 (2.89–9.53)
SSRIs/SNRIs				
Yes	19	119	1.54 (0.93–2.55)	1.34 (0.76–2.36)
SSRIs	16	116	1.33 (0.78–2.28)	1.21 (0.67–2.21)
<i>Paroxetine</i>	8	23	3.36 (1.49–7.59)	2.30 (0.90–5.83)
<i>Sertaline</i>	5	51	0.95 (0.37–2.39)	0.65 (0.23–1.83)
<i>Fluoxetine</i>	4	32	1.21 (0.42–3.44)	1.29 (0.44–3.79)
SNRIs	4	5	7.72 (2.06–29.0)	3.78 (0.81–17.6)
Initiation of SSRIs				
Prior to pregnancy or 1 st trimester	90	10	1.07 (0.55–2.09)	0.88 (0.42–1.85)
During 2 nd or 3 rd trimester	16	5	3.02 (1.10–8.31)	4.79 (1.66–13.9)
		.728	.344	0.73 (0.34–1.54)
		4.214	1.460	4.21 (1.46–12.16)
BZDs				
Yes	42	43	9.43 (6.04–14.7)	6.79 (4.01–11.5)
<i>One regimen</i>	20	23	8.39 (4.54–15.5)	5.56 (2.71–11.4)
<i>≥ 2 regimen**</i>	22	20	10.6 (5.71–19.7)	8.48 (4.03–17.8)
Lorazepam (specific)	40	33	11.7 (7.24–18.9)	7.94 (4.47–14.1)
Initiation of BZDs				
Prior to pregnancy or 1 st trimester	8	3	3.62 (0.95–13.7)	5.15 (1.34–19.8)
During 2 nd trimester	9	9	9.65 (3.79–24.6)	7.39 (2.35–23.2)
During 3 rd trimester	22	28	18.0 (9.49–34.2)	10.1 (4.84–21.1)
Hydroxyzine				
Yes	32	75	4.12 (2.67–6.36)	2.45 (1.44–4.15)
<i>Hydroxyzine only</i>	15	61	2.37 (1.33–4.24)	1.19 (0.57–2.50)
<i>Hydroxyzine combined with other types</i>	17	14	11.7 (5.71–24.1)	7.98 (3.51–18.2)

* Adjusted for maternal age, race/ethnicity, marital status, education, smoking during pregnancy, preeclampsia, parity, and singleton pregnancy

** Only 1 had two types of BZD.

SSRI: Selective Serotonin Uptake Inhibitors;

SNRI: Selective Serotonin and Norepinephrine Reuptake Inhibitors

BZD: Benzodiazepines.

Table 4

The association between treatment with psychoactive medications and adverse outcomes of birth associated with prematurity in a multivariate logistic regressions model after adjusted for age, race, marital status, education, smoking during pregnancy, preeclampsia, parity, and singleton pregnancy.

	Low Birth-Weight (LBW)	Small for Gestational Age infant (SGA)	APGAR Score at 5 minute <7	Neonatal Intensive Care Unit (NICU)
	AOR (95%CI)	AOR (95%CI)	AOR (95%CI)	AOR (95%CI)
Any Medication	2.12 (1.37–3.27)	1.36 (0.72–2.57)	2.46 (1.26–4.78)	1.90 (1.27–2.85)
SSRIs/SNRI	1.20 (0.56–2.57)	1.72 (0.71–4.15)	2.76 (1.09–6.00)	1.47 (0.78–2.78)
<i>SSRIs</i>	1.04 (0.45–2.39)	1.86 (0.77–4.48)	2.02 (0.68–6.00)	1.36 (0.70–2.67)
<i>SNRI</i>	2.14 (0.35–13.3)	---*	11.6 (1.85–72.6)	3.68 (0.76–17.8)
BZD	7.43 (4.15–13.3)	0.83 (0.24–2.88)	3.87 (1.53–9.76)	4.33 (2.45–7.63)

* none of the Venlafaxine-treated had an SGA offspring

SSRI: selective serotonin uptake inhibitors;

SNRI: Selective Serotonin and Norepinephrine Reuptake Inhibitors

BZD: benzodiazepines.