# Prospective Longitudinal Study of Predictors of Postpartum-Onset Depression in Women With a History of Major Depressive Disorder

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## ABSTRACT

***Objective:*** Risk factors for postpartum depression in euthymic pregnant women with histories of major depressive disorder (MDD) were evaluated.

***Methods:*** From April 2003 to March 2009, 343 pregnant women with a history of Structured Clinical Interview for *DSM-IV* (SCID)–diagnosed major depressive disorder were prospectively assessed from the third trimester into the postpartum period using the SCID mood module and 17-item Hamilton Depression Rating Scale (HDRS). Data from 300 subjects who completed at least 2 mood module assessments (1 within 60 days before and the other within 60 days after delivery) were analyzed for predictive associations between variables assessed in the third trimester and the development of a postpartum depression.

***Results:*** The majority of women were euthymic in pregnancy by SCID criteria. Women with third trimester SCID-diagnosed depression (n = 45) versus euthymia (n = 255) had a significantly higher risk for having depression after delivery (24% vs 11%, $P = .013$). For pregnant euthymic women, third trimester total HDRS scores significantly predicted postpartum depression ($P < .0001$); specifically, scores on 3 HDRS items alone—work activities, early insomnia, and suicidality—significantly predicted postpartum depression. Antidepressant use in the third trimester in euthymic women did not confer protection against the onset of postpartum depression.

***Conclusions:*** Among women with a history of MDD who are euthymic in the third trimester, 3 HDRS items—work activities, early insomnia, and suicidality—may be useful as screening items for clinicians working with pregnant women with histories of MDD to identify a group at risk for developing postpartum depression. Additionally, in euthymic women with a history of MDD, antidepressant use in the third trimester may not reduce the risk of developing postpartum depression.

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Twenty percent of adult women will experience an episode of major depressive disorder (MDD) at some point in their lifetimes. Women with a history of depression are particularly vulnerable to depression in the postpartum period.[1,2] Postpartum depression has been recognized in the *DSM* as a specifier of major depressive disorder, rather than as a unique diagnostic entity. While 10%–20% of the general population of women will experience a major depressive episode in the postpartum period,[3] rates for women with a prior history of depression have been reported at 25%–40%.[4–6]

In a recent review of 203 studies assessing the magnitude and risk factors for postpartum depression in the general population,[7] antenatal depression and anxiety, previous psychiatric illness, poor marital relationship, stressful life events, negative attitude toward pregnancy, and lack of social support were all found to be significant contributors. Of note, only 10% of the studies in this review utilized structured clinical subject interviews. One study[8] that did utilize *DSM-IV* diagnostic criteria found that age, health status, and history of trauma were associated with a higher risk of psychiatric disorders in pregnant and postpartum women. Another recent study[9] utilizing *DSM-IV* criteria found that 82% of 104 women with postpartum depression had a prior history of depression, compared to 31% of 104 women without postpartum depression. In addition to these psychosocial, demographic, and clinical variables, biological factors including pregnancy biomarkers, heightened susceptibility to estrogen signaling,[10] and variability in the hypothalamic-pituitary-adrenal axis and inflammatory response[11] have been associated with an increased risk of postpartum depression.

While studies have assessed risk factors for postpartum depression in the general population[7,12–14] and also risks for postpartum depression in women with prior histories of postpartum depression,[15] few studies have examined the risk factors involved in developing postpartum depression in women with known prior histories of recurrent mood disorders,[5,16] and data on predictors of postpartum depression in women with prior histories of depression who are euthymic in pregnancy are lacking. The current study sought to fill a void in the literature. Using structured clinical diagnostic interviews, we prospectively evaluated demographic, clinical, and illness

**Clinical Points**

- While women with a history of major depressive disorder (MDD) are vulnerable to depression after delivery, factors that may predict which pregnant women in this population are at increased risk for developing postpartum depression have not been identified.
- For pregnant women with a history of MDD who are euthymic at conception, depression during pregnancy significantly increases the risk of depression after delivery.
- For pregnant euthymic women with a history of MDD, third trimester total scores on the Hamilton Depression Rating Scale are predictive of postpartum depression. The 3 specific items related to work activities, early insomnia, and suicidality may be particularly useful for clinicians to identify those women at risk for developing postpartum depression.

history risk factors associated with developing postpartum depression in a large sample of women with prior histories of MDD. We focused on non-biological predictors that would allow clinicians to readily identify women with histories of MDD who might be at risk for postpartum depression.

