Phenotypic Differences Between Pregnancy-Onset and Postpartum-Onset Major Depressive Disorder

Margaret Altemus, MD; Christine C. Neeb, BA; Alida Davis, BA; Mallay Occhiogrosso, MD; Theresa Nguyen, NP; and Kathryn L. Bleiberg, PhD

ABSTRACT

Objective: To compare clinical features of major depression that begins during pregnancy to clinical features of postpartum-onset depression. The hormonal environments of pregnancy and postpartum periods are quite different and therefore may promote distinct subtypes of major depression.

Method: Data were collected from medical records of 229 women who were evaluated in an academic medical center reproductive psychiatry clinic. All patients evaluated between 2005 and 2010 who were pregnant or in the first year postpartum and received a *DSM-IV* diagnosis of major depressive disorder were included. Comparisons between the pregnancy-onset and postpartum-onset subjects included demographics, psychiatric diagnostic history, psychosocial stressors, reproductive history, and current episode symptoms. Time of onset within trimesters of pregnancy and within the postpartum year as well as the effects of discontinuation of antidepressant medication were also examined.

Results: Women with major depressive episodes that began during pregnancy had higher rates of prior episodes of postpartum and nonperinatal major depression (both *P* values < .001). Major depression that began during pregnancy was also more commonly associated with psychosocial stressors. Obsessive-compulsive symptoms and psychotic symptoms were more common in postpartum-onset depression. These findings were also evident in the subgroup of 176 subjects who did not discontinue antidepressant medication during the year prior to development of perinatal depression. The onset of 94% of postpartum major depressive episodes occured within the first 4 months postpartum. Episodes of major depression during pregnancy were more likely to develop in the first trimester for women who discontinued antidepressant medication within the past year; otherwise, depression onset was more evenly distributed across trimesters.

Conclusions: Women with a history of perinatal and nonperinatal major depression are more likely to relapse during pregnancy than postpartum, a finding that points to the need for closely monitoring these women for depression during pregnancy. In addition, these findings of differences in risk factors and clinical features suggest that postpartum-onset major depression may have a pathophysiology distinct from major depression that begins during pregnancy. Time of onset of perinatal depression should be considered in the design of genetic and treatment studies.

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Corresponding author: *Margaret Altemus, MD, Box 244, 1300 York Ave, New York, NY 10064 (maltemus@med.cornell.edu).*

Despite widespread use of the term *postpartum depression*, the disorder has not been empirically validated as a distinct subtype of depression. It is unclear whether postpartum major depression is a syndrome with distinct pathophysiology, risk factors, and treatment response compared to nonperinatal major depression. It is not commonly appreciated that, in prospective studies, 18%–50% of major depressive episodes that are detected postpartum actually have an onset during pregnancy.[1–4] Postpartum depression is thought to be precipitated, at least in part, by hormonal changes. If so, major depression that begins during pregnancy, while reproductive hormone levels are very elevated, may have a different pathophysiology than depression that has a postpartum onset, when reproductive steroid levels are low.

In the vast majority of studies, the time of onset of postpartum depression is not clearly specified; only the prevalence of depression at each study time point assessment is reported.[5–8] A comprehensive review[9] of studies that used structured interviews to diagnose depression found that prevalence and incidence rates of major depression were not altered during pregnancy or postpartum compared to time periods not associated with pregnancy. There is some evidence[10] that rates of minor depression are increased in the early postpartum period. In contrast, there is broad agreement regarding a greatly increased risk of psychoses in the first month postpartum, which is most likely an expression of bipolar disorder and occurs much more rarely, with incidence rates of 0.1%–0.4%.[11–13]

There have been a few comparisons of characteristics of postpartum depression versus nonperinatal depression. Two studies[7,14] did not find differences in clinical features or risk factors between depression that was present postpartum and nonpregnancy-related depression. One study[15] used the 16-item Quick Inventory of Depressive Symptomatology,[16] and found that women with postpartum major depression had less sad mood, less suicidal ideation, and less loss of interest but more impairment of concentration and more restlessness/agitation than women whose depression was not related to pregnancy.

