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Prenatal Antidepressant Use and Risk of Adverse Neonatal Outcomes

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abstract

OBJECTIVES: To estimate the risk of neonatal outcomes from patterns of prenatal antidepressant use.

METHODS: From the OptumLabs Data Warehouse, 226 932 singleton deliveries were identified. Antidepressant claims with coverage between the last menstrual period and 35 weeks' gestation were converted to fluoxetine equivalents, and a longitudinal cluster analysis was performed. Outcomes included major cardiac malformations (11.7 of 1000 births), preterm birth (75.7 of 1000 births), and newborn respiratory distress (54.2 of 1000 births). The lowest trajectory was the primary reference group, and depression and anxiety with no antidepressant claims served as secondary reference groups.

RESULTS: From 15 041 (6.6%) pregnancies exposed to an antidepressant, use patterns were best described as (1) low use (~10 mg/day) with first-trimester reduction, (2) low sustained use (~20 mg/day), (3) moderate use (~40 mg/day) with first-trimester reduction, (4) moderate sustained use (~40 mg/day), and (5) high sustained use (~75 mg/day). Moderate sustained use increased the risk of major cardiac malformations, although results included the null when compared with depression or anxiety reference groups. Moderate sustained (adjusted risk ratio [RR] 1.31; 95% confidence interval [CI] 1.16–1.49) and high sustained (adjusted RR 1.78; 95% CI 1.48–2.14) trajectories were associated with an increased risk of preterm birth. All 4 trajectories increased the risk of neonatal respiratory distress in a dose-response fashion (adjusted RRs 1.36 [95% CI 1.20–1.50] to 2.23 [95% CI 1.83–2.77]).

CONCLUSIONS: Although findings support continuation of the lowest effective dose to treat depression or anxiety, which benefits the mother, they also highlight an increased risk for newborn respiratory distress in all groups and preterm birth at moderate to high sustained doses.

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Dr Bandoli conceptualized and designed the study, performed analyses, and prepared and reviewed the final manuscript; Dr Chambers conceptualized the study and reviewed the final manuscript; Mr Wells consulted on analyses and reviewed the final manuscript; Dr Palmsten conceptualized the study, assisted in preparation of the final manuscript, and reviewed the final manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Prenatal antidepressant use has been inconsistently associated with adverse neonatal outcomes. Previous studies have relied on broad categorizations of antidepressant use that preclude investigation into how timing and dose affect specific offspring outcomes, which have different sensitive periods and etiologies.

WHAT THIS STUDY ADDS: Through a longitudinal cluster analysis, we identified 5 patterns of prenatal antidepressant use. There was an increased risk of preterm birth among the highest-use groups, and all patterns of use were associated with greater risk for neonatal respiratory distress.

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Major depression affects ~8% of pregnant women in the United States,[1] and 7% to 13% of pregnant women use antidepressants during pregnancy.[2–4] Untreated prenatal depression is associated with maternal and offspring morbidity,[5] and pharmacologic or nonpharmacologic interventions are encouraged.[6] However, previous studies have yielded inconsistent associations of prenatal antidepressant use and neonatal outcomes. Preterm birth, major cardiac malformations, and neonatal respiratory distress have been associated with prenatal antidepressant use,[7–13] although other large studies have failed to confirm these findings.[14–16]

Some of the discrepancy is likely due to exposure classification. Often, studies of antidepressant use during pregnancy classify exposure dichotomously or as a count of days or cumulative dose across gestation. This approach removes information on the specific timing associated with frequency of use or changes in dose that is important for understanding how antidepressants are used during pregnancy. In addition, this categorization precludes investigation of how the timing and dose together affect specific birth outcomes, which have different sensitive periods and etiologies.

Recently, researchers have employed longitudinal cluster analysis on medication use in pregnancy to address these limitations.[17,18] These methods classify individuals with similar dose and frequency of use over time into groups, allowing for more precise comparisons among more homogenous groups. We previously performed a longitudinal cluster analysis on antidepressant use in pregnancy in a small hospital-based cohort and found differential risk estimates for birth weight by antidepressant use patterns.[19]

Identification of antidepressant patterns independently linked with lower risk for adverse offspring outcomes is highly relevant to informing the management of these common treatments in pregnant women. Our objective for this study was to estimate the risk of select neonatal complications associated with specific patterns of prenatal antidepressant use in a US cohort of privately insured women.

METHODS

Data Source and Study Cohort

We conducted a retrospective study using OptumLabs Data Warehouse (OLDW), which includes deidentified medical and pharmacy claims, laboratory results, and enrollment records for commercial and Medicare Advantage enrollees. The database contains longitudinal health information on >200 million unique lives, representing a mixture of ages, ethnicities, and geographical regions across the United States.[20,21]

There were 585 902 eligible female patients aged 12 to 49 who delivered a live-born infant between January 1, 2012, and December 31, 2016, on the basis of delivery-related diagnosis and procedure codes. Women were required to have continuous enrollment with medical and pharmacy benefits 3 months before the last menstrual period (LMP) through 3 months after delivery. Newborns were required to have continuous medical and pharmacy coverage during the first 3 months of life. Women were linked to newborns by matching on family identification and by matching the newborn's earliest date of insurance coverage with the date of the woman's delivery-related code associated with a delivery episode.[21] After implementing mother-newborn linkage (18% cohort attrition) and applying mother and newborn continuous enrollment criteria (49% cohort attrition) and restricting to singleton births, 226 932 unique deliveries from 208 271 unique women remained (Fig 1). *International Classification of Disease, Ninth Revision* (ICD-9) and *International Classification of Diseases, 10th Revision* (ICD-10) diagnosis and procedure codes and *Current Procedural Terminology* (CPT) procedure codes used to define outcomes, covariates, and medications of interest are listed in Supplemental Table 3.