## METHODS

### Sample Selection

This study was a prospective longitudinal naturalistic investigation of predictors of postpartum depression conducted from April 2003 until March 2009. Pregnant women (N = 343) were enrolled at 3 academic centers with expertise in the treatment of psychiatric illness during pregnancy (Perinatal and Reproductive Psychiatry Clinical Research Program, Massachusetts General Hospital, Boston, Massachusetts; Women's Mood Disorders Research Program, University of California, Los Angeles, California; and the Women's Mental Health Program, Emory University School of Medicine, Atlanta, Georgia). Women were recruited from women's psychiatry and obstetric clinics at each of the 3 institutions, direct referrals from community obstetrical practices, and through advertisements.

Participants were eligible if they (1) met *DSM-IV*[17] criteria for a lifetime diagnosis of MDD prior to pregnancy, (2) reported euthymia at the time of conception, (3) were at less than 36 weeks' gestation, (4) were between the ages of 18 and 45 years, (5) had capacity to give informed consent, and (6) could read English and understand the study procedures and self-rating instruments. Patients were excluded if they (1) were actively suicidal; (2) met *DSM-IV* criteria for organic mental disorders, substance use disorders, bipolar disorder, schizophrenia, delusional disorder, or current psychotic disorder; (3) had a medical condition associated with depressive symptomatology or had abnormal laboratory values that could be associated with depression; (4) had miscarriage or termination of current pregnancy; or (5) had a positive urine toxicology screen for drugs of abuse. The study protocol was approved by the Institutional Review Board at each of the 3 collaborating centers, and all patients gave informed consent after the procedures and potential risks were fully explained. Participants were not randomly assigned to take (or not take) antidepressant medication; that decision was made by each subject in consultation with her treating clinician, unrelated to study participation.

### Assessments

Subjects were enrolled between 12 and 36 weeks' gestation except for 1 subject who enrolled at 37.5 weeks. A *DSM-IV* lifetime diagnosis of MDD was confirmed at enrollment by (1) clinical interview conducted by study psychiatrist and (2) administration of the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID)[18] by trained clinical research raters. These methods were also used to assess for comorbid psychiatric illness. Information regarding variables that might influence risk of depression in the postpartum period was collected, including demographic data; number of prior depressive episodes; total duration of illness; length of current depressive episode, if depressed; and the current use of psychotropic medication, if any.

For subjects enrolled prior to the third trimester, 1 study visit per trimester, which included a clinical interview and an assessment of mood and psychotropic medication usage, occurred for study retention purposes. The first assessment for data analysis purposes occurred within the third trimester, and the remaining longitudinal assessments occurred after delivery at 4, 8, 12, and 24 weeks. At each longitudinal assessment, a rater blinded to the patient's current medication status and specific clinical history variables prospectively administered the SCID mood module for depression and the 17-item Hamilton Depression Rating Scale (HDRS).[19] All raters received joint training supervised by the investigators and achieved excellent interrater reliability for the SCID diagnosis of depression and HDRS total scores ($\kappa \geq 0.7$). Reliability was retested to assess for rater drift at least annually. Additionally, an unblinded rater assisted patients in pregnancy and in the postpartum to complete a questionnaire regarding their current psychotropic medication use during pregnancy and at the time of delivery.

To be included in the current analysis, subjects must have completed all items in 2 SCID assessments—1 within 60 days before and the other within 60 days after delivery. Of the 343 women in the data set, 300 met these criteria. A positive SCID diagnosis of MDD required reaching threshold (a score of 3) on 5 or more of the 9 depression items; at least 1 of which had to include depressed mood or loss of interest.