There also has been little examination of whether depression that begins during pregnancy differs from depression that begins postpartum. To date, a few studies[8,17,18] have reported that psychosocial stressors were more commonly associated with pregnancy-onset major depression than with postpartum-onset major depression. In addition, the study by Stowe et al[18] found more severe symptoms and more frequent history of depression if major depression began during pregnancy compared to the postpartum period.

None of these comparative studies considered what proportion of women discontinued psychotropic medication for their pregnancy, which is known to greatly increase risk of relapse

Clinical Points

- Risk of relapse of major depression may be higher during pregnancy than postpartum for women with a history of major depression, even if the prior major depression occurred postpartum.
- Among women seeking care at a psychiatric clinic, 94% of cases of major depression that had an onset during the postpartum period began within the first 4 months postpartum.

Table 1. Timing of Depression Onset

Depression Onset	All Subjects, n (%)	Antidepressant Discontinued, n (%)[a]	Antidepressant Independent, n (%)
Pregnancy	n = 113	n = 38	n = 75
First trimester	53 (47)	23 (61)	30 (40)
Second trimester	36 (32)	13 (34)	23 (31)
Third trimester	24 (21)	2 (5)	22 (29)
Postpartum, mo	n = 116	n = 15	n = 101
0–1	63 (54)	11 (73)	52 (51)
2–4	46 (40)	3 (20)	43 (43)
5–12	7 (6)	1 (7)	6 (6)

[a]Discontinued antidepressant medication includes the year prior to the start of the perinatal depression episode.

of recurrent unipolar depression and bipolar illness.[19,20] Studies of the risk factors associated with perinatal depression and timing of episodes may be confounded by relapses that are precipitated by discontinuation of antidepressant medication.

If there are pathophysiologic differences between pregnancy-onset depression and depression that has an onset postpartum, these differences would be important to consider in genetic studies and in the design of prevention and treatment efforts. To further examine this question, we conducted a chart review study comparing the clinical features of major depressive episodes that began during pregnancy to those that began postpartum.

METHOD

Data were collected from consecutive medical records of 229 women evaluated between 2005 and 2010 in a reproductive psychiatry outpatient program by experienced clinicians. The protocol was approved by the Weill Medical College Institutional Review Board. Subjects were included in the study if they were given a diagnosis of major depressive disorder that had an onset either during pregnancy or during the first year postpartum. Subjects were included only if they were assigned a *DSM-IV* diagnostic code of major depressive disorder by the clinician during the initial evaluation or subsequent treatment. No subjects with retrospectively diagnosed episodes were included. Most subjects were diagnosed with major depressive disorder during their initial evaluation in the clinic, but 15 subjects developed major depressive disorder during the course of ongoing monitoring or treatment.

Data were collected by reviewers blind to the hypotheses of the study. Ninety-two percent of charts were contained in an electronic medical record system. The initial evaluation electronic record contained fillable prompts for the psychiatric and psychosocial variables collected, except for whether the pregnancy was planned. Clinicians used a paper template during the evaluation interview to collect the information required in the electronic medical record. A narrative description was included in the electronic medical record for the initial evaluation and any subsequent visits.

Occurrence of intrusive violent thoughts and other obsessive-compulsive disorder (OCD) symptoms were included in the electronic medical record and scored as present for this study if they caused significant distress or functional impairment based on the narrative description. Because all subjects had a new-onset episode of major depression as the primary diagnosis, if subjects had obsessive-compulsive symptoms limited to the current depressive episode, a diagnosis of OCD was not made.

Most variables were rated as dichotomous, but 3 levels of severity were defined for pregnancy complications, nausea, partner discord, and social support: none, mild/moderate, and severe. Severity level was assigned based on narrative comments in the medical record. The highest level of severity was assigned for pregnancy complications that required hospitalization or caused functional impairment, hyperemesis, domestic violence or acrimonious separation from partner, and lack of any close friends or family able to provide support. In the analyses, the none rating and the 2 lower levels of severity were combined and compared to the highest level of severity. Information on whether the pregnancy was planned was missing for 57 subjects.

We used χ^2 statistics to compare categorical data between pregnancy- and postpartum-onset groups. Continuous variables were compared between pregnancy- and postpartum-onset groups by using 2-tailed *t* tests. The subgroup of women who had not discontinued antidepressant medication during the year prior to the start of this depressive episode (n = 176) was examined separately for some analyses.

