RESEARCH ARTICLE

Trajectories of Depressive and Anxiety Symptoms Across Pregnancy and Postpartum in Selective Serotonin Reuptake Inhibitor-Treated Women

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Objective: Tracking perinatal mood and anxiety disorders is championed by the American Psychiatric Association and the International Marcé Society for Perinatal Mental Health. We conducted this study to examine trajectories of monthly depressive and anxiety symptoms through pregnancy and postpartum.

Methods: This is a prospective longitudinal observational cohort study of pregnant women interviewed at baseline (≤18th gestational week), every four weeks through delivery and at 6 and 14 weeks postpartum at three urban academic medical centers ($N = 85$) and a single rural health center ($N = 3$) from 2016 to 2020. Pregnant women had at least one prior episode of major depressive disorder, were not in a current episode, and were treated with sertraline, fluoxetine, citalopram, or escitalopram. Of 192 women screened, 88 (46%) women enrolled, and 77 (88%) women completed the postpartum follow-up. Symptom trajectories were generated with scores from the Edinburgh Postnatal Depression Scale, the Quick Inventory of Depressive Symptoms, the Generalized Anxiety Disorder Scale, 7-item, and the Patient-Reported Outcomes Measurement Information System Global Health measure. A semi-parametric, group-based mixture model (trajectory analysis) was applied.

Results: Three relatively stable depression trajectories emerged, described as Minimal, Mild, and Subthreshold, in each group across pregnancy. Two of the four anxiety trajectories were stable, including Asymptomatic and Minimal, while the third, termed Breakthrough, was ascending with increasing symptoms and the fourth trajectory, described as Mild, had descending symptoms.

Conclusions: Screening for anxiety with depression for pregnant women will yield a comprehensive view of psychiatric symptoms and treatment targets in perinatal women.

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Sustaining remission through the use of medication of perinatal major depressive disorder (MDD) is essential for achieving optimal maternal and offspring health (1, 2). Given the high comorbidity, clinical guidelines recommend screening for anxiety disorders in women with perinatal MDD (3–7), the individual symptom trajectories of anxiety and depression vary across pregnancy to postpartum (8–11). Multilevel modeling of self-report measures of perinatal depressive and anxiety symptoms reflect symptom heterogeneity within samples and identify distinct groups of women (12), though this approach has yet to elucidate these trajectories in perinatal women treated with antidepressants, despite the large number of women who rely on this treatment modality (13).

Studies of cohort and community samples (3, 11, 14–20) from general populations of pregnant women support three observations about the naturalistic trajectories of anxiety and depressive symptoms. First, a significant proportion of women (14.6% of Swedish cohort sample (16); 42.3% of Canadian community sample (11); 30% of a Finnish community sample (14); and 23.4% of a Brazilian cohort sample (19)) report chronic depression and/or continuous anxiety symptoms during the perinatal period. Second, between three to five trajectory groups emerge, characterized by descriptors of symptom severity (low, moderate), timing (antepartum, postpartum), and chronicity (stable, variable) (3, 11, 14–20). Third, the reported symptom intensity is greater in women with established

depression risk factors, which include pre-pregnancy depression, psychosocial stressors and socioeconomic disadvantage (3, 19, 20). Collectively, these naturalistic studies show that chronic depressive and anxiety symptoms across the perinatal period may be understood as trajectories defined by symptom severity, timing, and course stability.

The expected result of antidepressant maintenance treatment during pregnancy and postpartum is the continuous control of depressive and anxiety symptoms. Selective serotonin reuptake inhibitor (SSRI) antidepressants are commonly prescribed to treat MDD and anxiety disorders in pregnant women (2); however, sustaining response during pregnancy is a clinical challenge due to its dynamic physiology and unique psychosocial milieu (16). In the FinnBrain Birth Cohort study of >3000 women (15), 3.1% were treated with SSRI during the third trimester. Two depression trajectory groups were identified in the SSRI-treated women (stable-high severity or increasing from moderate to high severity). These findings demonstrate that the SSRI are not fully effective in symptom control during pregnancy; however, the adequacy of treatment at study entry was not reported. The trajectory patterns, number of groups, and proportion of the sample of women who continue to respond to SSRI treatment across pregnancy remain undefined as prior studies did not report SSRI use (3, 14, 16, 18, 19) or excluded drug-treated women from enrollment (21). Our goal is to analyze the depressive and anxiety symptom trajectories across pregnancy and after birth in women who did not have syndromal MDD at entry and who were maintained on one of the four commonly prescribed SSRI antidepressants that have equivalent effectiveness (22).