### Statistical Analysis

Predictive associations of variables assessed during pregnancy with the presence of depression in the postpartum period were analyzed. Predictor variables included age, age at onset of first depression, prior number of lifetime depressive episodes, prior number of postpartum depressive episodes, presence of depression in pregnancy measured by the SCID, severity of depression in pregnancy as assessed using the total score on the HDRS (17-item), chronicity of depression

**Table 1. Demographic and Clinical Characteristics of the Total Sample (N = 300)[a]**

| Variable | EM N = 124 (41%) | MGH N = 59 (20%) | UCLA N = 117 (39%) | $F^b$ | $\chi^2$ (*df*) | *P* | Site Differences |
|---|---|---|---|---|---|---|---|
| Age, mean (SD), y | 32.7 (4.7) | 33.4 (4.3) | 31.7 (5.5) | 2.41 | | .096 | MGH > UCLA |
| Age at illness onset, mean (SD), y | 21.3 (8.1) | 20.2 (6.7) | 16.5 (6.6) | 11.2 | | < .0001 | EM > MGH, UCLA |
| Chronicity index,[c] mean (SD), y | 0.16 (0.15) | 0.21 (0.16) | 0.24 (0.21) | 5.9 | | < .0032 | MGH, UCLA > EM |
| No. of prior major depressive episodes, mean (SD) | 3.3 (2.0) | 3.9 (2.0) | 4.6 (2.1) | 10.9 | | < .0001 | UCLA > EM, MGH |
| History of prior postpartum depressive episodes, % | 36 | 25 | 34 | | 2.4 (2) | .3 | NA |
| Married, n (%) | 95 (83) | 52 (88) | 77 (75) | | 4.7 (2) | .09 | NA |
| Education, % | | | | | 19.1 (4) | .0007 | |
| Graduate school | 33 | 56 | 36 | | | | MGH > EM, UCLA |
| Some college | 49 | 37 | 35 | | | | MGH > EM, UCLA |
| High school or less | 18 | 7 | 29 | | | | EM > MGH, UCLA |
| Race/ethnicity by self-report, n (%) | | | | | 15.6 (4) | .0034 | |
| White | 99 (87) | 52 (88) | 69 (71) | | | | MGH, EM > UCLA |
| African American | 11 (9.7) | 4 (6.8) | 11 (11.3) | | | | EM, UCLA > MGH |
| Asian | 2 (1.8) | 0 | 6 (6.2) | | | | NA |
| Other | 1 (0.9) | 3 (5.1) | 8 (8.25) | | | | UCLA > EM > MGH |
| Hispanic ethnicity (of any race) | 1 (0.9) | 0 | 3 (3.1) | | | | NA |

[a]Percentages are based on the total number of subjects with data for that variable: age (EM n = 114, MGH n = 58, UCLA n = 105), age at illness onset (EM n = 110, MGH n = 58, UCLA n = 89), chronicity index (EM n = 108, MGH n = 57, UCLA n = 88), no. of major depressive episodes (EM n = 114, MGH n = 58, UCLA n = 89), history of prior postpartum depressive episodes (EM n = 113, MGH n = 57, UCLA n = 89), marital status (EM n = 115, MGH n = 59, UCLA n = 103), education (EM n = 115, MGH n = 50, UCLA n = 107), and race/ethnicity (EM n = 114, MGH n = 57, UCLA n = 97).
[b]All *F* ratios have numerator of *df* = 2 and denominator *df* range of 239–277.
[c]Operationalized as number of depressive episodes divided by duration of illness.
Abbreviations: EM = Emory University, MGH = Massachusetts General Hospital, NA = not applicable, UCLA = University of California at Los Angeles.

(operationalized as number of episodes/duration of illness), race, marital status, education, and use of antidepressant medication in pregnancy near the time of delivery.

Depression rates in the postpartum period were first calculated separately for women with a major depressive episode during the third trimester versus women who were euthymic in the third trimester. Subsequent analyses involved only the subset of women who had onset of their current depression after delivery (that is, they were euthymic in the third trimester) and thus met the *DSM-IV* definition of postpartum depression, which requires onset of depression in the postpartum period. Analyses were performed with the SAS 9.3 statistical library (SAS Institute, Cary, North Carolina). Predictors were examined using *t* tests and contingency table and logistic regression analyses. Following the separate analyses of each of the 12 variables, a multiple logistic regression model was used to simultaneously examine those predictors found to be significant at $P < .10$ in the prior step. Final significance was set at unadjusted $P < .05$.

