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Authors

Palmsten, Kristin
Chambers, Christina D
Wells, Alan
et al.

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Patterns of prenatal antidepressant exposure and risk of preeclampsia and postpartum hemorrhage

Kristin Palmsten, ScD[1,2,3], **Christina D Chambers, MPH, PhD**[2,3,4], **Alan Wells, MS**[2], **Gretchen Bandoli, PhD**[2,3,4]

[1.] Health Partners Institute, Minneapolis, MN

[2.] Department of Pediatrics, University of California San Diego, La Jolla, CA

[3.] OptumLabs Visiting Fellow, Cambridge, MA

[4.] Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA

Abstract

Background: Antidepressant use later in pregnancy has been associated with preeclampsia and postpartum hemorrhage (PPH) in some studies.

Objective: To evaluate the association between patterns of prenatal antidepressant dose across gestation and risk of precclampsia and PPH.

Methods: We utilized OptumLabs® Data Warehouse (2012–2016) administrative health care claims, identifying 226,932 singleton live-born deliveries for this retrospective cohort study. Antidepressant dispensing doses were converted to fluoxetine equivalents. Using k-means longitudinal, we identified women with similar patterns of antidepressant exposure, i.e., trajectory groups, during the first 20 and 35 gestational weeks. We estimated risk ratios (RR) and 95% confidence intervals (CI) for the association between trajectory groups and preeclampisa (20-week groups) and PPH (35-week groups), adjusting for demographics, comorbidities, and other psychotropic medications. Linear trend tests assessing increasing risk of the outcomes across groups were performed.

Results: Among 15,041 (6.6%) pregnancies exposed to an antidepressant, the following trajectory groups were identified: A-low exposure, starting pregnancy at ~10mg/day, with 1st trimester reduction/discontinuation, B-low sustained exposure of ~20 mg/day, C-moderate exposure (~40mg/day) with 1st trimester reduction/discontinuation, D-moderate sustained exposure of ~40 mg/day, and E-high sustained exposure of ~75mg/day. In the low exposure with reduction/discontinuation trajectory, risks were 8.2% for preeclampsia and 2.7% for PPH. Compared with this group, low, moderate, and high sustained trajectories were associated with preeclampsia [adjusted (a)RR: 1.17 (95% CI: 1.01, 1.34), aRR: 1.31 (95% CI: 1.12, 1.54), aRR:

Kristin Palmsten, HealthPartners Institute, Minneapolis, MN, USA Kristin.K.Palmsten@HealthPartners.com.

Social media quote: Compared with first trimester antidepressant dose reduction/discontinuation, sustatined doses were associated with increased preeclampsia and postpartum hemorrhage risks. Many antidepressant exposure patterns were no worse for outcome risks than untreated depression.

The figure can be posted with the quote.

1.41 (95% CI: 1.05, 1.90), respectively] and PPH [aRR: 1.32 (1.05, 1.66), aRR: 1.35 (95% CI: 1.03,1.78), aRR: 2.51 (95% CI: 1.69, 3.71), respectively]; p<0.01 for linear trend tests for both outcomes. There was no increased risk for either outcome for moderate exposure with reduction/discontinuation (trajectory C).

Conclusions: Women with sustained antidepressant exposure, especially at higher doses, were at increased risk for preeclampsia and PPH, but underlying depression and anxiety may contribute to the increased risk.

Keywords

Antidepressants; anxiety; depression; pregnancy; postpartum hemorrhage; preeclampsia

Background

Untreated prenatal depression is associated with poor self-care, unhealthy behaviors, sucide attempts, and adverse offspring outcomes.[1–4] In the US, 7–13% of pregnant women use antidepressants during pregnancy.[5–7] Some studies have found antidepressant exposure during pregnancy to be associated with a range of adverse perinatal outcomes including preeclampsia, especially for exposures into the second trimester, and postpartum hemorrhage (PPH), for late-pregnancy exposures.[8–19] Other studies,generally those with smaller numbers of exposed cases, conclude no association between antidepressants and preeclampsia and PPH.[20–23]

Recently, studies have used longitudinal cluster analysis to classify medication use during pregnancy instead of a dichotomous “any use” versus “no use” approach.[24–28] These methods classify individuals with similar patterns of use, allowing for comparisons across groups with less within-group heterogeneity in dose and gestational timing of use that may be important for understanding risks for preeclampsia and PPH.

To better understand potential risks associated with antidepressant use during pregnancy, we identified antidepressant exposure patterns with respect to dose and gestational timing in a large US cohort of commercially insured women. The objective of this study was to estimate the risk of preeclampsia and PPH associated with patterns of prenatal antidepressant exposure.

Methods

Data source and study cohort

We utilized OptumLabs® Data Warehouse (OLDW), an administrative health care datasource of commercially insured enrollees with comprehensive insurance coverage for physician, hospital and prescription drug services. Specifically, we used a de-identified claims database that contains longitudinal health information on over 200 million unique lives, including a mixture of ethnicities and US geographical regions.[29] Analyses were performed using R. Per OptumLabs policy, counts less than 11 and corresponding crude risk ratios were suppressed. The research was determined to be exempt from oversight by the University of California San Diego Institutional Review Board.

