Maternal Depression and Anxiety Differentially Impact Fetal Exposures During Pregnancy

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ABSTRACT

Objective: To examine the association between severity of maternal depression and anxiety during pregnancy and the maternal use of medicinal agents and habit-forming substances.

Method: Participants in a prospective study of prenatal *DSM-IV* depressive and anxiety disorders at the Emory Women's Mental Health Program who completed weekly documentation of prenatal drug exposure and ≥ 3 administrations of the Hamilton Depression Rating Scale (HDRS) or Hamilton Anxiety Rating Scale (HARS) were included. The primary outcome measures were the HDRS and HARS. Correlation coefficients were computed for cumulative drug exposure with HDRS area under the curve (AUC) and HARS AUC. Data collection was completed between January 2007 and June 2010.

Results: Among 195 participants, both HDRS AUC and HARS AUC were negatively correlated with prenatal vitamin exposure ($r = -0.22$ [$P = .002$] and $r = -0.26$ [$P = .0003$], respectively) and positively correlated with tobacco ($r = 0.21$ [$P = .003$] and $r = 0.20$ [$P = .006$], respectively) and hypnotic ($r = 0.28$ [$P < .0001$] and $r = 0.19$ [$P = .008$], respectively) exposure. Only HDRS AUC correlated with exposure to antiemetics ($r = 0.14$ [$P = .05$]), opioid analgesics ($r = 0.14$ [$P = .05$]), and all prescription drugs ($r = 0.16$ [$P = .02$]). Only HARS AUC correlated with benzodiazepine exposure ($r = 0.17$ [$P = .02$]).

Conclusions: Both prenatal depression and anxiety are associated with decreased prenatal vitamin compliance and increased use of hypnotics and tobacco, but only depression is associated with exposure to a broader array of medications targeting physical symptoms that often accompany depression. These findings confirm and extend previous studies, underscoring the importance of addressing prenatal depression and anxiety.

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Managing maternal mental illness during pregnancy dictates a measured approach that endeavors to maximize relative safety for both mother and fetus by weighing the reproductive risks of available treatments against the risks of untreated illness. Consequently, a thorough appreciation of the potential risks associated with both the illness and its treatment is requisite to evidence-based decision making.

One potentially overlooked consequence of maternal psychiatric symptoms during pregnancy is the potential for increased fetomaternal exposure to numerous pharmacologic agents, including psychotropic and nonpsychotropic prescription medications, over-the-counter medications, herbal remedies, and habit-forming substances. Whereas psychotropic medication use during pregnancy has garnered considerable attention, studies of obstetrical outcome associated with psychotropic administration have seldom controlled for the potential impact of concomitant exposure to other nonpsychotropic agents.

Yet, evidence indicates that use of nonpsychotropic agents is widespread during gestation. Studies of community-derived samples indicate that most pregnant women (56%–76%) were prescribed a prescription medication.[1,2] Moreover, Glover and colleagues[3] reported that over-the-counter medications were used more frequently during pregnancy than prescription and herbal agents and that pregnant women with Medicaid coverage purchased twice as many over-the-counter medications as private-pay parties, suggesting that insurance coverage may play a role in dictating the pattern of pharmaceutical use during gestation. These studies confirm that pregnant women often take a variety of medications, with or without a prescription or a physician's knowledge. To date, studies of patient characteristics that influence prenatal medication exposure have emphasized demographic attributes[4] and whether the pregnancy was planned.[5]

The impact of maternal psychiatric symptoms on the level of prenatal prescription and over-the-counter medication use remains obscure. In contrast, numerous studies have reported that depressed gravidas are more likely to use tobacco,[6–12] alcohol,[6,7] and illicit substances.[6,7,10] Moreover, pregnant women who are depressed have also been reported to be less successful in their efforts to quit smoking.[9,10]

Recognizing that there has been limited systematic investigation of the impact of prenatal psychiatric symptoms on prenatal drug exposure, our objective in the current study was to address this gap in the literature by examining the association between the severity of maternal depression and anxiety during pregnancy and the extent of maternal use of medicinal agents and habit-forming substances.