We examine the following questions: What is the symptom course of SSRI-treated women across childbearing? Do depressive and anxiety symptoms vary together? Do symptoms increase after birth?

HIGHLIGHTS

- Question: What are the trajectories of depression and anxiety symptoms across pregnancy and postpartum in women who continue to take Selective serotonin reuptake inhibitor (SSRI) antidepressants?
- Findings: In this prospective longitudinal observational cohort study of pregnant women with antidepressant-treated remitted depression (N = 88), a substantive proportion of women had mild depression (32%) or anxiety (23%). Three trajectories were observed for depression, all relatively stable across time, and four were observed for anxiety, three stable and one increasing across time.
- Meaning: There is a relative stability of mild symptoms at study entry and across gestation in depression and anxiety symptom course, with three depression and four anxiety trajectories. There was one unique trajectory in anxiety symptom course with one group with ascending symptoms. Clinicians may use measures that are already part of perinatal visits to track and treat those women who fall into these trajectories to improve their mental health.

METHODS

Study Description

This prospective longitudinal observational cohort study entitled Optimizing Medication Management for Mothers with Depression (OPTI-MOM) included pregnant women (N = 88) enrolled in the NICHD-funded Obstetric-Fetal Pharmacology Research Center (OPRC) study (23). Women completed assessments every 4 weeks from study entry until delivery and at 6 and 14 weeks postpartum. Participants were enrolled at one of three urban academic medical centers (Northwestern University, University of Texas-Galveston, University of Pittsburgh; N = 85), or a rural health center (Marshfield Clinic Health System, WI, N = 3) from clinic referrals. The inclusion criteria included: (1) 18 to 45 years of age, (2) singleton pregnancy less than 18 weeks 0 days gestation, (3) a lifetime DSM-IV (24) diagnosis of MDD (any subtype), and (4) current treatment with sertraline, fluoxetine, citalopram, or escitalopram with the intent to continue through pregnancy and postpartum. The decision to continue SSRI treatment was made before enrollment by the subject and her prescriber, who continued to provide medication management. Subjects were excluded if they endorsed: (1) a lifetime Diagnostic and Statistical Manual Fourth Edition (DSM-IV) diagnosis of bipolar disorder or any psychotic episode, (2) substance dependence during the prior six months, or (3) a baseline Edinburgh Postnatal Depression Scale (EPDS) (25) score ≥ 15 or a score of 3 on EPDS item 10 (self-harm thoughts). A score of 15 or more is the validated EPDS screening cutoff for probable antenatal MDD (26). Women treated with other drugs or herbal supplements were excluded, with the exception of aspirin and drugs that are neither agonist nor antagonists of the study medications. All participants provided written informed consent approved by the Institutional Review Boards of the contributing sites and the STROBE criteria were followed.

Measures

To ascertain psychiatric history at study entry, evaluators used the *Mini-International Neuropsychiatric Interview* (27), a diagnostic evaluation based on Axis I DSM-IV (24). To ascertain depression symptom severity in the postpartum, the nine symptom domains of MDD, anxiety symptoms, and physical health at baseline and at each follow-up assessment, we used the following: 10-item *EPDS* (primary outcome measure, range 0–30) (25), the 16-item *Quick Inventory of Depressive Symptoms* (*QIDS-SR*$_{16}$) (28) (range 0–27), and the 7-item *Generalized Anxiety Disorder Scale, 7-item* (*GAD-7*) (29) (range 0–21), and

physical and mental T-scores on the 10-item *Patient-Reported Outcomes Measurement Information System Global Health* (*PROMIS-GH*) (30). T-scores are standardized to the general population.

Statistical Plan

We used descriptive statistics to summarize the demographic and clinical variables. Categorical variables are summarized as N (%) and continuous variables as mean ± standard deviation (SD). In cases of skewed distributions, we used median (interquartile range; IQR). For each of the continuous outcomes (EPDS, GAD-7, QIDS-SR_{16}, PROMIS-GH Physical and Mental), we summarized scores as mean ± SD by gestational age (weeks gestation).

To explore longitudinal patterns in these outcomes over time, we used a semiparametric, group-based, mixture modeling approach (trajectory analysis) with the SAS® Proc Traj plug-in (31). Trajectory analysis is a method of analyzing changes in outcome over time and grouping individuals according to patterns in trajectory shape. We allowed for one to five trajectories while analyzing each outcome separately. We used Bayesian Information Criteria to select the number of trajectories and to develop best-fitting trajectory shapes (Supplemental Analyses). After separating distinct trajectories and determining their shape(s), we evaluated the association of trajectory membership (outcome) with a set of pre-specified covariates (age, body mass index (BMI), race, and psychiatric comorbidities) with multinomial logistic regression models (age and BMI) and chi-squared (race and psychiatric comorbidities) or Fisher's exact tests in the presence of low cell counts. Trajectory information support clinical care: for example, a patient treated with SSRIs who endorses EPDS score below 4 at gestational month 4, analyses would assign them to a particular group (minimal symptoms) and a clinical could expect based on their trajectory to see their subsequent scores to stay low, that is, below 4, throughout pregnancy and the postpartum period.

