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Primacy of (hypo) mania in the postpartum period: a concept worth considering

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Primacy of (hypo) mania in the postpartum period: a concept worth considering

The traditional system of classifying postpartum psychiatric disorders into maternity blues, postpartum depression, and puerperal psychosis overlooks the clinical significance of hypomanic, manic, or mixed symptoms in the postpartum period. Although common after childbirth, episodes of hypomania or non-psychotic mania, as well as mixed states, are generally not included in the traditional nomenclature. The Diagnostic and Statistical Manual of Mental Disorders (DSM) first acknowledged the role of childbirth in the triggering of manic episodes 25 years ago with the publication of its fourth edition. The official recognition that episodes of hypomania can occur during or after pregnancy came in 2013 with the publication of DSM-5. Unfortunately, this endorsement by the DSM has not resulted in increased awareness of the common occurrence of hypomania or mania during the postpartum period.

In the nineteenth century, mania was a common diagnosis among women hospitalized after childbirth. In his classic text *Traite de la folie des femmes enceintes, des nouvelles accouchees et des nourrices*, Marcé reported 44 cases of puerperal psychosis, of which 29 were of mania.¹ He was the first to recognize mixed states during the puerperal and postpartum disorders: "...we find in the puerperal state a small number of mixed states that are impossible to classify or to clearly define..." In the book *Mental Maladies: A treatise on insanity*, Esquirol noted that 49 out of 92 women with severe postpartum psychiatric illness suffered from mania. Macleod made a distinction between cases that arise early and those that appear late in the postpartum period. Cases occurring early in the postpartum period were likely to have "excitatory or manic qualities" in contrast to the melancholic cases that generally but not always occurred later in the postpartum period. With the beginning of deinstitutionalization in the 1960s, the focus started

shifting from severe mental illnesses, such as mania or melancholia, to the study of more common postpartum clinical entities, such as the maternity blues and mild depression. The waning of interest in postpartum mania seems to have coincided with the discovery of antidepressants in the 1950s. Common usage of the term “puerperal psychosis” to capture cases of mania with or without psychotic features also resulted in lack of interest in the study of postpartum mania.

In women with bipolar disorder, postpartum mood episodes should be easily preventable because at-risk women can be easily identified, the nature of the trigger is known, and the risk period for occurrence of mood episodes is short. However, studies have found high rates of recurrence of mood episodes—particularly depression—despite the prophylactic use of pharmacotherapy.

Although sparse in nature, the extant literature on the acute or prophylactic treatment of postpartum mood disorders has demonstrated that medications are not particularly effective in reducing the depression morbidity after delivery. In spite of prophylactic treatment, women with bipolar disorder are at high risk for recurrence of mood or psychotic episodes in the postpartum period. A large study from the United States and Italy found that 52% of women with bipolar I or II disorder had recurrence of a mood or anxiety episode during the first 6 months postpartum.²

The primacy of mania hypothesis was proposed by Dr. Athanasios Koukopoulos. The primary empirical predictions based on the hypothesis are outlined in Panel 1. According to the hypothesis, manic and depressive states are intrinsically linked, and depression is a consequence of manic states. The connectedness of manic symptoms and depression is best exemplified by mixed states. In this context, the term “mania” includes not only episodic euphoria plus hyperactivity, but it encompasses a wide range of excitatory symptoms including irritability, psychomotor agitation and distractibility. Thus, the prevention or treatment of excitatory

behaviors that characterize mania should result in the prevention of ensuing depression.

Moreover, the use of antidepressants in patients with mixed episodes would be ineffective or would lead to mood instability.³

According to a recent systematic review, 9.6-49.1% of women have hypomanic symptoms after delivery. Of women referred to speciality clinics, 12-30% reported experiencing hypomanic or manic symptoms after childbirth.⁴ We argue that the primacy of (hypo) mania concept may be particularly relevant in the postpartum period due to the common occurrence of hypomanic/manic symptoms.^{2,4} Specifically, treatment approaches emphasizing prevention of hypomania or mania may be more effective in reducing postpartum morbidity and promoting safety in women with bipolar disorder.