METHOD

Women presenting to the Emory Women's Mental Health Program were enrolled in a prospective observational study of the course and sequelae of prenatal maternal mental illness. Pregnant women with a history of a depressive or anxiety disorder were eligible for participation. Those with lifetime histories of bipolar or psychotic disorders and those with acute suicidality or homicidality were excluded. The current report was limited to those enrollees who

had delivered a live infant by the time of data sequestration for analysis with (1) 3 completed assessments of depression or anxiety symptoms during gestation and (2) complete documentation of weekly drug exposure across pregnancy. Data collection was completed between January 2007 and June 2010. Written informed consent was obtained prior to study enrollment. The study was approved by the Emory University Institutional Review Board.

At the baseline study visit, demographic and obstetrical data as well as findings from the Structured Clinical Interview for *DSM-IV* Axis I Disorders-Patient Edition (SCID-I/P)[13] were collected. During serial prenatal visits, depression and anxiety symptoms were assessed using the Hamilton Depression Rating Scale (HDRS)[14] and the Hamilton Anxiety Rating Scale (HARS)[15] by raters masked to participant psychotropic treatment and other drug exposure. Prenatal drug exposure, encompassing medicinal agents and habit-forming substances, was documented by using a clinician-administered instrument that records the level of use of each agent on a week-by-week basis across gestation.

To maximize the utility of the study's rich longitudinal data, we examined the association between the *cumulative* severity of prenatal maternal depression and anxiety symptoms and the *cumulative* prenatal drug exposure. The cumulative severity of depression and anxiety symptoms was defined a priori as the area under the curve (AUC) for prenatal HDRS and HARS scores, adjusted to a standard 40-week pregnancy by dividing each participant's raw AUC total by the duration of her pregnancy and multiplying the result by 40.

The a priori definition for cumulative drug exposure for each agent was the number of weeks exposed to that agent during pregnancy, similarly adjusted to a standard 40-week gestation. Cumulative drug exposure was then aggregated as drug-weeks of exposure for all agents in a given class for each of the following drug classes: prescription drugs (psychotropic, obstetrical, other medical), nonprescription drugs (over-the-counter drugs, herbal remedies), prenatal vitamins, and habit-forming substances (tobacco, alcohol, caffeine, and illicit substances). For example, if a participant took 2 drugs in the same class throughout an entire 40-week pregnancy, then the cumulative drug exposure for that class would equal 80 drug-weeks.

Cumulative drug exposures were also aggregated using an additional functional drug classification scheme with the following classes: antidepressants, benzodiazepines, antipsychotics, and other psychotropic medications (antiepileptic drugs, stimulants); hypnotics; antiemetics and other gastrointestinal medications; opioid analgesics and other nonopioid analgesics; and tobacco, alcohol, and caffeine.

Finally, cumulative prenatal exposure to tobacco, alcohol, and caffeine was aggregated not only by weeks of exposure but also by total number of servings (ie, number of cigarettes, number of alcoholic or caffeinated beverages) consumed during gestation. These measures were also adjusted to a standard 40-week pregnancy.

Clinical Points

- Maternal depression or anxiety during pregnancy is associated with poorer compliance with prenatal vitamins and with increased fetal exposure to numerous substances, including tobacco, hypnotics, antiemetics, opioid analgesics, and benzodiazepines.
- The risk-benefit assessment for managing prenatal depression and anxiety must consider the risks of fetal exposure to these other substances.

A descriptive analysis was performed to summarize the characteristics of the study sample. This was followed by the assessment of the relationship between prenatal depression, anxiety, and drug exposure. A Pearson correlation coefficient was computed for cumulative depression (HDRS AUC), cumulative anxiety (HARS AUC), and cumulative drug-weeks of exposure within each drug class by using both drug classification schemes described above.

RESULTS

When data were sequestered for the current report, 393 women had enrolled in the study. Among these, 82 were active in the study but had not yet delivered, 77 had withdrawn prior to delivery, 32 had miscarried, and 202 had delivered. All but 7 of the 202 women who had delivered a live infant had completed the requisite number of prenatal measures for the HDRS or HARS, so that 195 women qualified for the current analysis.