We explored the association between depressive and anxiety symptom trajectories using Pearson Chi-squared tests, Spearman's correlation coefficient and Cohen's Kappa statistics. We summarized the number of prenatal and postpartum SSRI dose changes per woman both overall and by EPDS trajectory group with descriptive statistics. All analyses were conducted using SAS (The SAS Institute), assumed a two-sided, 5% level of significance, and did not include corrections for multiple hypothesis tests as the primary endpoint for this study was drug concentration and the present analyses are more exploratory in nature. The overall sample size and power considerations were originally guided by SSRI drug concentration endpoints (concentration analyses in process with results forthcoming). Therefore, no formal sample size calculations for symptom trajectory endpoints were developed. We planned to enroll a total of 200 participants treated with any of the four SSRIs. However, an interim analysis and the 2019 SARS CoV-2 pandemic-related cessation of recruitment resulted in the recommendation from our Data and Safety Monitoring Board to close enrollment at 88 participants. This interim analysis involved conditional power for the SSRI drug concentration outcome. The result of these analyses provided justification for early stopping based on that premise. No safety concerns occurred in this observational study.

All participants who were enrolled were included in analyses. There were no imputations for missing data, and the methods used in analyses based on maximum likelihood methodology are robust to unbalanced data.

RESULTS

Demographics

Among the 192 women completing eligibility screening, 88 (46%) were enrolled, with 77 (88%) contributing both prenatal and postpartum follow-up data (Figure 1). All participants identified as female, rather than transgender, nonbinary, or other. The mean gestational age at enrollment was 13 ± 3.1 weeks and women were 34 ± 3.4 years of age on average. Most women identified as White (89%), while 11% were Asian, Black/African American, Hispanic or multiracial (Table 1). All women remained on the same drug throughout pregnancy (sertraline, $n = 47$; fluoxetine, $n = 10$; citalopram, $n = 9$; escitalopram, $n = 22$).

Medical and psychiatric comorbidities. The mean pre-pregnancy BMI was 27 ± 5.8 kg/m^2, with 53% of participants classified as overweight or obese. Medical problems included reproductive health problems or infertility ($n = 18$, 20%); migraine headaches ($n = 16$, 18%); thyroid disorders ($n = 12$, 14%); and asthma ($n = 8$, 9%). None of the participants reported diagnoses of AIDS, HIV, cancer, chronic inflammatory bowel disease, stomach ulcer, diabetes, heart disease, hypertension, or stroke.

The majority (81%) of the participants were diagnosed with at least one psychiatric comorbidity: lifetime anxiety disorder ($n = 69$, 78%), substance abuse/dependence in the past 6–12 months ($n = 9$, 10%), or lifetime eating disorder ($n = 14$, 16%; Table 2). Three (3.4%) participants were diagnosed with all three comorbidities and 58% ($n = 51$) were diagnosed with a comorbid anxiety disorder only.

Trajectory Analysis

The mean and standard deviation for each relevant outcome across all study time points are summarized in Table 3. Three distinct trajectories emerged for EPDS scores across pregnancy and postpartum. For interpretation, we named these Minimal, Mild, and Subthreshold (Figure 2), which included 18%, 50%, and 32% of participants, respectively. The EPDS symptom scores in the Minimal trajectory tended to follow a quadratic trend ($\beta = -1.49$, p-value = 0.0248; β^2: 0.09, p-value = 0.0431),