Exposure

Women were exposed if they filled at least 1 prescription for an antidepressant with coverage (ie, fill date plus the number of days' supply dispensed) between the LMP and 35 gestational weeks. Consistent with previous research, the LMP was to set 35 weeks before delivery for preterm births and 39 weeks otherwise.[22] When this algorithm was measured against clinical gestational age in a validation study, deliveries were within 2 weeks of 35 or 39 assigned weeks in 75% of preterm births and 99% of term deliveries.[22] Because preterm delivery was assigned 35 weeks' gestation, exposure was only assessed through 35 weeks. All antidepressant fills were assigned to a pregnancy calendar with day 0 equal to the LMP. Coverage gaps were assigned no use for those days. Dosages of all antidepressants were converted into fluoxetine equivalents on the basis of published literature,[23] and multiple agents per day were summed. Overlapping coverage of the same medication (eg, refill of a prescription a few days early) was only counted once. Daily doses between the LMP and 35 weeks were expressed as the average daily dose (milligrams per day) per week.

Exposure Trajectories

To identify similar clusters of individual antidepressant trajectories, we employed the R statistical software package "kml."[24] Each observation is assigned to a cluster,

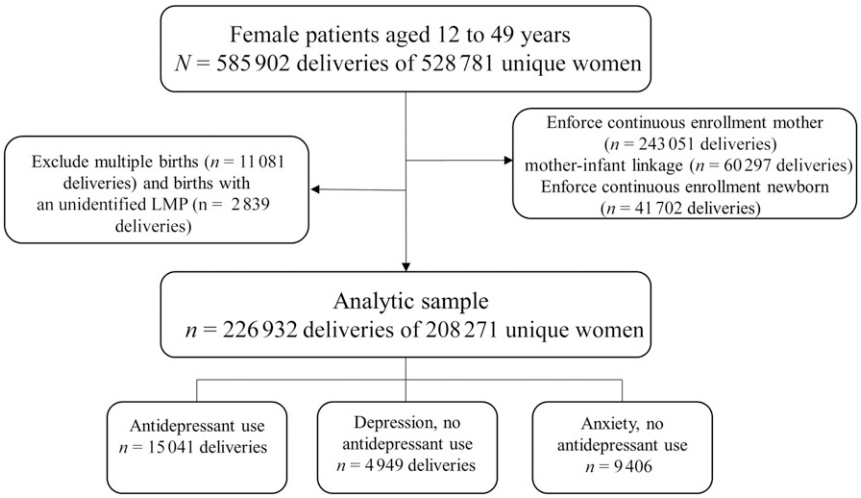

FIGURE 1
Cohort creation from live births between 2012 and 2016 from medical and pharmacy claims in the OLDW.

then the optimal clustering is reached by alternating the expectation phase, in which the centers of different clusters are computed, and the maximization phase, in which each observation is assigned to the nearest cluster.[25] We allowed k-means to run for 2 to 8 clusters 100 times each. There is no reliable method or formal test for determining the true cluster number. Therefore, selection of the number of clusters was based on (1) optimization of 3 statistical quality criteria,[26–28] (2) clinical relevance of the clusters with respect to standard doses, and (3) at least 200 individuals per cluster. We performed k-means longitudinal for 2 periods. First, trajectories were identified from the LMP to 12 gestational weeks to capture the risk period for the occurrence of major malformations. Antidepressant trajectories through 35 gestational weeks were identified to assess the risk of preterm birth and newborn respiratory distress. Five clusters (ie, trajectory groups) best described use in both of the risk periods (Fig 2).

Outcomes

Major cardiac malformations were identified from at least 2 *International Classification of Diseases* (ICD) codes or a procedure code and ICD code in infant records during the first 90 days after delivery, excluding anomalies related to preterm birth.[16,29] This algorithm has a positive predictive value of 77.6%.[29] Infants with chromosomal abnormalities or exposure to known teratogens were excluded from malformation analyses. Preterm birth was based on diagnosis codes in maternal files within 7 days of delivery; the algorithm has a published sensitivity of 98% and specificity 91%.[22] Newborn respiratory distress was identified by ICD codes in infant records within 7 days of delivery. To our knowledge, there are no validation studies for respiratory distress codes, and there may be heterogeneity in case definition between providers.

Covariates

Potential antidepressant indications (depression, anxiety, other mental health disorders, pain disorders, and sleep disorders) were identified from maternal records during 90 days before the LMP through 12 and 35 gestational weeks. Pharmacy fills for antipsychotic medications and benzodiazepines with any coverage between the LMP and 12 or 35 gestational weeks were captured. Maternal preexisting hypertension was assessed in the 90 days before the LMP. Finally, maternal age at delivery, race, and education information available closest to the time of the LMP was obtained from enrollment files.