The HDRS was completed at least 3 times during pregnancy by all 195 women. The mean ± SD number of prenatal HDRS administrations per participant was 5.4 ± 1.4 (range, 3–9), and the mean ± SD HDRS score was 10.2 ± 5.7 (range, 0–33). The HARS was completed at least 3 times during pregnancy by 192 women. The mean ± SD number of prenatal HARS administrations per participant was 5.2 ± 1.4 (range, 3–9), and the mean HARS score was 9.1 ± 5.5 (range, 0–35).

The mean ± SD age of the 195 participants was 33.5 ± 4.7 years old. The racial composition of the sample was 85.6% (n = 167) white, 10.3% (n = 20) black/African American, and 4.1% (n = 8) other races. Data on marital status showed that 87.2% (n = 170) of the participants were married, 4.6% (n = 9) were divorced or separated, and 8.2% (n = 16) had never been married. Obstetrical profiles included 27.7% (n = 54) unplanned pregnancies and 73.3% (n = 143) multigravid pregnancies. The mean estimated gestational age at delivery was 38.0 ± 2.0 weeks.

Lifetime psychiatric diagnoses, determined by the SCID-I/P, demonstrated considerable comorbidity, including the following disorders in descending order of prevalence: 84.1% (n = 164) major depressive disorder, 29.2% (n = 57) panic disorder, 27.2% (n = 53) generalized anxiety disorder, 19.0% (n = 37) posttraumatic stress disorder, 16.9% (n = 33) obsessive-compulsive disorder, 13.3% (n = 26) alcohol

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Table 1. Correlation Between Cumulative Maternal Symptom Severity and Cumulative Prenatal Drug Exposure (drug-weeks exposed)

Cumulative Maternal Symptom Severity	Prescription and Nonprescription Medications							Prenatal Vitamins	Habit Forming
	Prescription				Nonprescription				
	Psychotropic	Obstetrical	Other	All	Over the Counter	Herbal	All		
Depression (HDRS AUC)	$r=0.12$, $P=.11$	$r=-0.04$, $P=.57$	$r=0.14$, $P=.04$	$r=0.16$, $P=.02$	$r=0.07$, $P=.33$	$r=0.01$, $P=.85$	$r=0.16$, $P=.03$	$r=-0.22$, $P=.002$	$r=0.09$, $P=.22$
Anxiety (HARS AUC)	$r=0.07$, $P=.31$	$r=-0.02$, $P=.80$	$r=0.10$, $P=.19$	$r=0.11$, $P=.13$	$r=0.04$, $P=.54$	$r=-0.04$, $P=.59$	$r=0.10$, $P=.17$	$r=-0.26$, $P=.0003$	$r=0.08$, $P=.27$

Abbreviations: AUC = area under the curve, HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale.

Table 2. Correlation Between Cumulative Maternal Symptom Severity and Cumulative Prenatal Drug Exposure (drug-weeks exposed) With Functional Drug Classifications

Cumulative Maternal Symptom Severity	Psychotropic					Gastrointestinal Agents		Analgesic		Habit Forming		
	Antidepressant	Benzodiazepines	Antipsychotics	Other[a]	Sleep[b]	Nausea[c]	Other[d]	Prescription Opioid	Other[e]	Tobacco	Alcohol	Caffeine
Depression (HDRS AUC)	$r=-0.05$, $P=.53$	$r=0.12$, $P=.09$	$r=0.13$, $P=.08$	$r=-0.01$, $P=.89$	$r=0.28$, $P<.0001$	$r=0.14$, $P=.05$	$r=0.12$, $P=.11$	$r=0.14$, $P=.05$	$r=0.05$, $P=.45$	$r=0.21$, $P=.003$	$r=-0.00$, $P=.99$	$r=-0.01$, $P=.93$
Anxiety (HARS AUC)	$r=-0.09$, $P=.23$	$r=0.17$, $P=.02$	$r=0.09$, $P=.21$	$r=0.01$, $P=.87$	$r=0.19$, $P=.008$	$r=0.06$, $P=.40$	$r=0.12$, $P=.09$	$r=0.10$, $P=.15$	$r=0.04$, $P=.61$	$r=0.20$, $P=.006$	$r=0.00$, $P=.95$	$r=0.00$, $P=.99$