RESULTS

Demographics and Antidepressant Use

One hundred thirteen women had onset of major depression during pregnancy, and 116 developed major depression during their first year postpartum. Twenty-seven women (24%) in the pregnancy-onset group did not present for consultation until after delivery. Proportions of subjects who had onset of major depression in each trimester and in postpartum month 1, months 2–4, and months 5–12 are presented in Table 1. There were no differences in demographic variables between the pregnancy-onset and postpartum-onset groups (Table 2).

Fifty-three of the 229 subjects (23%) discontinued antidepressant medication during the year prior to the start

Table 2. Psychiatric History and Risk Factors

Variable	Pregnancy Onset (n = 113), n (%)	Postpartum Onset (n = 116), n (%)	χ^2	*P* value
Demographic				
Age, y	32.4 ± 0.6[a]	31.9 ± 0.6[a]	0.3[b]	.6
Primiparous	63 (56)	75 (65)	1.9	.2
White	85 (75)	88 (76)	0.4	.9
African American	8 (7)	6 (5)		
Asian	6 (5)	6 (5)		
Mixed race	7 (6)	8 (7)		
Hispanic	7 (6)	9 (8)	0.2	.6
Psychosocial and medical risk factors				
Hyperemesis	2 (2)	4 (3)	0.6	.4
Maternal pregnancy complication	8 (7)	21 (18)	6.3	< .01
Infant medical complications	7 (6)	22 (19)	8.8	< .01
Single mother	11 (10)	7 (6)	1.1	.3
Partner discord	19 (17)	11 (10)	2.7	.1
Social support low	21 (19)	8 (7)	7.6	< .01
Abuse history	31 (27)	18 (16)	4.7	< .03
Unplanned pregnancy	33 (38)[c]	20 (23)[c]	4.6	< .04
Infertility treatment	11 (10)	14 (12)	0.3	.6
Psychiatric history				
Major depressive disorder	89 (79)	52 (45)	27.9	< .0001
Nonperinatal depression	75 (66)	47 (41)	18.4	< .0001
Prior postpartum depression	28 (57)[d]	6 (15)[e]	17.0	< .0001
Obsessive-compulsive disorder	3 (3)	5 (4)	0.5	.5
Panic disorder	21 (19)	16 (14)	0.9	.3
Bipolar disorder	5 (4)	6 (5)	0.1	.8
Generalized anxiety disorder	37 (33)	39 (34)	0.1	.7
Suicide attempts	19 (17)	12 (10)	2.0	.2
Antidepressant discontinued < 1 year prior to onset	38 (34)	15 (13)	14.1	< .001
Taking antidepressant at onset	17 (15)	9 (8)	3.1	.1

[a]Value indicates mean ± SD. [b]*F* test. [c]n = 86. [d]n = 49. [e]n = 40.

of the perinatal depression episode. More women in the pregnancy-onset group than the postpartum-onset group had discontinued antidepressant medication within the year prior to onset of depression (34% vs 13%, $\chi^2 = 14.1$, $P < .001$). Among the women who had depression that began during pregnancy, medication discontinuation was associated with a higher likelihood of onset during the first trimester of pregnancy (Table 1).

Twenty-eight subjects developed major depression despite use of antidepressant medication. This disorder occurred in 17 women (15%) in the pregnancy group and 9 women (8%) in the postpartum group, which was not a statistically significant difference ($P = .1$; Table 2).

Several clinical features differed between the pregnancy-onset and postpartum-onset groups. There were differences in psychiatric history, psychosocial risk factors, and differences in symptom profile of the current episode.

Psychiatric History

Women who had developed major depression during pregnancy were much more likely to have a history of major depression (Table 2). Although more women had recently discontinued antidepressant medication in the pregnancy-onset group, the higher rates of prior depressive episodes were also evident in the subgroup of 176 subjects who had not discontinued antidepressant medication in the previous year (pregnancy onset, 52/75 [69%] vs postpartum onset, 40/101 [40%]; $\chi^2 = 15.5$, $P < .0001$). In the postpartum group, a past history of major depression was more common among women who developed major depression during the first month postpartum (34/63 [54%]) than among women who had depression onset within the following 3 months (15/46 [33%], $\chi^2 = 23.9$, $P < .0001$). However, rates of prior major depression were still lower in the early postpartum–onset group compared to the group who had major depression develop during pregnancy (54% vs 79%, $\chi^2 = 23.9$, $P < .0001$).