Analyses

We categorized pregnancies as follows: having antidepressant exposure, having a depression or anxiety diagnosis without antidepressant exposure, and all other pregnancies. For primary analyses, we restricted to antidepressant-exposed pregnancies and performed log-linear regression with a Poisson distribution to estimate risk ratios (RRs) for trajectory groups of antidepressant exposure and the outcomes. Robust SEs were reported to account for correlations within women with >1 delivery in the time frame. We analyzed 12-week trajectory groups for major cardiac malformations and 35-week trajectory groups for preterm birth and newborn respiratory distress. In all models, the lowest trajectory group was the referent group. Models were adjusted for maternal age, race and/or ethnicity, education, depression, anxiety, pain, other mental health disorders, antipsychotic medications, and benzodiazepines. Mental health diagnoses and concomitant psychotropic medication use were assessed only in the same gestational period as each model's exposure period (ie, 12 or 35 weeks). For each model, we performed a linear test for trend by including a continuous variable of trajectory groups and continuous and quadratic terms to assess quadratic trend. To provide clinically relevant information with respect to the decision of whether to use an antidepressant in pregnancy, we repeated all models for pregnancies with a depression diagnosis or an anxiety diagnosis (during the relevant exposure period) without antidepressant fills as the reference groups.

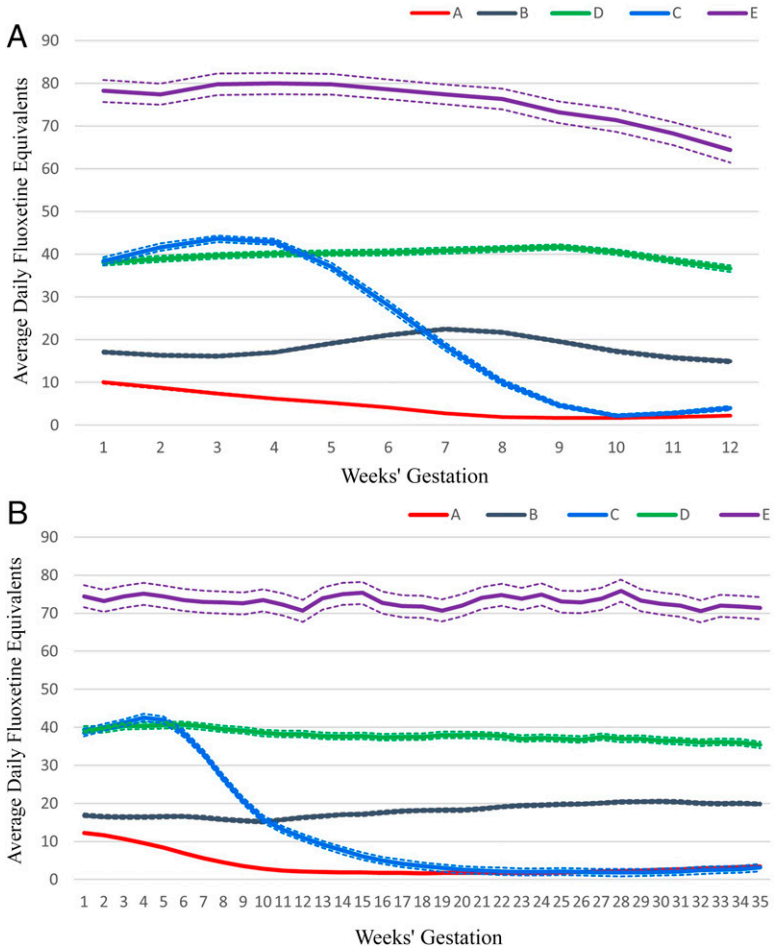

FIGURE 2

A and B, Mean trajectories (solid line) with 95% CIs (hashed lines) for 12- and 35-week antidepressant use among 15 041 deliveries with at least 1 antidepressant claim between the LMP and 35 weeks' gestation. C, The average daily fluoxetine equivalents and SD for each trajectory group.

In previous reports, authors have differentiated the safety of different antidepressant types in pregnancy and perinatal outcomes.[16,30–32] Although our sample was not sufficient to compare selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and buprenorphine, we performed a sensitivity analysis restricting to pregnancies exposed only to an SSRI and repeated the primary analyses.

All analyses were performed by using R. Precision around estimates for measures of association were estimated with 2-sided 95% confidence intervals (CIs). No adjustments were made for multiple comparisons. Per OptumLabs policy, cell sizes and corresponding crude relative risks are suppressed for cells <11.[20]

The research was determined to be exempt by the University of California, San Diego Institutional Review Board.

RESULTS

Description of Cohort and Trajectory Profiles

There were 15 041 (6.6%) pregnancies exposed to an antidepressant between the LMP and 35 gestational weeks. Women with antidepressant claims were more likely to be non-Hispanic white and have lower education levels compared with women without antidepressant claims (Table 1). Compared with women with an anxiety or depression diagnosis and no antidepressant claims, they differed little on other indications such as other mental health disorders, pain, or sleep disorder diagnoses.

Antidepressant Use

Sertraline (32.4%) was the most commonly filled antidepressant, followed by citalopram, fluoxetine, escitalopram, and bupropion, each at 13% of antidepressant fills. Among women with antidepressants, 69.9% had SSRI monotherapy, 6.6% had SNRI monotherapy, and 8.9% had

TABLE 1 Maternal Characteristics From the Full Sample of 226 932 Pregnancies Between 2012 and 2016 From OLDW