[a]Antiepileptic drugs and stimulants.
[b]Prescription hypnotics.
[c]Prescription antiemetics.
[d]All prescription and over-the-counter gastrointestinal agents except antiemetics.
[e]All nonopioid prescription and over-the-counter analgesics.
Abbreviations: AUC = area under the curve, HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale.

dependence, 10.8% (n = 21) social anxiety disorder, 9.2% (n = 18) anxiety disorder not otherwise specified (NOS), 8.7% (n = 17) anorexia nervosa, 6.7% (n = 13) specific phobia, 5.6% (n = 11) bulimia nervosa, 3.1% (n = 6) binge eating disorder, 2.6% (n = 5) agoraphobia, 2.6% (n = 5) cannabis dependence, 2.1% (n = 4) depressive disorder NOS, and 2.1% (n = 4) cocaine dependence.

Tables 1 and 2 present the correlations between the cumulative severity of maternal depression and anxiety as represented by HDRS AUC and HARS AUC, respectively, and the cumulative drug-weeks of exposure for various drug classes.

The general drug classification scheme (Table 1) demonstrated significant negative correlations between weeks of prenatal vitamin exposure and both depression severity (HDRS AUC) and anxiety severity (HDRS AUC). In addition, depression was significantly associated with the drug-weeks of exposure to general medical prescription medications, all prescription medications collectively, and all prescription and nonprescription agents collectively. No other significant associations were found between anxiety and drug exposure using the general classification scheme.

Organizing drug exposures by functional classifications (Table 2) revealed additional significant associations. The severity of both maternal depression and maternal anxiety were positively and significantly correlated with drug-weeks of exposure to hypnotic agents and tobacco. Furthermore, when operationalizing the level of tobacco exposure as the total number of cigarettes smoked throughout gestation, the positive associations with the severity of both maternal depression ($r=0.16$, $P=.02$) and anxiety ($r=0.14$, $P=.05$) remained. Neither prenatal alcohol nor prenatal caffeine exposure was significantly associated with the severity of maternal depression or anxiety.

The severity of maternal anxiety was positively correlated with drug-weeks of benzodiazepine exposure; however, the severity of maternal depression surprisingly was not associated with drug-weeks of antidepressant exposure. Instead, maternal depression was positively correlated with drug-weeks of exposure to antiemetics and opioid analgesics.

DISCUSSION

The current study represents the most comprehensive examination to date of the association between fetal drug exposure and the severity of maternal depression during pregnancy. In addition, it is the first report regarding the association between maternal anxiety during gestation and fetal drug exposure.

The current data suggest that maternal health behaviors during pregnancy are influenced by both symptoms of anxiety and depression. For example, consistent with previous studies, we observed highly significant associations for the severity of depression with prenatal vitamin noncompliance[6] and heightened tobacco use[6–12] during gestation. Similar associations were observed between maternal anxiety and prenatal vitamin noncompliance and maternal smoking; the latter finding has not been previously described during pregnancy but is consistent with reports of anxiety and smoking in nonpuerperal adults.[16–18]

The study produced several key findings with respect to maternal depression. First, it is somewhat surprising that depression severity was not associated with the level of antidepressant exposure. This finding is potentially explained by certain common, yet contrasting, patterns of prenatal antidepressant use. Some women, concerned about antidepressant-reproductive safety, may accept the potential for worsening depression in an effort to avoid prenatal antidepressant therapy, producing an inverse association between depression and antidepressant exposure. Others, with histories of severe or difficult-to-manage depression, concerned about the reproductive impact of severe depression, may instead opt for aggressive (eg, 2-drug) prenatal antidepressant therapy, producing a positive association between depression and antidepressant exposure. Thus, the absence of an overall correlation between depression and antidepressant exposure may be a product of the opposing associations produced by such disparate approaches to therapy.