Thirty-eight percent of multiparous women reported a history of postpartum depression, although we were unable to determine from the chart reviews whether these episodes began during a prior pregnancy or the postpartum period. Among women who reported a prior postpartum depression, the current episode was more likely to begin during pregnancy versus postpartum (Table 2). This difference was not related to medication discontinuation since it was still evident in the subgroup of subjects who did not use antidepressants in the year preceding the current episode (19/24 [79%] vs 5/24 [21%], $\chi^2 = 16.9$, $P < .0001$).

Rates of premorbid panic disorder, OCD, generalized anxiety disorder, and bipolar disorder did not differ between pregnancy-onset and postpartum-onset groups (Table 2). The rate of prior suicide attempts was 14% and did not differ between groups.

Psychosocial and Medical Risk Factors

History of physical or sexual abuse or both, poor current social support, and unplanned pregnancy were significantly higher in the group who had a new episode of major

Table 3. Symptom Profile

Symptom	Pregnancy Onset (n = 113), n (%)	Postpartum Onset (n = 116), n (%)	χ^2	*P* Value
Intrusive violent thoughts	5 (4)	20 (17)	10.3	< .01
Other OCD symptoms	5 (4)	15 (13)	5.4	< .02
Agitation	11 (10)	12 (10)	0.0	.88
Psychomotor retardation	11 (10)	10 (9)	0.1	.77
Insomnia	82 (73)	76 (66)	1.1	.29
Hypersomnia	7 (6)	6 (5)	0.1	.75
Panic attacks	21 (19)	21 (18)	0.0	.95
Psychosis	2 (2)	12 (10)	8.0	< .01
Suicidal ideation	24 (21)	34 (29)	3.4	.18

depression during pregnancy. On the other hand, maternal pregnancy complications and infant medical complications were higher in the postpartum-onset group. The groups did not differ in rates of single motherhood, partner discord, infertility treatment, or hyperemesis (Table 2). Within the subgroup of patients who did not discontinue antidepressant medication, 2 of the following 3 psychosocial risk factors were also more likely to be associated with pregnancy-onset than postpartum-onset major depression: physical or sexual abuse ($\chi^2 = 2.4$, $P = .1$), low social support ($\chi^2 = 6.1$, $P < .05$), and unplanned pregnancy ($\chi^2 = 4.9$, $P < .03$). Rates of reproductive stressors in prior pregnancies were 13% for pregnancy losses, 10% for elective termination, and 14% for medically complicated pregnancy, and they did not differ between the 2 groups of subjects.

Symptom Profile

The incidence of intrusive violent thoughts was significantly higher in women with postpartum-onset depression than in those with pregnancy onset (Table 3). The same increased incidence of intrusive violent thoughts was evident within the medication independent subgroup (n = 176; 19% vs 6%, $\chi^2 = 7.0$, $P < .01$). Other OCD symptoms were also more common if major depression began postpartum (Table 3). Only 3/25 women (12%) who had intrusive violent thoughts during their perinatal depression had a history of OCD, and 2/25 (8%) had a history of subclinical obsessive-compulsive symptoms. A history of OCD was more common in women who had other obsessive-compulsive symptoms during their perinatal depression: 6/20 (30%) had a history of OCD and another 4 women (20%) had a history of subclinical OCD symptoms. Of note, 4 of the 27 subjects who had major depression that started during pregnancy and presented for evaluation postpartum had comorbid obsessive-compulsive symptoms, which, in all 4 cases, emerged after delivery.

As expected, psychotic symptoms were more common when depression began postpartum (Table 3). Among the 27 women with pregnancy-onset depression who presented for evaluation in the postpartum period, none developed psychotic symptoms postpartum.

Regarding other current episode symptoms, there was no difference between pregnancy and postpartum groups in incidence of insomnia, hypersomnia, panic symptoms, psychomotor retardation, agitation, or suicidal ideation (Table 3).

DISCUSSION

This study revealed several differences between major depressive episodes that began during pregnancy and episodes that began postpartum.