International Classification of Disease (ICD) 9 or 10 diagnosis or procedure codes and Current Procedural Terminology (CPT) procedure codes used to define deliveries, outcomes, and covariates, and medications of interest are listed in the supplement (eTable 1).

We identified 585,902 live-born deliveries between 2012 and 2016 among females ages 12–49 using delivery-related diagnosis and procedure codes. Women could have more than one delivery identified because of more than one birth during the study period or because of multiple delivery-related claims for the same delivery. Therefore, we linked mothers and newborns to eliminate multiple delivery dates for the same delivery by matching on Family ID and by matching the newborn's earliest insurance coverage date with the date associated with the woman's delivery-related code. Because gestational age at delivery was not available, we set the date of the last menstrual period (LMP) to 35 weeks before delivery for those with diagnosis codes for preterm birth and 39 weeks otherwise, consistent with previous research.[30] Then, to help ensure complete claims information during the study period, we excluded deliveries from women who did not have continuous enrollment with medical and pharmacy benefits 3 months before LMP through 3 months post-delivery. We excluded deliveries with newborns who did not have continuous benefits during the first 3 months after birth. There were 226,932 deliveries from 208,271 women after implementing linkage, applying enrollment criteria, and restricting to singleton births.

Outcomes

Preeclampsia was identified from diagnosis codes present from 140 gestational days through 14 days after delivery.[9,10] PPH was based on diagnosis codes within 14 days after delivery.

Antidepressant exposure

We used antidepressant pharmacy dispensing information from 3 months before the LMP through 35 gestational weeks, i.e., consistent with the assigned gestational length for preterm births. Dispensing date plus the number of days supply of antidepressant that was dispensed was used to determine days with antidepressant exposure between LMP and 35 gestational weeks. Dose on each day was determined by multiplying the antidepressant's strength by the number of drug units per day and then converting to fluoxetine-equivalent dose.[31] The doses for multiple antidepressant agents per day were summed. However, multiple overlapping dispensings for the same antidepressant agent per day were counted only once, retaining exposure from only the highest dose. Doses were expressed as average daily dose (mg/day) per week.

Antidepressant trajectories

We used k-means longitudinal to cluster women into groups with similar individual trajectories of antidepressant exposure.[32] We implemented the method using R statistical software package '*kml*'[33] allowing for k=2 to k=8 clusters. We selected the number of clusters for further analysis based on: 1) optimization of 3 statistical quality criterion,[32] 2) clinical relevance of the trajectories, and 3) at least 200 women per cluster. To assess the association with preeclampsia, we identified antidepressant trajectories from LMP through 20 gestational weeks. Although the pathophysiology of preeclampsia may initiate earlier, preeclampsia diagnosis occurs at 20 weeks or later.[34] For PPH, we identified antidepressant

trajectories from LMP through 35 gestational weeks. We plotted the mean dose for each cluster, i.e., trajectory group, for each gestational week during the period of interest. Five clusters best described both periods (Figure 1).

Covariates

Depression, anxiety, other mental health disorders, pain disorders and sleep disorders, i.e., possible antidepressant indications, were identified from diagnosis codes from LMP through 20 gestional weeks for preeclampsia and through 35 gestational weeks for PPH, and antipsychotic and benzodiazepine exposures were identified from pharmacy dispensings with supply overlapping the same time frames. Diagnosis of maternal preexisting hypertension was assessed in the 3 months before LMP. Finally, we obtained information on maternal age at delivery, race, and education closest to the LMP from enrollment files. We did not have data on parity, although we do not consider it to be a confounder in this study as we do not expect it to be associated with antidepressant exposure patterns independent of age.

Analyses

We estimated risk ratios (RR) and 95% confidence intervals (CI) for the association between exposure groups and the outcomes using log-linear regression with a Poisson distribution and robust standard errors to account for correlations within women with more than one delivery identified during the study period.[35] For the primary analysis, we a priori restricted to antidepressant-exposed pregnancies and the lowest trajectory group was the referent group. We used an active comparator as the reference in the primary analysis to reduce confounding by disease severity because we expected pregnant women with antidepressant exposure to be more similar with respect to unmeasured confounders than pregnant women with depression or anxiety who are treated versus not treated with antidepressants. We adjusted for potential confounders including maternal age, race/ethnicity, education, depression, anxiety, pain, other mental health disorders, antipsychotic medications and benzodiazepines. Even with the large data set, some trajectories had 50 or fewer outcomes. Therefore, we aimed for parsimonious models and did not adjust for maternal preexisting hypertension or sleep disorders because they did not vary greatly by exposure status. Moreover, we did not adjust for delivery year because doing so did not materially change our estimates. For each model, we created a categorical variable for trajectory group (one level per group) and included it as a continuous variable to assess linear trend of increasing trajectory group with increasing outcome risk, and included continuous and quadratic terms to assess quadratic trend.