	No Depression and No Antidepressant Use (n = 199 311)	Depression and No Antidepressant Use (n = 4949)[a]	Anxiety and No Antidepressant Use (n = 9406)[a]	Antidepressant Use (n = 15 041)
Maternal age, y				
<25	6333 (3.2)	162 (3.3)	254 (2.7)	404 (2.7)
25–34	135 108 (67.8)	3102 (62.7)	6023 (64.0)	9356 (62.2)
>34	57 870 (29.0)	1685 (34.0)	3129 (33.3)	5281 (35.1)
No. births in period				
1	183 447 (92.0)	4343 (87.8)	8334 (88.6)	13 922 (92.6)
2+	15 914 (8.0)	606 (12.2)	1072 (11.4)	1119 (7.4)
Maternal race				
White	135 734 (68.1)	3741 (75.6)	7161 (76.1)	12 512 (83.2)
African American	14 474 (7.3)	378 (7.6)	598 (6.4)	870 (5.8)
Hispanic	21 515 (10.8)	454 (9.2)	936 (10.0)	1034 (6.9)
Other or unknown	27 588 (13.8)	376 (7.6)	711 (7.6)	625 (4.2)
Education				
Less than or equal to high school or unknown	21 361 (10.7)	725 (14.6)	1233 (13.1)	2467 (16.4)
Less than bachelor's degree	108 118 (54.2)	2756 (55.7)	4939 (52.5)	8623 (57.3)
Bachelor's degree or higher	59 932 (30.1)	1468 (29.7)	3234 (34.4)	3951 (26.3)
Comorbidities and coexposures[b]				
Depression diagnosis	0 (0.0)	4949 (100.0)	1775 (18.9)	5575 (37.1)
Anxiety diagnosis	0 (0.0)	1775 (35.9)	9406 (100.0)	6293 (41.8)
Other mental health diagnosis	3584 (1.8)	1334 (27.0)	1909 (20.3)	3206 (21.3)
Pain diagnosis	15 631 (7.8)	855 (17.3)	1825 (19.4)	2667 (17.7)
Sleep disorder diagnosis	1109 (0.6)	220 (4.5)	499 (5.3)	847 (5.6)
Hypertension	2120 (1.1)	128 (2.6)	268 (2.8)	421 (2.8)
Antipsychotics	50 (0.0)	50 (1.0)	52 (0.6)	265 (1.8)
Benzodiazepines	1522 (0.8)	220 (4.4)	731 (7.8)	1610 (10.7)

All data are presented as n (%). Cell sizes <11 are suppressed per requirements of OptumLabs.

[a] A total of 1775 pregnancies included depression and anxiety diagnoses and are in both strata.

[b] Comorbidities and coexposures with claims between the LMP and 35 wk gestation.

bupropion monotherapy (data not shown).

In the cluster analysis, 5 trajectories best described antidepressant use through 12 and 35 gestational weeks (Fig 2). For each of the periods, trajectory groups were characterized as follows: trajectory A, low use beginning at 10 mg/day with first-trimester reduction or discontinuation; trajectory B, low sustained use of ~20 mg/day; trajectory C, moderate initial use (~40 mg/day) with first-trimester reduction or discontinuation; trajectory D, moderate sustained use of ~40 mg/day; and trajectory E, high sustained use of ~75 mg/day. With respect to the reduction or discontinuation trajectories (A and C), the percentages of women who had no antidepressant use beyond week 13 were 60% and 61%, respectively. The percentages of women with no antidepressant use beyond week 27 were 71% and 82%, respectively.

Maternal characteristics differed between 35-week trajectory groups (Table 2). Women with first-trimester antidepressant reduction or discontinuation, either from low or moderate doses (trajectories A and C, respectively) were more likely to be African American or Hispanic and have a high school diploma or less education compared with those who sustained low, moderate, or high doses. Women in the high sustained group (trajectory E) were more likely to have a psychiatric diagnosis between 90 days before the LMP and 35 gestational weeks than women in the other groups and were much more likely to have other psychotropic medication fills.

Neonatal Outcomes

Major Cardiac Malformations

In the full cohort, 1.2% of infants had a major congenital malformation (Supplemental Table 4). Pregnancies exposed to moderate, sustained antidepressant use (trajectory D) had an increased risk for major cardiac malformations relative to the lowest trajectory (2.4% vs 1.5%; adjusted RR 1.6 [95% CI 1.2–2.3]). The highest-use trajectory group had a 73% increase in risk; however, CIs included the null with only 13 exposed cases (Fig 3). All CIs crossed or were below the null when trajectories were compared with women with a diagnosis of depression or anxiety and no antidepressants (Fig 3).

Preterm Birth

Approximately 7.6% of pregnancies were delivered prematurely

TABLE 2 Maternal Characteristics of 15 041 Pregnancies With an Antidepressant Claim in the First 35 Weeks' Gestation Between 2012 and 2016 in OLDW