First, women with major depression that developed during pregnancy had much higher rates of prior episodes of major depression. When major depression did occur in the postpartum period, its onset was rarely after the first 4 months postpartum. These findings are consistent with one prior study by Stowe et al[18] comparing major depression that began during pregnancy versus postpartum. In contrast to results in the study by Stowe et al,[18] we found that the early postpartum–onset group (0–4 weeks postpartum) still had a lower rate of prior history of depression than the group who had major depression during pregnancy. This difference between studies could be owing to the larger number of pregnant subjects in our study. Also in contrast to the study by Stowe et al[18] is our finding of a significantly higher rate of history of nonperinatal depression in the pregnancy-onset versus the postpartum-onset group, again possibly due to the larger number of pregnant patients in our study.

Although we were not able to determine whether prior episodes of postpartum depression began during pregnancy or postpartum, the finding that a prior episode of postpartum depression was associated with onset of the subsequent episode during pregnancy suggests that the initial episode of postpartum depression may cause a lasting change in vulnerability to depression during pregnancy. This finding is consistent with an experimental study by Bloch et al,[21] in which subjects with a history of postpartum depression were administered estradiol and progesterone in doses to mimic pregnancy levels of these hormones. Subjects with a history of postpartum depression relapsed during the weeks of hormone administration, and the depression persisted into the "postpartum" period after hormone dosing was discontinued.

Our finding of increased likelihood of major depression beginning during pregnancy versus postpartum in women with a history of major depression contrasts with a recent study by Viguera et al,[22] who collected primarily retrospective reports of perinatal depression from a large sample of women undergoing treatment for recurrent major depression. In that study, women who had episodes of major depression prior to their first pregnancy had an increased

risk of recurrence of major depression postpartum but not an increased risk of recurrence during pregnancy. More careful prospective study of the actual time of onset of perinatal depression episodes in women with a history of depression is needed to resolve these conflicting findings.

Second, depression that began during pregnancy was differentially associated with lack of social support, unplanned pregnancy, and a history of physical or sexual abuse, a result that is consistent with several other studies[8,17,18] which found that psychosocial stressors were more often associated with depression during pregnancy versus postpartum depression. The lack of association of single motherhood with pregnancy-onset compared to postpartum-onset depression in our sample, in contrast to other studies, is most likely because of the very small number of single mothers in our study. Rates of maternal and infant medical complications are most likely higher in the postpartum group because subjects in the pregnancy group were assessed prior to delivery and thus had less potential exposure to these stressors. A lower rate of medication discontinuation in the postpartum depression group is more likely a result of most medication discontinuation occurring in preparation for pregnancy rather than a differential impact of medication discontinuation as a risk factor in pregnancy versus postpartum.

Third, the symptom profile differed between pregnancy-onset major depression and postpartum-onset major depression. Women with major depression that began postpartum were more likely to experience distressing intrusive violent thoughts and other obsessive-compulsive symptoms, a finding that is consistent with multiple reports of high rates of obsessive-compulsive symptoms in women with postpartum depression.[23–25] The course of OCD and OCD symptoms that develop during the perinatal period remains to be described. There is evidence that subclinical OCD symptoms in pregnant women who are not depressed may decrease postpartum[26] and that subclinical intrusive thoughts of harming the infant that begin in the early postpartum are much less frequent by 12 weeks postpartum.[27] Retrospective studies[28–30] of the perinatal experiences of women with chronic OCD indicate a heterogeneous response to pregnancy; perinatal new onset of OCD was equally likely to occur during pregnancy or postpartum, and equal proportions of women with OCD reported experiencing worsening or improvement associated with pregnancy. Women who had a history of perinatal onset or worsening of OCD were more likely to report premenstrual worsening of OCD, suggesting a subtype of OCD that is sensitive to gonadal steroids.[28] Two studies,[26,31] but not a third study,[28] found increased rates of aggressive obsessions in OCD that began in the perinatal period compared to nonperinatal-onset OCD.

In addition, women with major depression that began postpartum were more likely to have psychotic symptoms than those who developed major depression during pregnancy. This finding is consistent with a prior study[32] of hospitalized women with major depression that demonstrated higher rates of psychosis in postpartum compared to nonpostpartum women. Women with a premorbid diagnosis of bipolar disorder were not excluded from this study, but rates of this diagnosis were very low and did not differ between the pregnancy-onset and postpartum-onset groups. Of note, none of the 27 women in this study who had major depression that began during pregnancy and who presented for evaluation postpartum developed psychotic symptoms postpartum.