We conducted a multiply adjusted probabistic bias analysis of the crude associations comparing highest versus lowest trajectory groups, adjusting for differential exposure misclassification due to incorrect estimation of the LMP, adjusting for unmeasured confounding due to obesity and smoking, and accounting for random error.[36,37] We report 95% simulation limits and median simulation RR estimates. Additional methodologic details are in the supplement (eMethods). Separately, we calculated E-values from adjusted RRs comparing the highest versus lowest trajectory groups (Tables 3–4) to identify the minimum

association needed between an unmeasured confounder and the exposure and the outcome, conditional on the adjusted covariates, to nullify the RRs.[37,38]

In secondary analyses, we included women with a depression diagnosis or an anxiety diagnosis (during the relevant exposure period) without antidepressant dispensings as the reference groups, separately. We made this comparison to help inform the risk-benefit tradeoff of antidepressant treatment that women and their providers may consider when making decisions about treatment of depression and anxiety during pregnancy. Previous studies have reported differing risks of preeclampsia and PPH according to antidepressant class, e.g., serotonin-norepinephrine reuptake inhibitors (SNRI) and tricyclic antidepressants were associated with stronger risks for preeclampsia than selective serotonin reuptake inhibitors (SSRI),[9,10] and SNRIs were associated with a stronger risk for PPH than SSRIs.[18] In a sensitivity analysis, we restricted to pregnancies exposed to SSRIs only; the study size was insufficient to compare non-SSRIs.

Results

Cohort characteristics

Between LMP and 35 gestational weeks, there were 15,041 (6.6%) pregnancies exposed to an antidepressant, 4,949 (2.2%) with a depression diagnosis not exposed to an antidepressant, and 9,406 (4.4%) with an anxiety diagnosis not exposed to an antidepressant. Of the latter two groups, 1,775 had both a diagnosis of depression and anxiety. Overall, the 27,621 women with antidepressants, or depression or anxiety disorders were most often between the ages of 25–34 years old, White, and had more than a high school degree and less than a Bachelor's degree (Table 1). Women with depression and anxiety diagnoses without antidepressants during the first 35 gestational weeks were more often non-White compared with those with antidepressants. Among women with antidepressant exposure, 69.9% had SSRI monotherapy, 6.6% had SNRI monotherapy, and 8.9% had bupropion monotherapy.

Trajectory groups

In the k-means longitudinal analysis, 5 trajectories best described antidepressant exposure through 20 and 35 gestational weeks (Figure 1, Table 2). For both of these timeframes, trajectory groups were characterized by (A) low exposure of approximately 10mg/day with 1st trimester reduction or discontinuation, (B) low sustained exposure of approximately 20 mg/day, (C) moderate exposure of approximately 40mg/day with 1st trimester reduction or discontinuation, (D) moderate sustained exposure of approximately 40 mg/day, and (E) high sustained exposure of approximately 75mg/day. As illustrated by the median average daily fluoxetine equivalent dose of 0 mg/day in trajectories A and C, discontinuation was common in these groups. For the 35-week reduction/discontinuation trajectory groups (A, C), the percentages of women that had no antidepressant exposure beyond week 13 were 60% and 61%, respectively, and the percentages with no antidepressant exposure after week 27 were 71% and 82%, respectively.

Maternal characteristics differed by 35-week trajectory groups (Table 1). Women with 1st trimester antidepressant reduction or discontinuation, either from low or moderate doses (Trajectories A and C), more often were Black or Hispanic and had a high school diploma or less education compared with those that had sustained low, moderate or high doses. Women who reduced or discontinued from low doses (Trajectory A) tended to be younger with fewer mental health diagnoses and less psychotropic medication exposure than women in other trajectories, however these patterns did not hold for women who reduced or discontinued from moderate doses (Trajectory C). Women in the high sustained group (Trajectory E) more often had psychiatric diagnoses and antipsychotic or benzodiazepine exposure between 3 months before the LMP and 35 gestational weeks than women in the other trajectories.

Preeclampsia

The risk for preeclampsia in the lowest trajectory group was 8.2% (Table 3). Compared with this group, low, moderate, or high sustained antidepressant exposure (Trajectories B, D, and E) were associated with increased preeclampsia risk [adjusted (a)RR: 1.17 (95% CI: 1.01, 1.34), aRR: 1.31 (95% CI: 1.12, 1.54), aRR: 1.41 (95% CI: 1.05, 1.90), respectively], and $p < 0.01$ for linear trend. Moderate exposure with 1st trimester reduction/discontinuation (Trajectory C) was not associated with an increased risk of preeclampsia. In secondary analysis, the risk for preeclampsia among women with depression and no antidepressant exposure was 8.5% and it was 8.2% among women with anxiety and no antidepressant exposure (Table 3). All trajectory groups included 1 in the confidence interval when compared with a depression diagnosis without antidepressants, although the moderate and high sustained exposure groups (Trajectories D and E) suggested an increased risk of preeclampsia. When compared with an anxiety diagnosis without antidepressants, associations with preeclampsia appeared to be elevated with moderate sustained (Trajectory D) and high sustained (Trajectory E) exposures.