Second, the severity of depression was positively associated with prenatal exposure to hypnotics, antiemetics, and opioid analgesics. The causal direction of this relationship is unclear, and, in fact, may be bidirectional. Whereas pain and medical illness undermine well-being and may thus contribute to greater depressive symptoms, there is also evidence that depression may cause not only sleep disturbance but also pain and physical symptoms as well.[19,20] In any event, depressed patients suffer with myriad physical discomforts and, in this study, received pharmaceutical remedies targeting their physical symptoms, even during gestation. In comparison to the more indiscriminate use of pharmaceuticals observed in association with depression, the correlation between the severity of anxiety and prenatal drug exposure was limited to agents, ie, benzodiazepines and hypnotics, that target the core features of the anxiety itself.

The ultimate clinical import of the current findings may lie in determining whether high utilization of nonpsychotropic medications by pregnant women is a behavioral marker for unrecognized psychiatric symptoms. Although the current study design precluded direct assessment of the prevalence of depression and anxiety in pregnant women receiving antiemetics, hypnotics, or opioid analgesics, the results suggest that clinicians should explore the presence of maternal anxiety and depression in women receiving multiple nonpsychotropic interventions.

Beyond the study's clinical implications, its novel results hold additional ramifications for the design and interpretation of outcome investigations of prenatal mental illness and psychotropic medication exposure. The extant literature is discordant at best with respect to the potential adverse impact of prenatal antidepressant exposure. The inconsistent findings in existing studies of antidepressant reproductive safety may be attributable, at least in part, to the failure to control for the potential confounding impact of the concomitant exposures and/or nonpsychiatric symptoms observed in the current prospective sample.

The principal strength of the current investigation is that it is the first study to examine associations between maternal depression, maternal anxiety, and prenatal drug use by utilizing cumulative measures of exposure collected prospectively across the entirety of pregnancy. Prior studies have chiefly relied upon either a single cross-sectional prenatal evaluation or a retrospective assessment completed weeks to months after delivery. We have previously shown that retrospective (at 6 months postpartum) recall of prenatal depression and prenatal pharmacologic exposure is subject to a significant recall bias in which psychotropic exposure is accurately recalled but prenatal depression and prenatal use of nonpsychotropic agents is systematically underreported.[21]

The chief limitation of this study is its reliance on maternal self-report to document prenatal pharmacologic exposure. Although the prospective data collection minimizes the potential for recall bias, patients may attempt to hide noncompliance with recommended therapies or use of tobacco, alcohol, and other substances discouraged during pregnancy. In fact, we have previously reported evidence that women may deliberately withhold details regarding alcohol use during gestation[21]; therefore, the current study's failure to demonstrate an association between depression, anxiety, and prenatal alcohol use is perhaps attributable to underreporting of alcohol use. In addition, the use of a clinical sample, rather than a community sample, may limit the generalizability of the results. However, the clinical sample provides critical data immediately relevant to decision making in the care of pregnant women experiencing depression or anxiety and serves as an initial foray toward the elucidation of the association between psychiatric symptoms and prenatal drug exposure, thereby standing to serve as a template for future studies using community samples.

In summary, pregnant women with mental illness are frequently encouraged to discontinue psychotropic therapy. Although the underlying desire to avoid fetal psychotropic exposure is laudable, such recommendations are arguably made with limited consideration of the potential adverse obstetrical effects of untreated maternal mental illness. The current study indicates maternal depression and anxiety are associated with heightened fetal exposure to numerous substances. In our previous collaborative study,[22] we reported that discontinuing antidepressant therapy proximate to conception was associated with a high rate of prenatal recurrence of depression. In combination, these findings suggest that a potential unintended consequence of discontinuing therapy for prenatal depression and anxiety is that it may increase fetal exposure to other agents. Consequently, the risk-benefit assessment for managing depression and anxiety during pregnancy should consider not only the immediate consequences of maternal symptoms but also the indirect impact on maternal health behaviors and the use of other agents taken by pregnant women experiencing symptoms of depression and anxiety.

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