Diagnostic and treatment implications

Over the last few decades, unipolar postpartum depression has been the focus of major research inquiry. Due to the increased awareness of associated morbidity and mortality, and of its deleterious effects on child health and development, women are more likely to be screened for depression than for hypomanic or manic symptoms. The common knowledge of available treatments, including antidepressants and psychotherapy, has made it easier for women to seek help for depression in the postpartum period. Despite clear guidance from major classification manuals that women with major depressive disorder or bipolar disorder can experience a depressive episode in the postpartum period, the term postpartum depression has become synonymous with unipolar postpartum depression.

Our emphasis on the detection and management of hypomania or mania to prevent postpartum depression is a paradigm shift from how postpartum mood disorders are currently assessed and

managed. Unless asked specifically, women do not generally report symptoms of postpartum hypomania or mania. Clinicians may focus solely on unipolar depression and not ask pertinent questions to clarify the bipolar diathesis of postpartum depression. Episodes of hypomania can be easily missed because they are generally not severe enough to cause marked social or occupational impairment, or necessitate hospital admission. Moreover, it can be difficult to distinguish between symptoms of hypomania and normal elation accompanying the birth of a child.

Major depressive disorder with mixed features (mixed depression), generally considered a pre-bipolar condition, first appeared as a diagnostic entity in the DSM-5. The DSM-5 allows the use of the mixed features specifier to characterize a current mood episode in the context of bipolar I, bipolar II, or major depressive disorder. At least three hypomanic or manic symptoms that do not overlap with symptoms of a major depressive episode are required for application of the mixed features specifier in patients with major depressive disorder. According to the primacy of (hypo) mania hypothesis, antidepressants should play a limited role in the management of postpartum mood disorders and should only be considered in women with non-mixed depression.

Despite the paucity of controlled data on their efficacy, antidepressants are commonly prescribed for the acute and preventative treatment of postpartum depression. Due to their ease of use and reduced liability for weight gain, clinicians may be more comfortable prescribing antidepressants than atypical neuroleptics or other mood stabilizers. Women with a bipolar diathesis may be more agreeable to try selective serotonin reuptake inhibiting antidepressants because these drugs are perceived as less stigmatizing than atypical antipsychotics or mood stabilizers.

A personalized and targeted approach to pharmacotherapy of postpartum mood disorders, guided by the primacy of (hypo) mania hypothesis, may reduce the need for polypharmacy and lessen

side effect burden. Given the frequency of hypomanic or manic symptoms immediately following delivery and their association with postpartum depression, strategies aimed at prevention or treatment of these symptoms may be more effective in preventing episodes of depression. Drug treatment of hypomania is generally not recommended unless symptoms are severe or functionally impairing; however, the prevention or treatment of these symptoms may be effective in preventing episodes of postpartum depression. Similarly, mood stabilizers and atypical neuroleptics may be better choices than antidepressants in the treatment of mixed depression after delivery since antidepressants may be ineffective or may exacerbate subthreshold manic symptoms.

Limitations

A major limitation of the primacy of (hypo) mania hypothesis is that it has not been tested in the postpartum population. In fact, this concept is not very popular even among researchers in the bipolar field. Given the reasons outlined in this article we believe that the primacy of (hypo) mania hypothesis may be particularly relevant in the postpartum period. Episodes of hypomania or mania do not always precede or co-occur with episodes of depression. Symptoms of hypomania can be difficult to detect in the postpartum period, particularly among women with no prior history of these symptoms. Also, a large number of women do not receive an accurate diagnosis of bipolar disorder before they have children and hence may not be referred for psychiatric care during or after pregnancy.

Future research

It is hoped that the proposed reconceptualization of postpartum mood disorders would stimulate research on alternate ways of assessing and treating postpartum mood disorders. The postpartum period should provide a remarkable opportunity to test the validity of the primacy of (hypo) mania hypothesis because symptoms of hypomania or mania are common after delivery and they usually precede rather than follow postpartum depression. Moreover, the time interval between the end of hypomania or mania and ensuing depression is generally short, which should make it easier to assess the impact of acute and preventative treatment strategies in postpartum mood disorders.

