Are Mixed Symptoms a Red Flag for Conversion of Postpartum Depression to Bipolar Disorder?

To the Editor: Hypomanic and manic symptoms are common in the postpartum period and can occur alone or in combination with symptoms of depression.[1] The *DSM-5* mixed-features specifier requires the presence of 3 or more hypomanic or manic symptoms in a major depressive episode occurring as part of bipolar disorder or major depressive disorder.[2] Given the ubiquity of hypomanic and manic symptoms after delivery, mixed symptoms may be more common after childbirth compared to other periods in a woman's life.[3] A recent study[4] from Turkey found that approximately 71% of women in the postpartum period had 3 manic symptoms; however, it is unclear how many of the women with manic symptoms met *DSM-5* criteria for major depressive disorder.

In a US study[5] on the treatment of bipolar depression, Young Mania Rating Scale (YMRS) scores at baseline were associated with treatment-emergent hypomania or mania following use of antidepressants. The YMRS items that predicted treatment-emergent mania in this study[5] included increased motor activity, speech, and language-thought disorder. Similarly, use of antidepressants can lead to emergence of mixed states, increased cycle frequency, and postpartum psychosis in women with postpartum depression. Discontinuation of antidepressants and treatment with mood stabilizers often leads to better outcomes in these patients.[6] Women with mixed symptoms in the postpartum period are also at greater risk of developing thoughts of self-harm.[1] Thus, consideration of mixed symptoms is important for selection of safe and efficacious treatments for women with postpartum depression.

Here, case histories are presented of 2 women with mixed depression who were previously treated with antidepressants but developed mood instability after retrials of previously effective and well-tolerated antidepressants. The role of mixed features in the induction of hypomania is discussed, and suggestions are made for management of postpartum depression with mixed features.

Case 1. A 27-year-old married woman was referred to a psychiatry clinic by her family physician for postpartum depression that began within 2 weeks after her first delivery. Her family history was positive for untreated postpartum depression in her sister.

Diagnostic assessment at our clinic confirmed the *DSM-5* diagnosis of major depressive disorder with mixed features and peripartum onset. The mixed features included pressured speech, racing thoughts, and increased goal-directed activity. She endorsed 4 items with co-occurrence of symptoms and no functional impairment on the Mood Disorder Questionnaire (MDQ).[7] Due to the presence of mixed symptoms, a trial of quetiapine was recommended, but the patient opted instead for a retrial of sertraline, stating that she did not wish to try an antipsychotic drug. She had tried sertraline 150 mg for depression in the past and felt it was effective and well tolerated. Sertraline was started at 25 mg, and the dose was optimized to 100 mg over a 2-week period.

When reassessed a month later, the patient admitted to using alcohol for insomnia and anxiety and stated that she had been having cravings for cocaine, which she had used as a teenager. Upon questioning, she endorsed symptoms suggestive of hypomania including euphoria, racing thoughts, risk-taking behavior, pressured speech, decreased sleep requirement, and increased sexual desire. She scored 10 on the MDQ with co-occurrence of symptoms and moderate functional impairment, indicating a positive screen for bipolar disorder. The diagnosis was changed to bipolar II disorder (per *DSM-5*). She was treated with quetiapine 50 mg at bedtime after tapering off sertraline. At her next appointment a month later, the symptoms had fully resolved. She has maintained improvement in her mood and has been free of mood symptoms for 8 months.

Case 2. A 23-year-old married woman was referred to a psychiatry clinic with a history of recurrence of depression during her first pregnancy. There was no known family history of psychiatric illness. At the time of initial consultation at 35 weeks' gestation, she denied any current symptoms of hypomania. She met *DSM-5* criteria for major depressive disorder with peripartum onset.

The patient endorsed only 1 item (racing thoughts) on the MDQ. Due to the moderate severity of depression, an antidepressant was recommended, but she refused to take the medication due to concerns regarding the safety of the fetus. She agreed, however, to regular follow-up appointments for symptom monitoring during and after pregnancy. The depression persisted during pregnancy with worsening of symptoms immediately after delivery.

When assessed 3 weeks after delivery, the patient endorsed 4 items on the MDQ including pressured speech, increased energy, decreased sleep requirement, and racing thoughts. This time she met *DSM-5* criteria for a mixed specifier. Due to the worsening of depressive symptoms, she agreed to a trial of citalopram, which she had tried in the past with benefit and no occurrence of hypomania. She was prescribed citalopram 10 mg for 1 week, and the dose was doubled thereafter. Two weeks following the initiation of citalopram, she was seen on an urgent basis with complaints of worsening of racing thoughts, agitation, and irritability. She was advised to stay on the current dose of citalopram, and quetiapine 25 mg a day was added.