## RESULTS

Site-specific demographic data for the 300 women included in the analyses are shown in Table 1. Clinical assessments were completed a mean (SD) of 21.3 (12.6) days prior to delivery and 31.4 (10.5) days after.

Of the 300 women, 13% (n = 39) of the sample met criteria for MDD in the postpartum period. Depression in pregnancy was associated with higher risk of being depressed in the postpartum period. Eleven (24%) of the 45 who met criteria for MDD in pregnancy versus 28 (11%) of the 255 women who were euthymic in the third trimester met criteria for MDD in the postpartum period ($\chi^2 = 6.13$, $P = .013$). As the current study was focused on predictors of postpartum depression in subjects who were euthymic in the third trimester of pregnancy, the 45 women already depressed during pregnancy were excluded from further analyses. Tables 2 and 3 report the demographic and clinical variables assessed as predictors of postpartum depression in only those 255 women who were euthymic in pregnancy.

### Hamilton Depression Rating Scale Scores

Even in the women who were clinically euthymic by SCID criteria in the third trimester, the HDRS total score at third trimester assessment was a significant positive predictor of depression in the postpartum period ($\chi^2_1 = 21.7$, $P < .0001$). Figure 1 displays the relationship of total HDRS scores during the third trimester of pregnancy to the onset of a postpartum depression.

### Specific HDRS Items Predicting Postpartum Depression

To assess which items on the HDRS scale might individually predict postpartum depression, all items were analyzed using multiple logistic regression with stepwise selection. Three items were found to be significantly predictive when taken in conjunction with each other: work activities (item 7), suicidal thoughts (item 3), and early insomnia (item 4). Item 7 was found to be highly significantly predictive of postpartum depression even with Bonferroni correction ($\chi^2_1 = 10.9$, $P = .001$). Items 3 ($\chi^2_1 = 5.3$, $P = .021$) and 4 ($\chi^2_1 = 5.2$, $P = .023$) were also significant predictors. When these items were entered into a multiple logistic regression model, none of the other HDRS items significantly improved prediction.

**Table 2. Dichotomous and Ordinal Predictors[a] of Postpartum Depression (PPD) in Women Euthymic in the Third Trimester (n = 255)[b]**

| Variable | n | % | % With PPD | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| Education[c] | | | | 3.60 | .058 |
| Graduate/professional | 97 | 40 | 6 | | |
| College | 102 | 42 | 14 | | |
| Some college | 29 | 12 | 10 | | |
| High school or less | 13 | 5 | 23 | | |
| Marital status[c] | | | | 0.00 | 1.000 |
| Married | 193 | 81 | 11 | | |
| Unmarried | 46 | 19 | 11 | | |
| Race/ethnicity[c] | | | | 0.03 | .850 |
| White | 195 | 83 | 11 | | |
| Other | 39 | 17 | 10 | | |
| No. of prior live births | | | | 0.02 | .88 |
| 0 | 131 | 54 | 13 | | |
| 1 | 74 | 31 | 5 | | |
| 2 | 24 | 10 | 13 | | |
| 3 | 6 | 2 | 17 | | |
| 4 or more | 6 | 2 | 17 | | |
| Primigravida | | | | 0.82 | .36 |
| Yes | 74 | 31 | 14 | | |
| No | 167 | 69 | 10 | | |
| No. of prior episodes of MDD | | | | 0.25 | .620 |
| 0–1 | 44 | 20 | 11 | | |
| 2 | 39 | 17 | 5 | | |
| 3 | 35 | 16 | 9 | | |
| 4 | 21 | 9 | 10 | | |
| 5–9 | 30 | 13 | 20 | | |
| 10–30 | 27 | 12 | 15 | | |
| Chronic[d] | 29 | 13 | 7 | | |
| Prior episodes of postpartum-onset depression | | | | 0.79 | .37 |
| 0 | 82 | 54 | 12 | | |
| 1 | 58 | 38 | 7 | | |
| 2 or more | 12 | 8 | 8 | | |
| On antidepressants in the third trimester | | | | 0.69 | .41 |
| Yes | 146 | 57 | 10 | | |
| No | 109 | 43 | 13 | | |