	35-wk Trajectory Group				
	Low Use With Reduction (A), *n* = 7622	Low Sustained Use (B), *n* = 3170	Moderate Use With Reduction (C), *n* = 1907	Moderate Sustained Use (D), *n* = 1918	High Sustained Use (E), *n* = 424
Maternal age, y					
<25 y	269 (3.5)	69 (2.2)	44 (2.3)	18 (0.9)	<11 (<2.6)
25–34 y	4942 (64.8)	1936 (61.1)	1146 (60.1)	1101 (57.4)	>224 (>52.8)
>34 y	2411 (31.6)	1165 (36.8)	717 (37.6)	799 (41.7)	189 (44.6)
No. births in study period					
1	7065 (92.7)	2915 (92.0)	1797 (94.2)	1761 (91.8)	384 (90.6)
2+	557 (7.3)	255 (8.0)	110 (5.8)	157 (8.2)	40 (9.4)
Maternal race					
White	6148 (80.7)	2738 (86.4)	1585 (83.1)	1676 (87.4)	365 (86.1)
African American	503 (6.6)	140 (4.4)	124 (6.5)	80 (4.2)	23 (5.4)
Hispanic	643 (8.4)	155 (4.9)	119 (6.2)	93 (4.9)	24 (5.7)
Other or unknown	328 (4.3)	137 (4.3)	79 (4.1)	69 (3.6)	12 (2.8)
Education					
Less than or equal to high school degree or unknown	1400 (18.4)	427 (13.5)	358 (18.8)	236 (12.2)	46 (10.9)
Less than bachelor's degree	4401 (57.7)	1825 (57.6)	1062 (55.7)	1091 (56.9)	244 (57.6)
Bachelor's degree or higher	1821 (23.9)	918 (29.0)	487 (25.5)	591 (30.8)	134 (31.6)
Comorbidities and coexposures[a]					
Depression diagnosis	2270 (29.8)	1279 (40.4)	812 (42.6)	932 (48.6)	282 (66.5)
Anxiety diagnosis	2838 (37.2)	1406 (44.4)	867 (45.5)	924 (48.2)	258 (60.8)
Other mental health diagnosis	1360 (17.8)	754 (23.8)	429 (22.5)	506 (26.4)	157 (37.0)
Pain diagnosis	1349 (17.7)	514 (16.2)	355 (18.6)	345 (18.0)	104 (24.5)
Sleep disorder diagnosis	427 (5.6)	145 (4.6)	133 (7.0)	109 (5.7)	33 (7.8)
Hypertension	210 (2.8)	73 (2.3)	62 (3.3)	63 (3.3)	13 (3.1)
Antipsychotics	55 (0.7)	44 (1.4)	52 (2.7)	74 (3.9)	40 (9.4)
Benzodiazepines	657 (8.6)	292 (9.2)	280 (14.7)	269 (14.0)	112 (26.4)

All data are presented as *n* (%). Cell sizes <11 are suppressed per requirements of OptumLabs.

[a] Prescription fills through 35 wk gestation.

(Supplemental Table 5). Pregnancies with moderate or high sustained antidepressant use (trajectories D [15%] and E [24%]) were at an increased risk of preterm birth (*P* for quadratic trend < .001). There was little to no attenuation in the point estimates when compared with those of women with depression or anxiety without antidepressants (Fig 4).

Neonatal Respiratory Distress

From the full cohort, 5.4% of infants had claims for neonatal respiratory distress (Supplemental Table 6). All groups had an elevated risk of neonatal respiratory distress compared with the lowest trajectory group, and all but the lowest-use trajectory group had an elevated risk of neonatal respiratory distress when compared with depression or anxiety reference groups (Fig 5). There was a linear trend for the trajectory groups ($P < .001$) but not a quadratic trend. There was a slight attenuation when comparing trajectory groups with the anxiety group, as opposed to the lowest antidepressant trajectory group, and no attenuation when comparing the trajectories with the depression group.

SSRI-Only Models

After restricting to pregnancies with SSRI monotherapy, results did not differ in any meaningful or systematic way (Supplemental Table 7).

DISCUSSION

Given the risks to both the mother and fetus of untreated maternal depression, foregoing antidepressant treatment throughout pregnancy is often not an option for women with moderate to severe depression.[6] Therefore, a clinically relevant question is whether the risk for adverse perinatal outcomes linked with antidepressants can be reduced by particular antidepressant regimes. We found that compared with the lowest antidepressant trajectory group, all other groups were at an increased risk for neonatal respiratory distress in a dose-response manner. Additionally, we found that groups with moderate or high sustained antidepressant use were at higher risk for preterm birth. However, we cannot rule out confounding by disease severity as an explanation of these findings. Finally, although moderate sustained antidepressant use was associated with increased risk of major congenital malformations, estimates attenuated to include the null on comparison with the untreated reference groups.