PPH

The risk for PPH in the lowest trajectory group was 2.7% (Table 4). Compared with this group, low, moderate or high sustained antidepressant exposure (Trajectories B, D, and E) was associated with increased risk of PPH [aRR: 1.32 (1.05, 1.66), aRR: 1.35 (95% CI: 1.03,1.78), aRR: 2.51 (95% CI: 1.69, 3.71), respectively], and $p < 0.01$ for linear trend. Moderate dose with reduction or discontinuation early in pregnancy (Trajectory C) was not associated with an increased risk of PPH (Table 4). In secondary analysis, the risk for PPH among women with depression and no antidepressant exposure was 3.4% and it was 2.7% among women with anxiety and no antidepressant exposure (Table 4). Findings generally attenuated when compared with women with depression and no antidepressants, although the risk for PPH remained elevated among women with high sustained exposure (Trajectory E; aRR: 2.09 (95% CI: 1.41, 3.08)). The associations indicating increased PPH risk for low, moderate and high sustained antidepressant exposure (Trajectories B, D, and E) were similar between the primary comparison group and when the reference group was women with anxiety and no antidepressans [Table 4; aRR: 1.34 (95% CI: 1.07, 1.67), aRR: 1.39 (95% CI: 1.06, 1.81), aRR: 2.62 (95% CI: 1.78, 3.85), respectively].

Bias analyses

The crude RR comparing the highest versus the lowest trajectory groups attenuated for preeclampsia (median simulation RR: 1.33, (95% simulation limits: 0.99, 1.76)) and did not change materially for PPH (median simulation RR: 2.67, (95% simulation limits: 1.87, 3.89)) when adjusting for differential exposure misclassification due to incorrect estimatimation of the LMP and confounding by obesity and smoking. The E-value indicating the minimum association between an unmeasured confounder and the exposure and the outcome needed to explain the aRR comparing the highest versus lowest trajectory group and preeclampsia was 2.17, and it 4.46 was for PPH.

SSRI only analyses

After restricting to pregnancies with SSRI monotherapy, the risk of preeclampsia and PPH tended to be lower compared with examining all antidepressants, particularly at higher doses. These lower risks resulted in slightly attenuated risk ratios for the highest dose trajectory group (Table 5).

Comment

Principal findings

Women with sustained antidepressant exposure, compared with women who started pregnancy with low antidepressant exposure and reduced dose or discontinued during the first trimester, were at increased risk for preeclampsia and PPH. There was a trend of higher dose exposures being associated with the highest risk of these outcomes.

Furthermore, we observed that after adjusting for potential measured confounders, the risk for preeclampsia and PPH was somewhat similar between women with depression without antidepressant exposure and most antidepressant exposure groups, with the exception of the high sustained exposure groups. This finding informs risk-benefit tradeoff of antidepressant use during pregnancy, suggesting that many patterns of antidepressant exposure are no worse for preeclampsia and PPH than depression not treated with antidepressants, or factors associated with untreated depression. In contrast, risk for PPH was higher in the sustained antidepressant exposure groups than anxiety not treated with antidepressants. Preeclampsia risk was higher across all groups (8%−13%) than the expected 5%,[39] whereas PPH risk was similar (3%−7%) to previous reports of 3–6%.[40,41]

Interpretation

We observed a group of women who reduced or discontinued antidepressants in the first trimester, which has been reported in previous studies.[5,8,24] These women tended to have lower risks for preeclampsia and PPH than women with sustained antidepressant exposure. However, results may reflect confounding by underlying disease severity associated with sustained antidepressant exposure as we did not have clinical measures of depression and anxiety severity.[42] We attempted to mitigate this by adjusting for co-exposure to other psychotropic medications and central nervous system comorbidities.

Similar to our study, use of antidepressants into the second trimester has been associated with an increased risk of preeclampsia in some previous studies.[8–13] Studies have differed in whether SSRI antidepressants in particular are associated with preeclampsia or not. In our study, moderate and high sustained SSRI exposure appeared to be associated with at least a borderline increased risk of preeclampsia.