FIGURE 1. CONSORT flow diagram

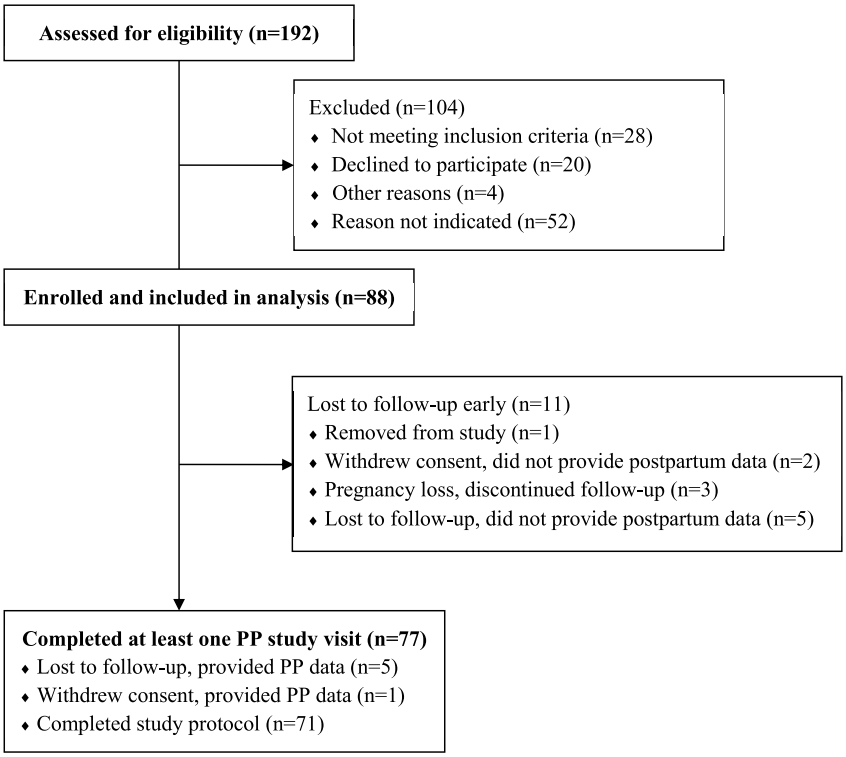


TABLE 1. Participant demographics and characteristics at study entry

Variable	Summary statistic or category	Summary statistic value
Age	Mean (std), range (year)	34 (3.4), (24–42)
Gestational age	Mean (std), range (weeks)	13 (3.1), (5–18)
Race	Asian, black, multiple races	10 (11%)
	White	78 (89%)
Ethnicity	Non-Hispanic	82 (93%)
	Hispanic	6 (7%)
Marital status	Married	82 (93%)
	Unmarried, living with a romantic partner	3 (3%)
	Never married or divorced	3 (3%)
Education	2-year post high school degree or less	7 (8%)
	4-year college degree	34 (39%)
	Advanced degree	47 (53%)
Occupation	Currently not employed	10 (11%)
	Currently employed	78 (89%)
Work status	Unemployed	10 (11%)
	Occasional or part-time	9 (10%)
	Full-time	69 (78%)
Insurance	Public (medicare/medicaid)	2 (2%)
	Private	86 (98%)
Income	Less than $50K	4 (5%)
	[$50K–$110K)	19 (22%)
	[$110K–$150K)	13 (15%)
	[$150K–$200K)	23 (26%)
	$200K or more	29 (33%)
Alcohol use	No	76 (94%)
Smoker	No	81 (100%)
Passive smoke	No	78 (97%)
	Yes	2 (3%)

TABLE 2. Psychiatric comorbidities

Variable	Overall *N* (%)
Anxiety disorder	69 (78%)
Panic disorder current	7 (8%)
Panic disorder lifetime	40 (45%)
Agoraphobia current	15 (17%)
Social phobia current	1 (1%)
Social phobia lifetime	17 (19%)
Obsessive compulsive disease, current	4 (5%)
Obsessive compulsive disease, lifetime	9 (10%)
Posttraumatic stress disorder current	4 (5%)
Posttraumatic stress disorder lifetime	13 (15%)
Generalized anxiety disorder current	25 (28%)
Generalized anxiety disorder lifetime	38 (43%)
Substance use	9 (10%)
Alcohol abuse or dependence (past year[a])	8 (9%)
Substance abuse or dependence (past year[a])	2 (2%)
Eating disorder	14 (16%)
Anorexia nervosa binge eating/Purging type current	1 (1%)
Anorexia nervosa lifetime	8 (9%)
Bulimia nervosa current	1 (1%)
Bulimia nervosa lifetime	8 (9%)

[a] Participants were not excluded if they endorsed substance use between 6 and 12 months prior to assessment.

with EPDS scores remaining low (<5) throughout the follow-up period. The mean EPDS score for participants in the Mild trajectory group (50%) remained constant around a score of 5 from the fourth month of gestation through postpartum. The EPDS symptoms score for the 32% in the Subthreshold group also followed a quadratic trend ($\beta = -2.06$. p-value = 0.0003; β^2: 0.13, p-value = 0.0006), whereby they entered the study with a relatively higher mean EPDS score of 11, decreased to a mean score of 8 by the ninth month of gestation, then increased postpartum.