This study expands previous literature by discerning patterns of

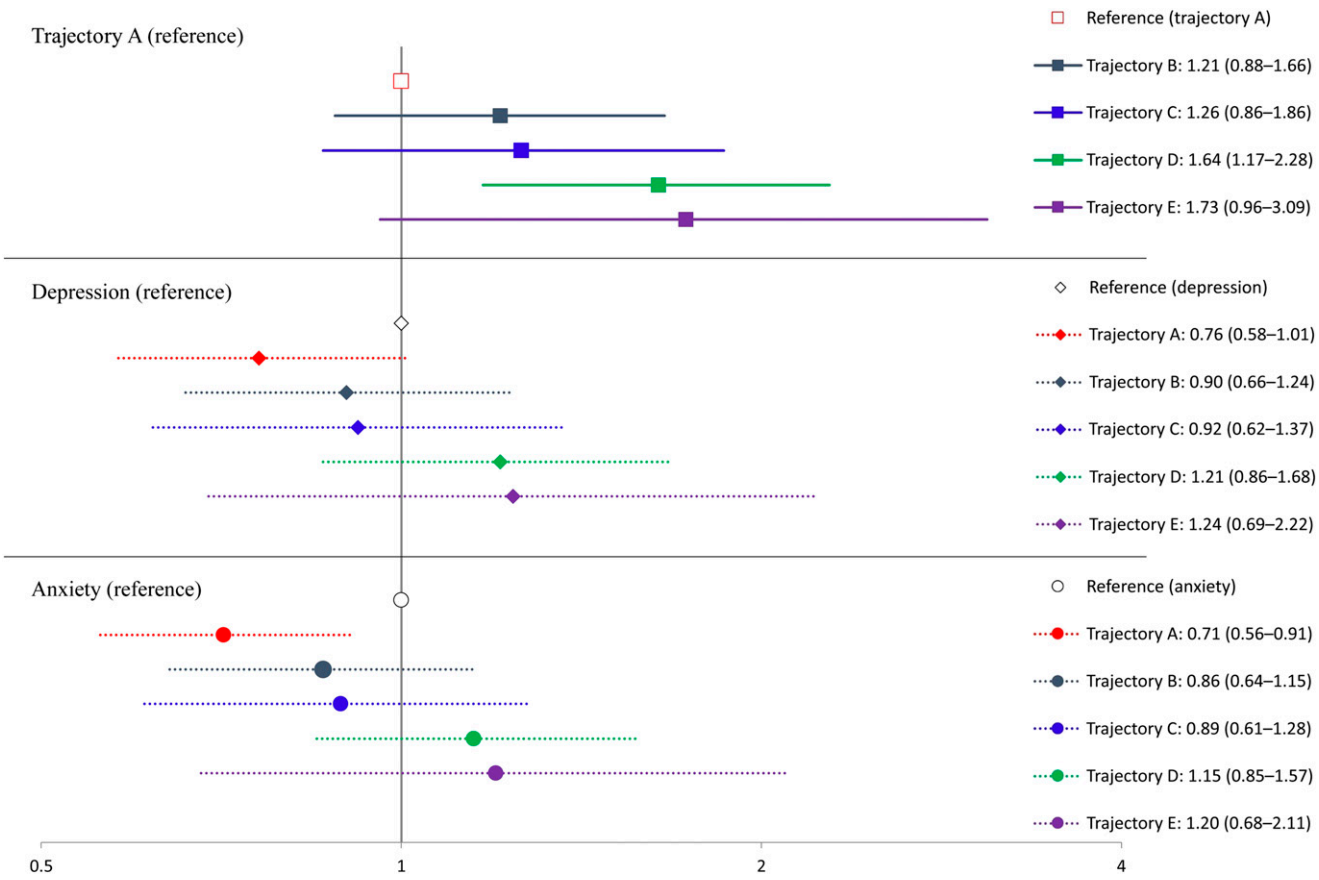

FIGURE 3

Adjusted RRs for antidepressant trajectories and major cardiac malformations. Twelve-week trajectory descriptions are as follows: trajectory A: low use with reduction or discontinuation; trajectory B: low sustained use; trajectory C: moderate use with reduction or discontinuation; trajectory D: moderate sustained use; and trajectory E: high sustained use. Solid lines indicate the trajectory mean; hashed lines indicate the 95% CI of the mean.

antidepressant use over 2 periods of pregnancy and then evaluating whether patterns of use (accounting for timing of exposure, dose, and duration) were associated with adverse neonatal outcomes. Consistent with previous work, we observed a subset of women who reduced or discontinued antidepressants in the first trimester.[4,19,33] For some, this may be due to concerns about the safety of antidepressants for the pregnancy and developing fetus.[34] Interestingly, the shape of these trajectories changed little after 12 weeks of pregnancy, suggesting that for many, decisions about antidepressant discontinuation tend to be made early in pregnancy. We did not find distinct trajectories of women beginning or resuming antidepressants later in pregnancy. However, in the post hoc analysis of 35-week trajectories, we found that 7.8% of women began antidepressants after the 20th week or later, and 93% of these women were in trajectory A, with the remainder in trajectory B.

A longitudinal cluster analysis provided a nuanced appreciation of patterns of use associated with perinatal outcomes. We observed a linear dose response with antidepressant trajectory groups and the risk of newborn respiratory distress, and these findings were unchanged when compared with those of the anxiety or depression reference groups. These results are of clinical interest because the lower trajectory groups were not associated with preterm birth (and therefore not explained by preterm birth), and the risk persisted at the group level even with the reduction or discontinuation of antidepressants in early pregnancy. Antidepressants have been associated with newborn respiratory distress in humans and reduced uterine blood flow and transient fetal hypoxemia in sheep.[8,11–13] Increased levels of 5-hydroxytryptamine in the fetus could alter respiratory maturation or adaptation to the extrauterine environment, leading to neonatal