Many studies have reported an increased[13,14,16–19] or borderline increased risk[43] for PPH associated with antidepressants late in pregnancy. The two studies that have not reported this association have had 18 or fewer exposed cases.[22,23] Our results are in line with previous large studies, each with more than 55 exposed cases, that found antidepressant use late in pregnancy was associated with an increased risk of PPH.[13,14,16–19] Related to our finding that higher sustained doses of antidepressants were associated with higher PPH risk, one previous study among low income women reported a dose response for serotonin reuptake inhibitors (SRI), but not non-SRIs.[14] Proposed mechanisms for the effect include interference by SRI antidepressants with serotonin-mediated platelet aggregation and uterine myometrial contraction after delivery.[14,44,45] Here, the cluster based analysis approach was of interest, as it allowed for the isolation of late exposure (Trajectories B, D and E) as opposed to early moderate exposure with reduction/discontinuation (Trajectory C). Our results of increased risk in the sustained exposure trajectories versus early reduction/ dicontinuation support targeted investigations into mechansisms in the later gestational weeks.

Limitations

In addition to being unable to account for depression and anxiety severity linked with higher antidepressant doses and sustained exposures, limitations of this research include that we had to make assumptions about antidepressant dose and gestational timing of use based on pharmacy dispensing data without maternal confirmation and gestational length from diagnosis codes for preterm birth instead of gestational age at delivery. The trajectory shapes and women's membership within the groups may have differed from what they would have been without exposure misclassification. Bias analysis adjusting for exposure misclassification due to LMP estimation indicated that this source of systematic error did not impact our point estimates greatly. Furthermore, a limitation of k-means longitudinal is that each trajectory group contains some individual heterogeneity in antidepressant exposure and only common patterns of antidepressant exposure emerge as separate trajectories. For example, we expect some women to initiate antidepressant use during pregnancy and some women in the high sustained exposure group to have dose reductions. However k-means longitudinal did not identify trajectory groups with such patterns and these women would have been included in other trajectory groups. Nevertheless, this approach allows for more well-defined exposure groups than the traditional any exposure vs none approach that is often used when studying antidepressants in pregnancy.

Additionally, we included live birth deliveries only and selection bias could impact the results if one of the exposure patterns were associated with pregnancy loss or stillbirth. Also, women in this study had commercial insurance who were enrolled before pregnancy and findings may not generalize to women with public insurance. Finally, variables such as

smoking, alcohol use and obesity are not captured well by health care claims data. Bias analysis indicated that overall, adjusting for smoking and obesity would likely have attenuated the results for preeclampsia but would not have strongly impacted the results for PPH. E-values indicated that very strong umeasured confounding would be needed to explain the association between high sustained antidepressant exposure versus low exposure with reduction/discontinuation and PPH.

Conclusions

Compared with the lowest antidepressant exposure pattern, sustained antidepressant exposure during gestation was associated with an increased risk of preeclampsia and PPH, especially for the highest antidepressant doses. Although in most cases, the risk for the outcomes associated with sustained antidepressant exposure was no higher or only modestly higher than the risk associated with depression not treated with antidepressants, suggesting the risks for preeclampsia and postpartum hemorrhage associated with untreated depression. Regardless of confounding by underlying depression and anxiety severity, providers should be aware of the increased risk of preeclampsia and PPH among women with sustained antidepressant use, especially use at higher doses, during pregnancy.

Clinical guidance supports pharmacologic or non-pharmacologic treatments of depression and anxiety disorders during pregnancy given the effects of untreated disorders.[1–4,46,47] Moreover, although the data are limited,[48–50] evidence suggests that women who discontinue antidepressant use during or shortly before pregnancy are at increased risk for depression relapse compared with women who continue to use antidepressants. Our study focuses on two perinatal outcomes and should be considered in context with data on the spectrum of maternal and child health outcomes to inform appropriate medication treatment decisions during pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Synopsis

Study question:

What is the association between patterns of prenatal antidepressant exposure, in terms of dose and gestational timing, and risk of precclampsia and postpartum hemorrhage?

What's already known:

Antidepressant exposures into the second trimester have been associated with preeclampsia and antidepressant exposures late in pregnancy have been associated with postpartum hemorrhage (PPH) in some studies. Other studies, particularly those with smaller numbers of exposed cases, conclude no association between antidepressants and these outcomes.

What this study adds:

Compared with first trimester reduction/discontinuation of antidepressant dose, sustatined antidepressant exposure was associated with increased preeclampsia and postpartum hemorrhage risks, especially for higher doses. However, our data suggested that many patterns of antidepressant exposure are no worse for preeclampsia and postpartum hemorrhage risk than untreated depression.