There was no significant association between EPDS trajectory group membership and the occurrence of an SSRI dose increase (Fisher's Exact p-value: pregnancy = 0.3746; postpartum = 0.3293). In the Minimal EPDS trajectory group, two (13%) of the participants had at least one dose increase during pregnancy, and four (27%) had at least one during the postpartum period. In the Mild trajectory group, eight (20%) participants reported a SSRI dose increase while five participants (13%) reported one during the postpartum period. Within the Subthreshold EPDS trajectory group, eight participants (32%) reported a dose increase during pregnancy and six (24%) reported one during the postpartum period.

Trajectory analyses for the QIDS scores also identified three distinct trajectories (Minimal, Mild, Subthreshold) with slightly varying shapes compared to those observed for EPDS (Figure 2). Because both are scales of depressive symptoms, we anticipated agreement between EPDS and QIDS trajectory membership (Cohen's Kappa = 0.5699, 95% CI [0.42, 0.71]). In contrast to depression scores, GAD-7 anxiety scores followed four trajectories, identified as Asymptomatic (7%), Minimal (53%), Breakthrough (increasing symptoms) (18%), and Mild (23%, Figure 2). In general, the anxiety trajectories were positively associated with the EPDS trajectory groups (Spearman correlation of 0.60 ($p < 0.0001$, 95% CI: [0.45–0.72]). For example, 100% of those participants in the Minimal EPDS trajectory group fell in one of the two lowest Generalized Anxiety Disorder (GAD) trajectory groups. Of those classified in the Subthreshold EPDS trajectory group, nearly 70% were also classified into one of the higher two scoring (Breakthrough and Mild) GAD trajectory groups.

Association Between Trajectory Membership and Covariates/participant Characteristics

Of the pre-specified covariates (race, history of anxiety disorder, history of eating disorder, history of substance abuse/dependence, age, and BMI) explored for association with trajectory membership (six covariates times five outcomes = 30 statistical tests), three significant associations were observed: (1) eating disorder and QIDS trajectory membership (Fisher's exact p-value = 0.0440), (2) BMI and PROMIS-GH Physical Score (Wald p-value = 0.0061), and (3) BMI and PROMIS-GH Mental Score (Wald p-value = 0.0159). Approximately 4% of participants in the Minimal QIDS trajectory group, 26% in the Mild, and 11% in the Subthreshold group reported an eating disorder.

DISCUSSION

This prospective longitudinal observational study assessed trajectories of depression and anxiety symptoms across pregnancy in an SSRI-treated cohort of women being treated for MDD. Upon study entry, the majority of participants were not in remission despite maintenance drug treatment (remission defined by DSM-IV criteria). We identified three relatively stable trajectories of depressive symptoms across the perinatal period. In contrast, the four anxiety symptom trajectories were stable in two groups with one ascending and one descending group. Aligned with prior studies of cohort and community samples (3, 11, 14–20), our results reveal that a substantive proportion of women treated with SSRIs report depressive and anxiety symptoms, that can be discerned into three depression trajectories and four anxiety trajectories. As with prior studies (3, 11, 14–20), specifiers that describe symptom severity, timing and course stability offer a systematic approach to classifying the course of perinatal conditions.

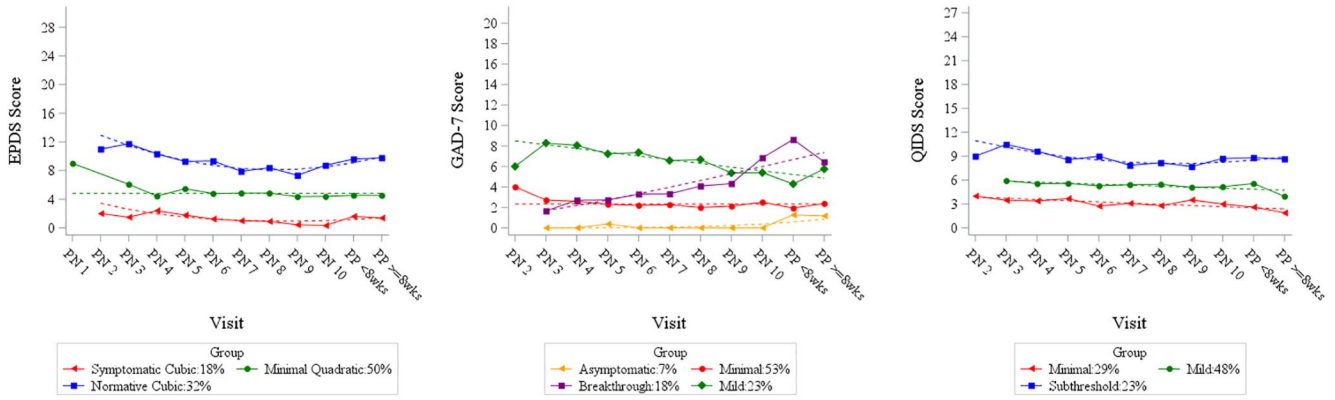
Our findings demonstrate that the treatment goal to achieve full resolution of maternal depression symptoms remains a clinical challenge. Despite maintenance treatment, pregnant women with MDD frequently had residual symptoms at enrollment and throughout pregnancy and postpartum. Specifically, only 18% (by EPDS) to 29% (by QIDS; see Figure 2) of the pregnant women in our cohort-maintained remission. The justification for