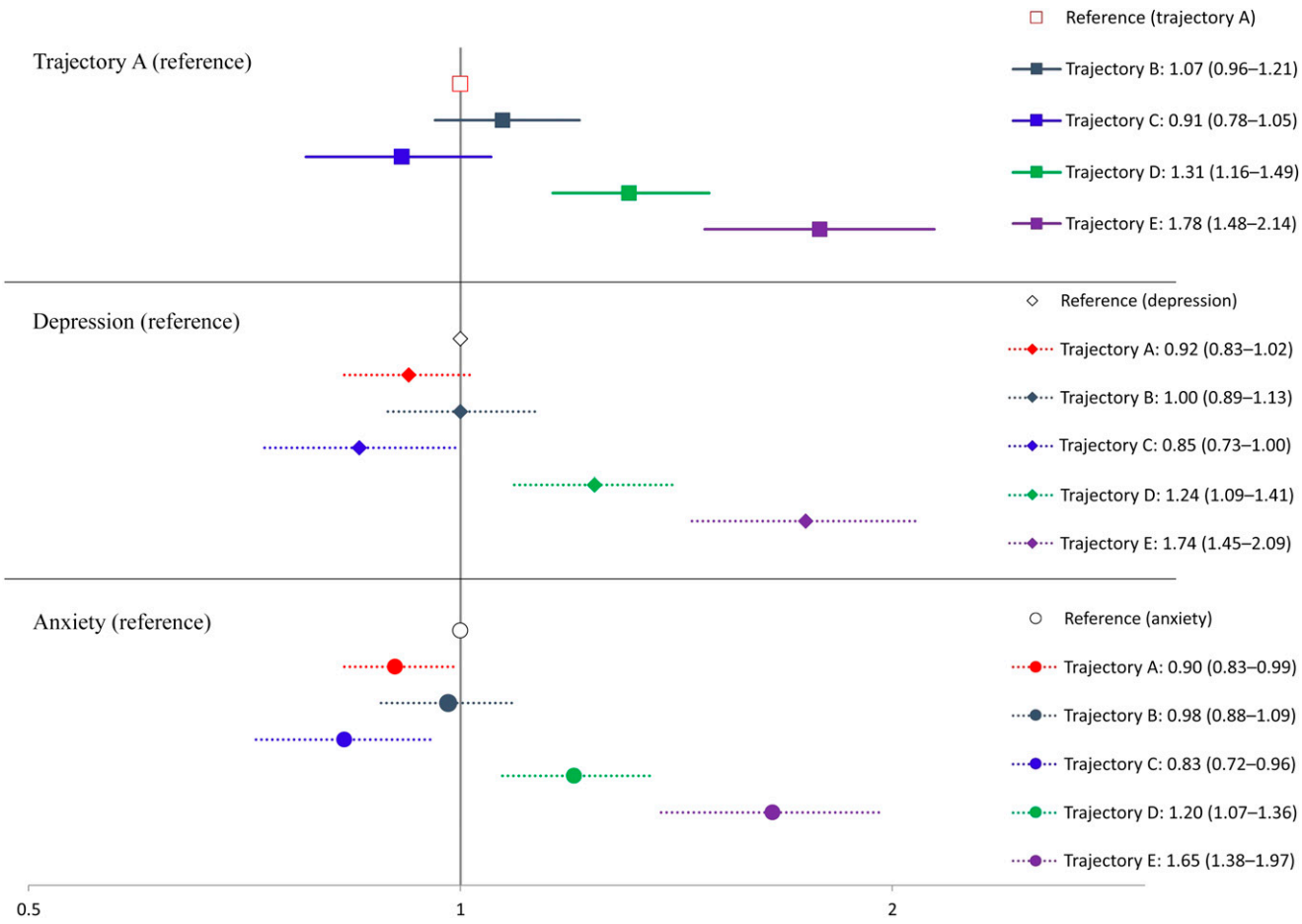

FIGURE 4

Adjusted RRs for antidepressant trajectories and preterm birth. Thirty-five-week trajectory descriptions are as follows: trajectory A: low use with reduction or discontinuation; trajectory B: low sustained use; trajectory C: moderate use with reduction or discontinuation; trajectory D: moderate sustained use; and trajectory E: high sustained use.

respiratory distress.[8] In previous perinatal studies, authors either considered second- or third-trimester exposure[11–13] or did not differentiate exposure periods.[8] It is possible that acute SSRI withdrawal may be misdiagnosed as respiratory distress and may contribute to the findings; however, our findings of sustained risk in this group are novel and warrant further investigation. Our findings that only sustained moderate or high doses of antidepressants were associated with increased risk for preterm birth may explain the heterogeneity in previous studies because lower doses were not associated with an increased risk of preterm birth and would have attenuated results if pooled into a binary exposure variable.[8,10,14] Finally, with respect to cardiac malformations, our findings were similar to those of a previous study (in which Medicaid data were used) that revealed no association between antidepressants and cardiac malformations after restricting to women with depression and adjusting for confounders.[16] However, it should be noted that point estimates for the 2 highest trajectories were still >1, and unmeasured confounders, such as smoking and alcohol use, may have been higher in women with unmedicated depression or anxiety, which would have attenuated findings.

This study has strengths in addition to highlighting the methodologic expansion of longitudinal cluster analysis. The large database of administrative claims permitted the assessment of multiple trajectory profiles. Additionally, we compared all results with those of contrast groups of depression and anxiety, the latter of which, to our knowledge, is rarely done. Given that more women with antidepressants had a diagnosis of anxiety than depression during pregnancy, it is critical to evaluate this reference group as well. Our findings that there were negligible differences between the 2 groups may support