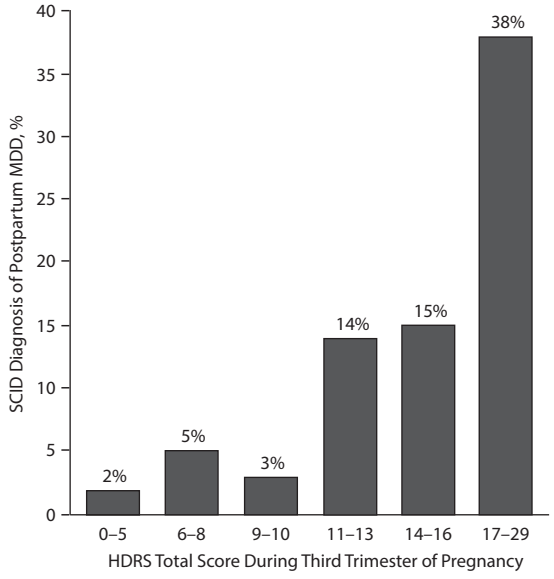
[a]For dichotomous predictors, statistics are Pearson $\chi^2$; for ordinal predictors, statistics are Mantel-Haenszel $\chi^2$ tests for linear association. All have *df* = 1.
[b]Percentages are based on the total number of subjects with data for that variable: education n = 241, marital status n = 239, race/ethnicity n = 239, no. of prior live births n = 241, primigravida n = 241, no. of prior episodes of MDD n = 225, prior episodes postpartum-onset depression n = 152, on antidepressants in the third trimester n = 255.
[c]Because of small cell frequencies, levels of education less than high school were pooled with high school and race/ethnicity (white vs other) and marital status (married vs not married) were both coded as dichotomies.
[d]Some women reported number of prior depressive episodes only as "chronic," and the distribution for those who reported a specific number was extremely skewed (median of 4; maximum of 30). For analysis, "number of prior episodes" was coded into categories (0–1, 2, 3, 4, 5–9, 10–30, "chronic") and treated as an ordinal variable.

**Table 3. Continuous Predictors of Postpartum Depression (PPD) in Women Euthymic in the Third Trimester (n = 255)**

| Predictor[a] | n | PPD+[b] | PPD–[b] | *t* | *df* | *P* | *d*[c] |
|---|---|---|---|---|---|---|---|
| Age, y | 238 | 30.8 (4.1) | 32.8 (5.0) | 1.89 | 236 | .060 | 0.40 |
| Age at onset, y | 220 | 18.0 (8.1) | 19.6 (7.6) | 0.96 | 218 | .339 | 0.21 |
| HDRS score in third trimester | 238 | 14.9 (5.4) | 9.6 (4.6) | −5.42 | 236 | <.0001 | 1.13 |
| Chronicity index[d] | 210 | 0.22 (0.17) | 0.18 (0.16) | −0.94 | 208 | .347 | 0.20 |

[a]The n values with after-delivery diagnosis of major depressive disorder by SCID are 25 (age), 24 (age at onset), 26 (HDRS), and 24 (Chronicity Index).
[b]Values shown as mean (SD).
[c]Effect sizes (*d*) are mean difference divided by pooled SD.
[d]Operationalized as number of depressive episodes divided by duration of illness.
Abbreviations: HDRS = Hamilton Depression Rating Scale, PPD+ = positive diagnosis of postpartum depression by SCID, PPD– = no postpartum depression diagnosis by SCID, SCID=Structured Clinical Interview for *DSM-IV* Axis I Disorders.

**Figure 1. Postpartum Depression as a Function of Pre-Delivery HDRS Score in Women Who Were Euthymic in the Third Trimester[a]**




[a]Includes only women who were euthymic during pregnancy who had third trimester HDRS scores (n = 238).
Abbreviation: HDRS = Hamilton Depression Rating Scale.

Table 4 indicates for each item 7 score the percentage of women with that score who were euthymic during pregnancy and later developed postpartum depression. Among those with scores of 0 or 1 (no or minimal impairment) on item 7 (work activities), 11 (6%) of 191 developed a postpartum depression versus 15 (32%) of 47 with a score of 2 or greater on this item (loss of interest in activity, hobbies, or work) ($\chi^2_1 = 26.5$, $P = .0001$).