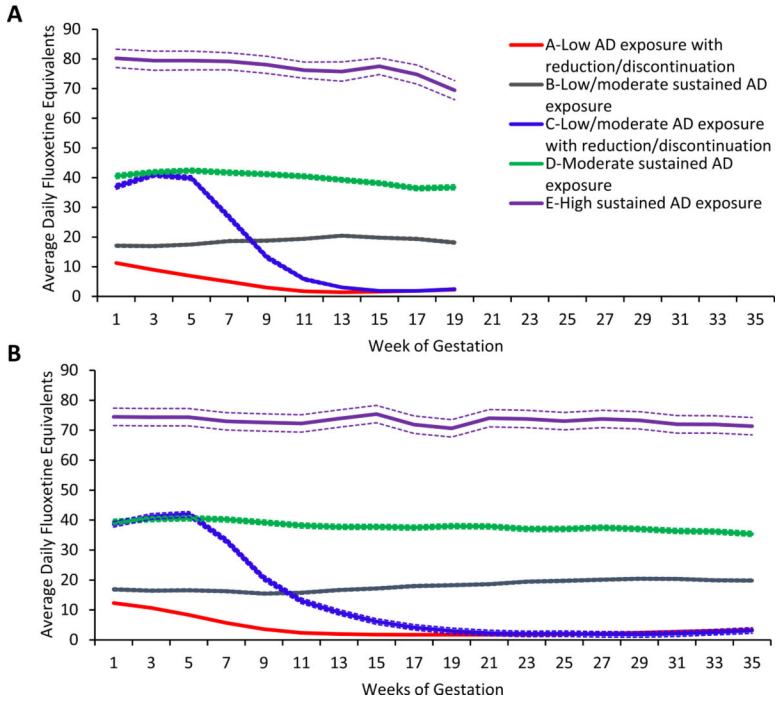

Figure 1.

Average daily flouxeine equivalent dose per week by gestational week for A) 20-week and B) 35-week antidepressant (AD) trajectory groups.

Table 1.

Maternal characteristics according to antidepressant trajectory group, depression with no antidepressants, or anxiety with no antidepressants during the first 35 weeks of gestation (n=27,621).

Characteristics n, (%)	Trajectory A Low AD exposure with reduction/ discontinuation	Trajectory B Low/ moderate sustained AD exposure	Trajectory C Moderate AD exposure with reduction/ discontinuation	Trajectory D Moderate sustained AD exposure	Trajectory E High sustained AD exposure	Depression no AD[a]	Anxiety no AD[a]
	n=7,622	n=3,170	n=1,907	n=1,918	n=424	n=4,949	n=9,406
Maternal age							
<25 years	269 (3.5)	69 (2.2)	44 (2.3)	18 (0.9)	<11 (<2.6)	162 (3.3)	254 (2.7)
25–34 years	4942 (64.8)	1936 (61.1)	1146 (60.1)	1101 (57.4)	>224 (>52.8)	3102 (62.7)	6023 (64.0)
>34 years	2411 (31.6)	1165 (36.8)	717 (37.6)	799 (41.7)	189 (44.6)	1685 (34.0)	3129 (33.3)
Number of births in study period							
1	7065 (92.7)	2915 (92.0)	1797 (94.2)	1761 (91.8)	384 (90.6)	4343 (87.8)	8334 (88.6)
≥2	557 (7.3)	255 (8.0)	110 (5.8)	157 (8.2)	40 (9.4)	606 (12.2)	1072 (11.4)
Maternal race							
White	6148 (80.7)	2738 (86.4)	1585 (83.1)	1676 (87.4)	365 (86.1)	3741 (75.6)	7161 (76.1)
Black	503 (6.6)	140 (4.4)	124 (6.5)	80 (4.2)	23 (5.4)	378 (7.6)	598 (6.4)
Hispanic	643 (8.4)	155 (4.9)	119 (6.2)	93 (4.9)	24 (5.7)	454 (9.2)	936 (10.0)
Other or unknown	328 (4.3)	137 (4.3)	79 (4.1)	69 (3.6)	12 (2.8)	376 (7.6)	711 (7.6)
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)	725 (14.6)	1233 (13.1)
Less than Bachelor's degree	4401 (57.7)	1825 (57.6)	1062 (55.7)	1091 (56.9)	244 (57.6)	2756 (55.7)	4939 (52.5)
Bachelor's degree or higher	1821 (23.9)	918 (29.0)	487 (25.5)	591 (30.8)	134 (31.6)	1468 (29.7)	3234 (34.4)
Comorbidities and co-exposures[b]							
Depression	2270 (29.8)	1279 (40.4)	812 (42.6)	932 (48.6)	282 (66.5)	4949 (100.0)	1775 (18.9)
Anxiety	2838 (37.2)	1406 (44.4)	867 (45.5)	924 (48.2)	258 (60.8)	1775 (35.9)	9406 (100.0)
Other mental health diagnosis	1360 (17.8)	754 (23.8)	429 (22.5)	506 (26.4)	157 (37.0)	1334 (27.0)	1909 (20.3)
Pain	1349 (17.7)	514 (16.2)	355 (18.6)	345 (18.0)	104 (24.5)	855 (17.3)	1825 (19.4)
Sleep disorder	427 (5.6)	145 (4.6)	133 (7.0)	109 (5.7)	33 (7.8)	220 (4.5)	499 (5.3)
Hypertension	210 (2.8)	73 (2.3)	62 (3.3)	63 (3.3)	13 (3.1)	128 (2.6)	268 (2.8)