TABLE 3. Summary statistics for primary and secondary outcomes of interest[a]

Variable		Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Delivery	PP < 8wk	PP ≥ 8wk
EPDS	*n*	*n* = 1	*n* = 2	*n* = 31	*n* = 57	*n* = 75	*n* = 75	*n* = 77	*n* = 76	*n* = 78	*n* = 59	*n* = 79	*n* = 65	*n* = 82
	Mean (Std)	9.0 (0.0)	6.5 (6.4)	6.5 (4.6)	5.8 (4.1)	5.9 (3.8)	5.4 (4.4)	4.9 (3.7)	5.2 (3.8)	4.6 (3.3)	5.1 (4.0)	5.2 (5.0)	5.3 (4.3)	5.4 (4.1)
	Range	(9.0–9.0)	(2.0–11.0)	(0.0–15.0)	(0.0–17.0)	(0.0–16.0)	(0.0–25.0)	(0.0–18.0)	(0.0–16.0)	(0.0–12.0)	(0.0–15.0)	(0.0–26.0)	(0.0–21.0)	(0.0–15.0)
GAD-7	*n*	*n* = 0	*n* = 2	*n* = 30	*n* = 57	*n* = 75	*n* = 75	*n* = 77	*n* = 76	*n* = 78	*n* = 59	*n* = 78	*n* = 65	*n* = 82
	Mean (Std)		5.0 (1.4)	4.0 (3.6)	3.7 (3.8)	3.4 (3.0)	3.3 (3.1)	3.1 (2.9)	3.2 (3.0)	3.3 (2.9)	3.7 (2.8)	3.8 (3.7)	3.5 (3.8)	3.8 (3.2)
	Range		(4.0–6.0)	(0.0–12.0)	(0.0–17.0)	(0.0–16.0)	(0.0–14.0)	(0.0–11.0)	(0.0–12.0)	(0.0–15.0)	(0.0–11.0)	(0.0–17.0)	(0.0–21.0)	(0.0–14.0)
QIDS	*n*	*n* = 0	*n* = 2	*n* = 30	*n* = 57	*n* = 75	*n* = 74	*n* = 77	*n* = 76	*n* = 78	*n* = 59	*n* = 76	*n* = 65	*n* = 82
	Mean (Std)		6.5 (3.5)	6.2 (3.6)	5.8 (3.2)	5.7 (2.6)	5.3 (3.2)	5.2 (2.7)	5.3 (2.9)	5.3 (2.4)	5.3 (2.6)	5.6 (3.6)	5.2 (3.6)	4.2 (3.2)
	Range		(4.0–9.0)	(1.0–13.0)	(0.0–17.0)	(1.0–13.0)	(0.0–18.0)	(1.0–14.0)	(0.0–15.0)	(0.0–13.0)	(1.0–12.0)	(0.0–24.0)	(0.0–16.0)	(0.0–18.0)
PROMIS-GH mental T-score	*n*	*n* = 0	*n* = 2	*n* = 30	*n* = 57	*n* = 75	*n* = 75	*n* = 77	*n* = 75	*n* = 78	*n* = 59	*n* = 0	*n* = 65	*n* = 82
	Mean (Std)		50.9 (7.2)	49.0 (5.7)	49.1 (6.7)	49.7 (6.1)	50.1 (6.3)	50.1 (6.9)	49.9 (6.5)	50.1 (6.4)	49.7 (5.8)		49.3 (6.2)	49.8 (6.6)
	Range		(45.8–56.0)	(41.1–62.5)	(31.3–67.6)	(25.1–62.5)	(25.1–67.6)	(25.1–67.6)	(28.4–67.6)	(33.8–67.6)	(38.8–62.5)		(33.8–62.5)	(31.3–67.6)
PROMIS-GH physical T-score	*n*	*n* = 0	*n* = 2	*n* = 30	*n* = 57	*n* = 75	*n* = 75	*n* = 77	*n* = 75	*n* = 78	*n* = 59	*n* = 0	*n* = 65	*n* = 82
	Mean (Std)		42.6 (7.3)	45.8 (2.9)	46.8 (3.0)	45.7 (2.8)	45.2 (3.2)	44.7 (3.5)	44.5 (3.2)	43.7 (3.3)	43.9 (3.0)		46.2 (2.9)	45.7 (3.0)
	Range		(37.4–47.7)	(37.4–50.8)	(37.4–50.8)	(39.8–50.8)	(34.9–50.8)	(34.9–50.8)	(37.4–50.8)	(34.9–50.8)	(34.9–50.8)		(37.4–50.8)	(39.8–50.8)