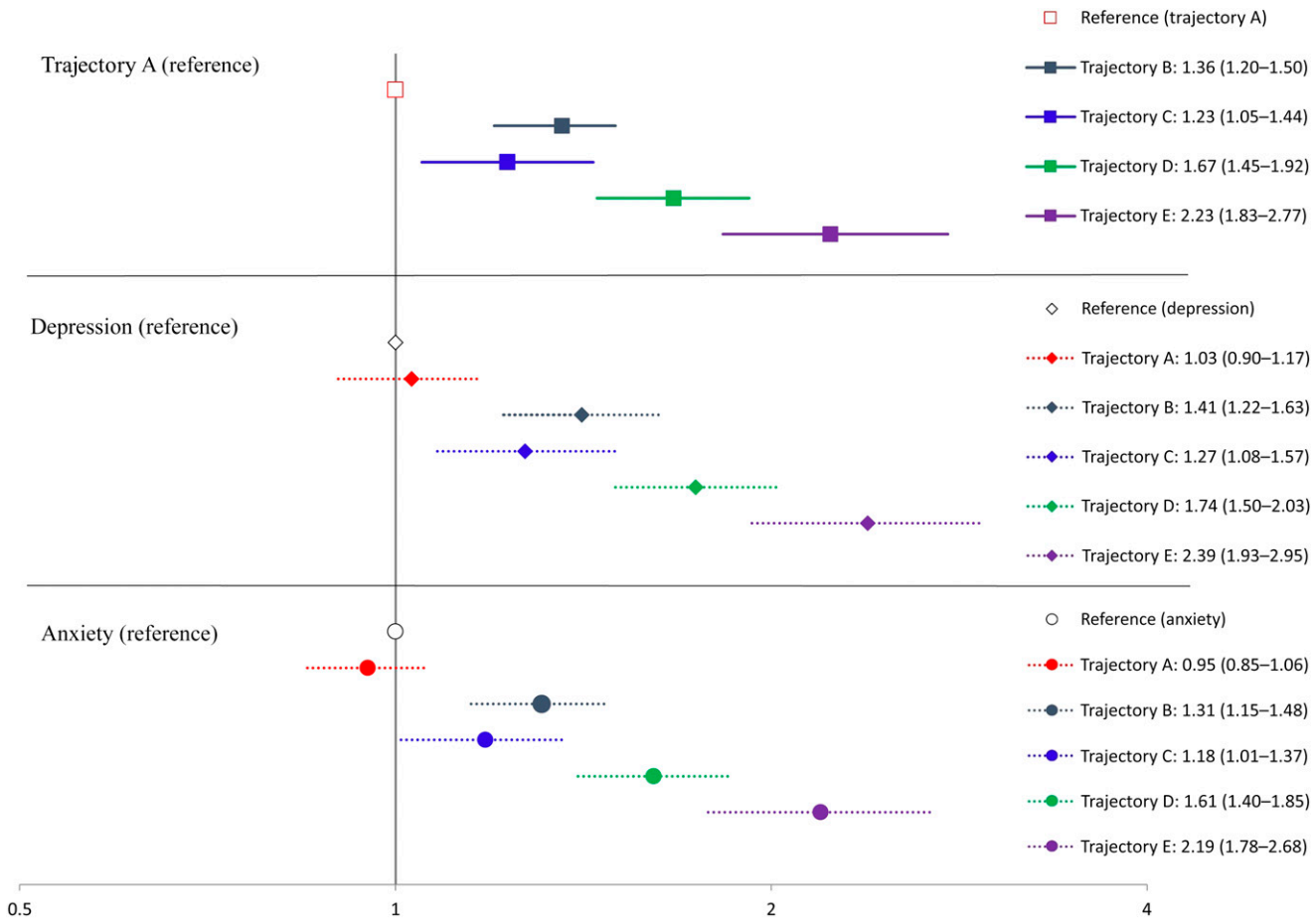

FIGURE 5

Adjusted RRs for antidepressant trajectories and newborn respiratory distress. Thirty-five-week trajectory descriptions are as follows: trajectory A: low use with reduction or discontinuation; trajectory B: low sustained use; trajectory C: moderate use with reduction or discontinuation; trajectory D: moderate sustained use; and trajectory E: high sustained use.

collapsing them in future studies into 1 reference group; however, those decisions should be made with respect to each outcome of interest.

Limitations of this research include the inability to confirm whether individuals with a claim for an antidepressant took the medication or used it as prescribed, which could bias results toward the null. Additionally, this study was performed on a database of individuals with continuous enrollment in commercial insurance; findings may not be generalizable to those less likely to have static commercial insurance coverage such as young women or more disadvantaged groups, including women receiving public insurance. Third, as with all observational studies, we cannot rule out confounding, particularly by smoking, alcohol use, or obesity, which are not well-captured in administrative data. This confounding may have been differential by exposure group, which could have influenced findings. To address these latter 2 limitations, a study replicating findings with a wider range of covariates and a wider cross-section of society is necessary. When studying antidepressants, confounding by indication or indication severity is always of concern, and we attempted to mitigate this by adjusting for other psychotropic medications and underlying central nervous system conditions. In addition, we included contrast groups of depression and anxiety disorders without antidepressant claims. However, without measures of symptom severity, we assume that residual confounding by indication remains, particularly for effect estimates of the highest trajectory groups. Finally, reliance on ICD-9 codes for gestational age may have resulted in misclassification of the LMP, and individuals with shorter gestations could have prepregnancy antidepressant use misclassified as prenatal use. However, we would not expect misclassification to be differential by antidepressant status or trajectory group and would expect bias to go toward the null.

CONCLUSIONS

Acknowledging the limitations to this study, these results largely confirm previous findings and reveal nuance that can be gleaned from this exposure modeling technique. Longitudinal cluster analysis enabled the creation of more well-defined exposure groups to assess risk of adverse birth outcomes. Compared with the lowest-dose trajectory group, all patterns of use increased risk for neonatal respiratory distress in a dose-dependent fashion, even in the group of women in which antidepressants were reduced or discontinued early in pregnancy. In addition, moderate to high sustained antidepressant use in gestation was associated with an increased risk of preterm birth. Our findings support the continued use of the methodology to further delineate risk by different patterns of antidepressant use. This approach can help clinicians counsel pregnant women on the use of antidepressants during gestation. In addition, it can help to identify groups whose infants may be at higher risk for preterm birth or neonatal respiratory distress.

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ABBREVIATIONS

CI: confidence interval
CPT: *Current Procedural Terminology*
ICD: *International Classification of Diseases*
ICD-9: *International Classification of Diseases, Ninth Revision*
ICD-10: *International Classification of Diseases, 10th Revision*
LMP: last menstrual period
OLDW: OptumLabs Data Warehouse
RR: risk ratio
SNRI: serotonin-norepinephrine reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor

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