Characteristics n, (%)	Trajectory A Low AD exposure with reduction/ discontinuation	Trajectory B Low/ moderate sustained AD exposure	Trajectory C Moderate AD exposure with reduction/ discontinuation	Trajectory D Moderate sustained AD exposure	Trajectory E High sustained AD exposure	Depression no AD[a]	Anxiety no AD[a]
	n=7,622	n=3,170	n=1,907	n=1,918	n=424	n=4,949	n=9,406
Antipsychotics	55 (0.7)	44 (1.4)	52 (2.7)	74 (3.9)	40 (9.4)	50 (1.0)	52 (0.6)
Benzodiazepines	657 (8.6)	292 (9.2)	280 (14.7)	269 (14.0)	112 (26.4)	220 (4.4)	731 (7.8)

AD=antidepressant; cell sizes <11 are suppressed per requirements of OptumLabs

[a]1,775 women have depression and anxiety diagnoses and are in both the depression and no AD group and the anxiety and no AD group.

[b]Diagnosis or pharmacy dispensing through 35 gestational weeks.

Table 2.

Mean, standard deviation (SD), and median, interquartile range (IQR) of average daily fluoxetine equivalent dose (mg/day) per week for 20- and 35-week trajectory groups.

	20-week trajectories fluoxetine equivalent dose mg/day			35-week trajectories fluoxetine equivalent dose mg/day		
Trajecory Group	**N**	**Mean (SD)**	**Median (IQR)**	**N**	**Mean (SD)**	**Median (IQR)**
Trajectory A-Low AD exposure with reduction/discontinuation	7414	4.2 (8.3)	0.0 (0.0)	7622	3.7 (8.2)	0.0 (0.0)
Trajectory B- Low/moderate sustained AD exposure	3108	18.6 (12.9)	20.3 (17.9)	3170	18.1 (13.4)	20.3 (15.9)
Trajectory C- Low/moderate AD exposure with reduction/discontinuation	2118	16.5 (22.0)	0.0 (20.3)	1907	12.5 (20.5)	0 (22.2)
Trajectory D-Moderate sustained AD exposure	2010	40.2 (18.8)	40.6 (14.4)	1918	37.9 (18.9)	40.6 (11.1)
Trajectory E-High sustained AD exposure	391	76.7 (30.9)	80.1 (21.2)	424	73.1 (30.4)	80 (20.9)

AD, antidepressant

Table 3.

Associations between antidepressant (AD) 20-week trajectory groups and risk of preeclampsia with women in trajectory group A as the primary comparison and women with depression and no AD and women with anxiety and no AD as secondary comparisons.

Exposure Group	Preeclampsia	Trajectory A as reference		Depression and no AD as reference		Anxiety and no AD as reference	
	n (%)	Crude RR (95% CI)	Adjusted RR (95% CI) [a]	Crude RR (95% CI)	Adjusted RR (95% CI) [a]	Crude RR (95% CI)	Adjusted RR (95% CI) [a]
Trajectory A-Low AD exposure with reduction/ discontinuation	606 (8.2)	1.00 (Reference)	1.00 (Reference)	0.97 (0.85, 1.09)	0.88 (0.77, 1.02)	0.99 (0.89, 1.11)	0.88 (0.79, 1.00)
Trajectory B-Low sustained AD exposure	295 (9.5)	1.16 (1.01, 1.33)	1.17 (1.01, 1.34)	1.12 (0.97, 1.30)	1.03 (0.88, 1.21)	1.16 (1.01, 1.32)	1.05 (0.91, 1.21)
Trajectory C- Moderate AD exposure with reduction/ discontinuation	178 (8.4)	1.03 (0.87, 1.22)	1.00 (0.84, 1.18)	0.99 (0.83, 1.18)	0.89 (0.74, 1.07)	1.02 (0.87, 1.20)	0.89 (0.75, 1.06)
Trajectory D-Moderate sustained AD exposure	221 (11.0)	1.35 (1.15, 1.57)	1.31 (1.12, 1.54)	1.30 (1.10, 1.53)	1.17 (0.99, 1.40)	1.34 (1.15, 1.55)	1.18 (1.01, 1.39)
Trajectory E-High sustained AD exposure	49 (12.5)	1.53 (1.15, 2.05)	1.41 (1.05, 1.90)	1.48 (1.10, 1.99)	1.28 (0.95, 1.74)	1.52 (1.14, 2.04)	1.29 (0.96, 1.74)
Depression no AD	419 (8.5)	NA	NA	1.00 (Reference)	1.00 (Reference)	NA	NA
Anxiety no AD	773 (8.2)	NA	NA	NA	NA	1.00 (Reference)	1.00 (Reference)

[a] Adjusted for maternal age, race/ethnicity, education, diagnosis of depression, anxiety, other mental health disorders, and pain disorder within first 20 gestational weeks, and benzodiazepines and antipsychotics dispensings overlapping with the first 20 gestational weeks.

Table 4.