[a] Delivery, delivery week; Month 1, [0,4) weeks gestation [Note "[" include the value, "(" do not]; Month 2, [4,8) weeks gestation; Month 3, [8,12) weeks gestation; Month 4, [12,16) weeks gestation; Month 5, [16,20) weeks gestation; Month 6, [20,24) weeks gestation; Month 7, [24,28) weeks gestation; Month 8, [28,32) weeks gestation; Month 9, [32,36) weeks gestation; Month 10, 36+ weeks gestation; PP < 8wk, first postpartum visit, within 8 weeks of delivery; PP ≥ 8wk, second postpartum visit, after 8 weeks and up to 12 weeks postpartum; Std, standard deviation. Delivery data are summarized here for participants submitting data at this time point; PROMIS-GH data were not collected as part of the study protocol at delivery, and analyses evaluating trajectory membership exclude delivery data due to variability in data collection at this time point (i.e., we treat delivery as an "interruption" in analyses).

FIGURE 2. Trajectory analyses of depression and anxiety symptoms[a]



[a]PN, prenatal month, PP, postpartum month. PN 1, [0,3) weeks gestation; PN 2, [4,8) weeks gestation; PN 3, [8,12) weeks gestation; PN 4, [12,16) weeks gestation; PN 5, [16,20) weeks gestation; PN 6, [20,24) weeks gestation; PN 7, [24,28) weeks gestation; PN8, [28,32) weeks gestation; PN 9, [32,36) weeks gestation; PN 10, 36+ weeks gestation; PP < 8 weeks, [0,8) weeks postpartum; PP ≥ 8wk, 8+ weeks postpartum. *Note*. "[" include the value, "(" do not. Figures displayed represent the observed and expected mean outcome scores over gestational month or time postpartum for the latter two time points. Both Edinburgh Postnatal Depression Scale (EPDS) and Quick Inventory of Depressive Symptoms (QIDS) trajectory analysis revealed three distinct trajectories, which we denote as red = Minimal, green = Mild, blue = Subthreshold. The figures display the percent of study participants whose outcome scores most closely follow each of these trajectories. **EPDS** trajectories followed quadratic (Minimal; $\beta = -1.49$, $p = 0.0248$; $\beta^2 = 0.09$, $p = 0.0431$), constant (Mild; intercept = 4.73), and quadratic (Subthreshold; $\beta = -2.06$, $p = 0.0003$; $\beta^2 = 0.13$, $p = 0.0006$) shapes. **QIDS** trajectories followed linear (Minimal; $\beta = -0.17$, $p = 0.0414$), linear (Mild; $\beta = -0.13$, $p = 0.0292$), and quadratic (Subthreshold; $\beta = -1.16$, $p = 0.0121$; $\beta^2 = 0.07$, $p = 0.0243$) shapes. **Generalized Anxiety Disorder Scale, 7-item (GAD-7)** analyses revealed four trajectories, which we denote as red = Asymptomatic, green = Minimal, blue = Breakthrough, yellow = Mild. **GAD-7** trajectories followed 1: Asymptomatic (linear pattern; $\beta = 0.70$, $p = 0.0169$), 2: Minimal (constant; intercept = 1.99), 3: Breakthrough (linear; $\beta = 0.70$, $p < 0.0001$), and 4: Mild (linear; intercept = 9.23, $\beta = -0.37$, $p = 0.0001$)

pharmacologic treatment of a pregnant woman is that the negative impact of the disease is greater than the risk of fetal drug exposure, such that providing drug treatment reduces disease expression and thereby its impact on pregnancy outcomes (32). One strategy to reduce the rate of inadequate intervention for MDD is measurement-based treatment, which is a critical component of the perinatal depression care pathway employed in obstetrical settings. Interventions are driven by serial administration of a quantitative symptom assessment tool with adaptation of the type and/or intensity of intervention until remission is achieved. This approach is particularly useful to personalize care during pregnancy, when multiple physiological and psychosocial factors are changing rapidly across childbearing.