Scores on item 3 were truncated since suicidal ideation was an exclusion criterion. Most subjects scored 0 on this item. However, of the 5 of 238 in the sample of women pregnant in the third trimester with a score of 1 ("feels life is not worth living") or greater, 3 (60%) experienced postpartum depression compared with 23 (10%) of 233 scoring 0 on the suicide item (no suicidal ideation) ($\chi^2_1 = 12.6$, $P = .0004$). On item 4, those with scores of 2 ("complains of nightly difficulty falling asleep") or higher were almost 4 times as likely (12/51 = 24%) to experience postpartum depression as those with scores of 0 or 1 ("no difficulty; occasional difficulty falling asleep") (14/187 = 7%, $\chi^2_1 = 10.6$, $P = .001$).

### Antidepressant Use in Pregnancy and Risk for Postpartum Depression

Among subjects who were euthymic in the third trimester, those women on antidepressants compared to those women off antidepressants were significantly more

**Table 4. Relationship of Score on HDRS Work Item to Risk for Postpartum Depression in Euthymic Women in the Third Trimester of Pregnancy[a]**

| HDRS Item 7 (Work) Score During Pregnancy | Description | Postpartum Depression, n/N (%) |
|---|---|---|
| 0 | No difficulty | 9/134 (7) |
| 1 | Thoughts and feelings of incapacity | 2/57 (4) |
| 2 | Loss of interest in activity, hobbies, work | 6/18 (33) |
| 3 | Decreased time spent in activities or decrease in productivity | 6/22 (27) |
| 4 | Stopped working because of present illness | 3/7 (43) |

[a]Includes only women euthymic during pregnancy who had third trimester HDRS scores (n = 238).
Abbreviation: HDRS = Hamilton Depression Rating Scale.

likely to be white (121/136 [89%] vs 74/98 [76%], $\chi^2 = 7.4$, $P = .006$), married (118/137 [86%] vs 75/102 [74%], $\chi^2 = 5.97$, $P = .0145$), and older (mean [SD] age = 33.5 [4.3] years vs 31.4 [5.5] years; $t_{236} = 3.42$, $P = .0007$). Antidepressant use in the third trimester was not associated with a significant effect on the risk for developing postpartum depression (Table 2). Ten percent (14/146) of those who were taking antidepressants in the third trimester versus 13% (14/109) of those who were not taking antidepressants in the third trimester developed postpartum depression ($\chi^2_1 = 0.69$, $P = .41$).

## DISCUSSION

To our knowledge this is the largest prospective study exploring risk factors for postpartum depression in women with prior histories of MDD who are euthymic during pregnancy. In our prospective, naturalistic study of women with a history of MDD, the rate of developing postpartum-onset depression in those women who were euthymic during pregnancy was 11%. This rate is substantially lower than the previously reported risk of 25%–40% for women with histories of recurrent affective episodes.[5] While our study evaluated risk factors for postpartum depression in women who were euthymic in pregnancy, a proportion of the sample inevitably became depressed in pregnancy. Our study found that, in women who were already depressed during pregnancy, the risk of depression after delivery was high (24%). Thus, it is possible that prior studies reporting higher rates of postpartum depression than what we found in our euthymic pregnant sample included women who were already depressed during pregnancy. Indeed, we have previously reported that in 22% of women referred for evaluation of postpartum depression, the onset of the episode occurred during gestation.[20] Additionally, there are reports that antenatal depression is a strong risk factor for postpartum depression.[7,21,22] Our data from subjects with histories of MDD who are euthymic in the third trimester suggest an 11% rate of depression in the postpartum period, equal to the rate of depression at any other time in a woman's life.