Currently, there are no studies on the potential effect of polarity of first onset on the sequence of mood episodes in the postpartum period.⁵ Such studies should provide crucial information to facilitate the early identification of women who develop hypomanic or manic episodes immediately after delivery, and therefore permit the implementation of a personalized treatment approach to prevent mood episodes. Studies using alternate drugs such as mood stabilizers or atypical neuroleptics are urgently needed given the limited evidence of antidepressant efficacy in the acute treatment of unipolar postpartum depression. Knowledge of the timing of onset of mood episodes (pregnancy vs. postpartum) and the nature of subthreshold symptoms preceding mood episodes is necessary for implementation of effective prophylactic interventions.

Similarly, there are no psychotherapeutic studies in the prevention of bipolar disorder in the postpartum period. According to the primacy of (hypo) mania hypothesis, psychotherapeutic strategies aimed at prevention of hypomania or mania may be effective in preventing depression. Circadian rhythm disruptions are particularly common in the postpartum period and may play a crucial role in triggering or exacerbating mood episodes in women with bipolar disorder. Thus the prophylactic use of interpersonal and social rhythm therapy—due to its emphasis on

promoting sleep—may be particularly effective in preventing subthreshold hypomanic or manic symptoms and therefore depression.

Conflicts of interest

Verinder Sharma reports personal fees from the Neuroscience Education Institute and grants from Assurex, Genome Canada, Sage Therapeutics, Stanley Medical Research Institute, and Sunovion Pharmaceuticals, and participation on the advisory boards for Sunovion Pharmaceuticals and Otsuka, outside the submitted work. Adele C Viguera reports grants from Alkermes, Otsuka America Pharmaceutical, Sage Therapeutics, Sunovion Pharmaceuticals, Teva Pharmaceutical and Forest/Actavis, outside the submitted work. All other authors declare no competing interests.

References

1. Trede K, Baldessarini RJ, Viguera AC, Bottro A. Treatise on insanity in pregnant, postpartum, and lactating women (1858) by Louis-Victor Marcé: A commentary. *Harv Rev Psychiatry*. 2009;17(2):157-165.
2. Viguera AC, Tondo L, Koukopoulos AE, Reginaldi D, Lepri B, Baldessarini RJ. Episodes of Mood Disorders in 2,252 Pregnancies and Postpartum Periods. *Am J Psychiatry*. 2011;168(11):1179-1185. doi:10.1176/appi.ajp.2011.11010148
3. Koukopoulos A, Ghaemi SN. The primacy of mania: A reconsideration of mood disorders. *Eur Psychiatry*. 2009;24(2):125-134.
4. Sharma V, Singh P, Baczynski C, Khan M. A closer look at the nosological status of the highs (hypomanic symptoms) in the postpartum period. *Arch Womens Ment Health*. February 2020.

5. Baldessarini RJ, Tondo L, Visioli C. First-episode types in bipolar disorder: Predictive associations with later illness. *Acta Psychiatr Scand.* 2014;129(5):383-392.

Panel 1: Empirical predictions based on the primacy of (hypo) mania hypothesis

1. There will be a shorter interval between the end of a manic episode and the onset of the next depressive episode compared to the interval between the end of a depressive episode and the onset of the next manic episode.
2. Mood stabilizers will be more effective in preventing mood episodes if started during a euthymic interval rather than during a manic episode.
3. Mood stabilizers will be ineffective (compared to placebo) in the treatment of pure depressive episodes (i.e., depressive episodes without concomitant hypomanic or manic symptoms).
4. Antidepressants will be ineffective in the treatment of depressive mixed states; conversely, mood stabilizers will be effective in these mood states.
5. Mood stabilizers will be more effective than antidepressants in the prevention of episodes of unipolar as well as bipolar depression.