Associations between antidepressant (AD) 35-week trajectory groups and risk of postpartum hemorhage (PPH) with women in trajectory group A as the primary comparisons and women with depression and no AD and women with anxiety and no AD as secondary comparisons.

Exposure Group	PPH	Trajectory A as reference		Depression and no AD as reference		Anxiety and no AD as reference	
	n (%)	Crude RR (95% CI)	Adjusted RR (95% CI) [a]	Crude RR (95% CI)	Adjusted RR (95% CI) [a]	Crude RR (95% CI)	Adjusted RR (95% CI) [a]
Trajectory A-Low AD exposure with reduction/discontinuation	204 (2.7)	1.00 (Reference)	1.00 (Reference)	0.78 (0.63, 0.96)	0.79 (0.65, 0.98)	0.99 (0.82, 1.19)	1.01 (0.84, 1.22)
Trajectory B- Low sustained AD exposure	116 (3.7)	1.36 (1.09, 1.72)	1.32 (1.05, 1.66)	1.07 (0.84, 1.35)	1.06 (0.83, 1.34)	1.36 (1.09, 1.69)	1.34 (1.07, 1.67)
Trajectory C- Moderate AD exposure with reduction/ discontinuation	50 (2.6)	0.98 (0.72, 1.33)	0.95 (0.69, 1.30)	0.76 (0.56, 1.05)	0.77 (0.56, 1.06)	0.97 (0.72, 1.31)	0.98 (0.72, 1.33)
Trajectory D-Moderate sustained AD exposure	73 (3.8)	1.42 (1.09, 1.86)	1.35 (1.03, 1.78)	1.11 (0.84, 1.46)	1.10 (0.83, 1.45)	1.41 (1.09, 1.83)	1.39 (1.06, 1.81)
Trajectory E-High sustained AD exposure	31 (7.3)	2.73 (1.87, 3.99)	2.51 (1.69, 3.71)	2.13 (1.45, 3.12)	2.09 (1.41, 3.08)	2.71 (1.86, 3.93)	2.62 (1.78, 3.85)
Depression no AD	170 (3.4)	NA	NA	1.00 (Reference)	1.00 (Reference)	NA	NA
Anxiety no AD	254 (2.7)	NA	NA	NA	NA	1.00 (Reference)	1.00 (Reference)

NA, not applicable.

[a]Adjusted for maternal age, race/ethnicity, education, diagnosis of depression, anxiety, other mental health disorders, and pain disorder during first 35 gestational weeks, and benzodiazepine and antipsychotic dispensings overlapping the first 35 gestational weeks.

Table 5.

Associations between antidepressant (AD) trajectory groups and risks of preeclampsia and postpartum hemorrhage (PPH) with women in trajectory group A as the comparison, restricting to selective serotonin reuptake inhibitor antidepressants (SSRIs).

20-Week trajectory groups	**N**	**Preeclampsia n (%)**	**Crude RR (95% CI)**	**Adjusted RR (95% CI)[a]**
Trajectory A-Low SSRI exposure with reduction/discontinuation	5546	424 (7.7)	1.00 (Reference)	1.00 (Reference)
Trajectory B- Low sustained SSRI exposure	2395	209 (8.7)	1.14 (0.97, 1.34)	1.14 (0.96, 1.33)
Trajectory C- Moderate SSRI exposure with reduction/discontinuation	1167	98 (8.4)	1.10 (0.89, 1.36)	1.06 (0.87, 1.31)
Trajectory D-Moderate sustained SSRI exposure	1241	127 (10.2)	1.34 (1.11, 1.62)	1.30 (1.07, 1.57)
Trajectory E-High sustained SSRI exposure	168	18 (10.7)	1.40 (0.90, 2.19)	1.28 (0.81, 2.01)
35-Week trajectory groups	**N**	**PPH n (%)**	**Crude RR (95% CI)**	**Adjusted RR (95% CI)[b]**
Trajectory A-Low SSRI exposure with reduction/discontinuation	5636	137 (2.4)	1.00 (Reference)	1.00 (Reference)
Trajectory B- Low sustained SSRI exposure	2430	105 (4.3)	1.78 (1.38, 2.28)	1.69 (1.31, 2.18)
Trajectory C- Moderate SSRI exposure with reduction/discontinuation	1057	21 (2.0)	0.82 (0.52, 1.29)	0.78 (0.50, 1.23)
Trajectory D-Moderate sustained SSRI exposure	1206	44 (3.7)	1.50 (1.07, 2.10)	1.38 (0.99, 1.93)
Trajectory E-High sustained SSRI exposure	188	<11 (<5.9)	suppressed	1.50 (0.73, 3.08)

[a] Adjusted for maternal age, race/ethnicity, education, diagnosis of depression, anxiety, other mental health disorders, and pain disorder during the first 20 weeks of gestation, and benzodiazepine and antipsychotic dispensings overlapping with the first 20 gestational weeks

[b] and the first 35 gestational weeks.

Cell sizes <11 are suppressed per requirements of OptumLabs.