There is ongoing controversy regarding the time of onset criteria for a postpartum depression diagnostic specifier. *DSM-IV-TR*[33] currently specifies onset within 4 weeks postpartum and *ICD-10*[34] within 6 weeks postpartum. In our clinic sample, 94% of the cases of postpartum major depression began within the first 4 months postpartum and 54% within the first 4 weeks. These rates are consistent with a similar study by Stowe et al,[18] in which 95% of postpartum depression onset occurred within the first 4 months postpartum and 75% onset occurred within the first 6 weeks postpartum. A longitudinal study found that insomnia and thoughts of death at 1 month postpartum predicted development of depression by 4 months postpartum,[35] suggesting that postpartum depression that meets criteria for major depression between 2 and 4 months postpartum may begin to develop within the first few weeks after birth.

In agreement with one prior study[36] but not others,[18,37] we found that major depression was more likely to have its onset in the first trimester compared to second or third trimester of pregnancy. In our sample, this finding was evident only in subjects who had discontinued medication within the previous year.

We are unable to comment on the natural course of untreated major depression that begins during pregnancy or postpartum since women in this study were either seen once in consultation or received medication, psychotherapy, or both, which would alter the natural course of the illness. In a large, longitudinal study[8] of low-income pregnant women, half of the cases of depression identified at week 15 of pregnancy had resolved by 3 weeks postpartum, but women with depression first detected at 3 weeks postpartum had only slight resolution of symptoms at 12 months postpartum and more complete remission at 24 months postpartum.

One of the limitations of our study is that it consists of women who presented for treatment, and, thus, the findings may not generalize to a community sample. In particular, the proportion of women who were using antidepressant medication in the year preceding pregnancy may be higher in this sample collected from a reproductive psychiatry clinic. In addition, we did not collect data on illness severity, alcohol use, lactation status, or socioeconomic status. Standardized rating scales were not used, but they could have provided more accurate severity ratings for depression, OCD symptoms, abuse, and social support. Our clinic is located in midtown Manhattan, a high-income area. This demographic is reflected in the low rate of single mothers and low rates of minority subjects. Another limitation is that we did not adjust statistical tests for the number of comparisons. However, all of our positive findings are supported in the existing literature. This study cannot distinguish whether differences

between pregnancy-onset and postpartum-onset depression are due to hormone differences or difference in psychosocial stressors between these 2 time periods. A comparison between adoptive and biological mothers of infants could be helpful in this regard.

These findings have important implications for perinatal depression screening. Women with a history of major depression should be screened beginning in the first trimester in order to ensure prompt detection and treatment to prevent adverse impact on the mother and infant. Depressed mood during pregnancy has been associated with poor attendance at antenatal clinics, substance misuse, low birth weight, and preterm delivery.[38] Differences between pregnancy-onset and postpartum-onset depression also should be considered in the design of biomarker and treatment studies. Genetic and other biological vulnerabilities that may predispose individual women to peripartum depression may be differentially amplified or mitigated during pregnancy, when levels of reproductive steroid hormones and corticotropin-releasing hormone are high, versus postpartum, when gonadal steroid levels drop precipitously and brain levels of lactational hormones are elevated.[39] Preliminary trials suggest that estrogen treatment may be effective for postpartum depression,[40] but women who have major depression that begins during pregnancy, when estradiol levels are high, may not respond as well to increased estradiol exposure.

In summary, findings from this chart review study provide further support for the notion that major depression that begins postpartum, particularly major depression that has an onset between 4 weeks and 4 months postpartum, is less related to the typical risk factors of psychosocial stress and prior history of depression and is distinguished by higher rates of clinically significant OCD symptoms. These observations point out the need for further studies to determine whether women with postpartum-onset depression have differential sensitivity to the hormonal changes of pregnancy and whether postpartum depression has a distinct pathophysiology.

Author affiliations: Department of Psychiatry, Weill Medical College, Cornell University, New York (Drs Altemus, Occhiogrosso, and Bleiberg and Mss Davis and Nguyen); and University of Rochester School of Medicine, Rochester (Ms Neeb), New York.
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