Perinatal women with lifetime MDD have a high rate of comorbid anxiety symptoms and disorders (6, 33). In our cohort, two of four anxiety symptom trajectories remained stable and represented asymptomatic (7%) and minimal (53%) symptom severities. The third trajectory group had high anxiety symptoms at enrollment that decreased across pregnancy and postpartum, but remained in the mild range of GAD-7 scores (Mild; 23%). The fourth group experienced low symptoms at intake, but then showed steadily increasing anxiety (18%; Breakthrough) that peaked after birth. This investigation and increasing evidence (5) document the co-occurrence of anxiety and depressive symptoms and the validity of the term perinatal mood and anxiety disorders in this clinical context. Notably, concurrent screening for both symptom sets in perinatal settings has been recommended in the United Kingdom by the National Institute for Health and Care Excellence (NICE).

Residual anxiety symptoms are common in treated depressed women and their presence extends the time to response, predicts more rapid recurrence, and signals impending relapse (34). In our SSRI-treated subjects, 41% had current clinically relevant anxiety symptoms, with substantially more women (18%) experiencing an increase in symptoms throughout pregnancy and postpartum compared to general perinatal populations (3, 11, 15, 17). This group of SSRI-treated women may represent a subgroup who, despite their low anxiety scores in early pregnancy, are sensitive to stress across pregnancy and require additional intervention to mitigate escalating symptoms as they prepare for birth (3, 11). Residual symptoms also may result from the loss of drug efficacy due to declining plasma concentrations across pregnancy (35). To mitigate symptoms, prescribers increased the SSRI dose in 28 of our participants, which suggests that concentrations became subtherapeutic during pregnancy. An in-depth presentation of these results with serial plasma SSRI concentrations from these women are being analyzed for a subsequent publication.

Pregnant women with SSRI-treated MDD experienced pre-pregnancy, sub-optimal health including elevated BMI and infertility, migraines, thyroid disorders and asthma. A history of eating disorders was predictive of elevated QIDS trajectory scores. Women with a history of eating disorders (36) were at increased risk of developing perinatal

depression (37). The QIDS items that assess appetite, weight fluctuations and self-perception likely explained this observation. Because the EPDS does not include these items, using the QIDS may better inform perinatal symptoms among women with risk for eating disorders.

This study's strengths include novel data from monthly self-report symptom assessments through pregnancy and after birth in women who were treated with an SSRI at enrollment. This sizable population of pregnant women are frequently excluded in depressive and anxiety symptom trajectory research (3, 14, 16, 18, 19, 21).

This study has limitations. First, the findings are generalizable to SSRI-treated women such as those in this sample, which includes predominantly white, married, educated women. In commercially insured pregnant women, treatment with SSRIs was more common among those who were older, white, college-educated and with higher incomes (>$100,000) (13, 32), which describes the participants in our sample. Although Black and Hispanic women are less likely to accept drug treatment for MDD than white women, deficits in detection, engagement, treatment access and insurance coverage amplify racial/ethnic disparities in maternal mental health care (38, 39). Studies to determine the symptom trajectories in specific populations of perinatal women at high risk of psychiatric and obstetrical morbidity are emerging to suggest ethnicity by trimester interactions (e.g., Latina women reported more positive depression and anxiety screens in the first trimester, compared to stable rates across all trimesters in non-Hispanic Black women) (40). The urgent need to reduce racial disparities in pregnant and postpartum Latina and Non-Hispanic Black women are the subject of national policy attention.

Second, we evaluated only women who were treated with SSRI and our findings are limited to this drug class. Future studies could expand this study to include women treated with other classes of antidepressants. Third, as mentioned, there were no formal sample size calculations for symptom trajectory endpoints, and we ultimately ended with a modest number of women ($N = 88$). However, each woman provided multiple consecutive data points which allowed for assessment of trajectory patterns in this group of women. Also, we lost 11 women to follow-up, which prevents a complete picture of the postpartum effects. Finally, provider treatment practices, not a prescribed treatment algorithm, may have influenced our results. Future studies could intensify their tracking using biological or ecological momentary assessment approaches in lieu of self-reports to identify endophenotypes or contextual factors related to trajectory changes. Also, future work could identify the effect of just-in-time treatments to constrain symptom increases across the perinatal phase.

Our findings support the implementation of measures of both anxiety and depression to obtain a more complete clinical assessment of residual symptoms during SSRI-maintenance treatment of maternal MDD. Additional intervention research is needed to enhance the effectiveness of maintenance medication especially for women in the highest scoring QIDS and EPDS trajectories, respectively.

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