Another explanation for the higher rates of postpartum depression found in other studies compared to ours might be their inclusion of women with other recurrent mood disorders, including bipolar disorder. Postpartum depression has been reported at higher rates in women with bipolar compared to major depressive disorder (unipolar).[5,23–27]

It is important to note that while HDRS scores can indicate a clinical depression in pregnancy,[28] a total HDRS score in the "depressed" range during pregnancy is not absolutely indicative of clinical depression. This lack of correspondence of total HDRS score with clinical depression may be because a number of the somatic items of the HDRS can be elevated in pregnant women, even when they are not clinically depressed.[29] Our study found, however, that 3 specific items on the HDRS during pregnancy were individually highly predictive of developing a postpartum depression: work (item 7), suicidality (item 3), and early insomnia (item 4). While the obstetric setting seldom provides adequate time and focused training to provide a comprehensive psychiatric assessment for the risk of postpartum depression, identification of answers to 3 specific questions could enhance screening for risk of postpartum depression in women with a history of major depressive episodes. Although results from our study are premature to make global clinical recommendations, they do suggest that a positive response on questions related to insomnia, suicidality, and work (Table 4) could alert clinicians to patients who, while euthymic in pregnancy, might be at high risk for development of a postpartum depression. These women may benefit from being referred to a psychiatrist for closer monitoring after delivery.

Our study found that women in the third trimester who were euthymic and were on treatment with antidepressants were at a similar risk of experiencing postpartum depression as those euthymic women who were not on treatment with antidepressants (10% versus 13%, respectively). While the prophylactic use of antidepressants immediately after delivery has been reported to reduce the risk of postpartum relapse in women with a prior history of postpartum depression,[30,31] data on the efficacy of prophylactic treatment in the third trimester of pregnancy to reduce the risk for postpartum depression in women with histories of nonpuerperal major depressive episodes who are euthymic going into delivery are limited.[16] One recent study found a 40% rate of postpartum depression in 38 subjects with a prior history of mood disorder who were psychiatrically well during the third trimester, 80% of whom were on psychiatric medications.[16] The higher rate than we found in our study may be due to the inclusion of subjects with bipolar disorder and many women with prior histories of postpartum depression. Our findings add to the few studies that address this euthymic population and do not suggest that effective treatment during the third trimester with antidepressant medication in euthymic women with a history of unipolar major depression was protective against the development of postpartum depression. However, Mehta et al[10] found that a particular biomarker panel, measured in the third trimester of pregnancy in currently euthymic, pharmacologically treated women with a prior history of a mood disorder, was predictive of postpartum depression. Those results suggest

that a subset of women may be biologically vulnerable to the onset of postpartum depression despite adequate and effective antidepressant treatment during pregnancy. While our study did not examine biological risk factors, further understanding of the biological mechanisms underlying susceptibility to postpartum depression in women with histories of MDD would be important in refining treatment strategies for this population.

Strengths of the current study include its large sample size, prospective design, and assessment of MDD and depressive symptoms using structured clinical scales by raters blinded to the patients' medication status and illness history. One limitation is use of the *DSM-IV* diagnosis for MDD with a postpartum onset specifier. In the *DSM-IV*, postpartum depression required the onset of depressive symptoms after delivery. In the current *DSM-5*,[32] the specifier has been changed to "with peripartum onset," defining the episode of MDD occurring during pregnancy or within 4 weeks following delivery. Our study found significantly different rates of depression after delivery in women who were depressed versus euthymic during the third trimester (24% vs 11%). If depression with onset in the postpartum represents a different phenomenon than depression in postpartum that has continued from pregnancy, it raises the question of whether *DSM-5* criteria may confound future studies evaluating predictors of depression in the postpartum period. Other study limitations include the exclusion of women with suicidal ideation and substance abuse, which may affect the generalizability of our results to these populations.

This study is, to our knowledge, the largest prospective study that investigates the risk of postpartum depression in euthymic pregnant women with prior histories of MDD. Our study found that in women with histories of MDD who were euthymic in the third trimester of pregnancy, third trimester scores on the HDRS significantly predicted postpartum depression and that 3 specific items—functioning at work, suicidality, and early insomnia—were highly predictive of postpartum relapse. These 3 areas of questioning may be effective for screening in the psychiatric or the obstetrics and gynecology setting to assist clinicians in identifying persons at risk for developing a postpartum depression. Our findings also suggest that for women with a history of MDD who are euthymic in the third trimester, being on treatment with antidepressants may not necessarily provide protection against risk for depression after delivery.

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