At her next appointment 2 weeks later, she was quite depressed but described having had a 4-day hypomanic episode in the interim. Her MDQ score had jumped to 11, and she met *DSM-5* criteria for bipolar II disorder. Citalopram was tapered off, and the quetiapine dose was increased to 75 mg at bedtime. Within a month, her mood had stabilized. She continued to do well on the same dose of quetiapine for 6 months, which she then tapered off due to weight gain.

These patients appear to have developed hypomanic symptoms for the first time after delivery. The symptoms evolved into hypomanic episodes after a rechallenge of previously effective antidepressants, suggesting that the common occurrence of mixed symptoms after childbirth may increase the risk for women to have first onset of hypomania when treated with antidepressants. It is possible that there were antidepressant-induced hypomanic symptoms in the past that were not elicited. This explanation is unlikely because collateral information obtained from family members did not support a history of hypomania in the past. An alternate explanation is that patients may respond differently to the same antidepressant at different times. In other words, childbirth may not have played a role in the emergence of hypomanic symptoms. Once again this is unlikely because the patient in case 2 had a progression in the MDQ score from pregnancy to postpartum with further increase following the initiation of citalopram.

These cases suggest that women presenting with major depressive disorder in the postpartum period should be assessed for hypomania or mania before initiating treatment. It is important

to note that the *DSM-5* does not allow the inclusion of irritability, distractibility, and psychomotor agitation toward diagnosis of mixed episodes even though these symptoms appear to be common in patients with mixed depression.[8] When considering the use of antidepressants, the risk of treatment-emergent mania or hypomania should be carefully weighed against the potential benefit of antidepressant treatment.[9] Women receiving antidepressants for major depressive disorder with postpartum onset should be informed of the risk of mood instability following the use of these drugs even when there is no prior history of antidepressant-induced hypomania.

The MDQ is a validated screening tool for bipolar disorder during or after pregnancy,[10,11] but there are no reports of its use in detecting emerging manic symptoms when depressed patients are followed over time. The MDQ, when administered serially, was helpful in the early identification of emerging manic symptoms in the patients presented here. The Clinically Useful Depression Outcome Scale supplemented with questions for the *DSM-5* mixed features specifier is a reliable and valid measure of the *DSM-5* mixed features specifier for MDD[12]; however, it has not been validated in the peripartum period. The modified Hypomania Checklist[13] is another useful tool that can be used to screen for hypomanic symptoms in patients with depression.

Antidepressants are the mainstay of pharmacologic treatment of postpartum depression in spite of the paucity of controlled studies demonstrating superiority of antidepressants over placebo. Antidepressants were more efficacious than placebo in only 2 studies of a total of 7 placebo-controlled randomized controlled trials.[14] The apparent poor performance of antidepressants in controlled trials in postpartum depression could have resulted from the failure of researchers to take into account the presence or absence of mixed features when reporting treatment effects.

Although there are no controlled trials of quetiapine in unipolar postpartum depression, there is preliminary evidence that the drug may be effective in women with bipolar postpartum depression.[15] Given the potentially serious consequences of antidepressant use, including increased risk of psychiatric hospitalization and safety concerns for the mother and her baby, a trial of quetiapine in a low dose should be considered in women presenting with mixed depression in the postpartum period. Quetiapine appeared effective in the acute and maintenance treatment of bipolar II disorder in the cases described here.

To make an informed decision on the appropriate route of treatment for mixed symptoms after childbirth, screening for hypomania and mania is recommended. Use of antidepressants may exacerbate mixed symptoms in the postpartum period, leading to an increased risk of first-onset hypomania. As such, careful attention to hypomanic symptoms is suggested when antidepressants are used in the treatment of postpartum depression.

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Potential conflicts of interest: Dr Sharma has received grant support from, participated on scientific advisory boards for, or served on speakers bureaus of Assurex, Genome Canada, Neurocrine Biosciences, Stanley Medical Research Institute, and Sunovion.

Funding/support: None.

Patient consent: Written consent was obtained from the patients to publish the cases, and information was de-identified to protect anonymity.

Published online: May 3, 2018.

Prim Care Companion CNS Disord 2018;20(3):17l02201

To cite: Sharma V. Are mixed symptoms a red flag for conversion of postpartum depression to bipolar disorder? *Prim Care Companion CNS Disord*. 2018;20(3):17l02201.

To share: https://doi.org/10.4088/PCC.17l02201