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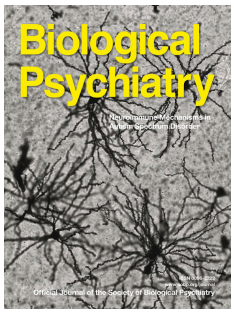

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Postpartum Psychosis and Bipolar Disorder: Review of Neurobiology and Expert Consensus Statement on classification.

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Abstract

Postpartum psychosis (PP) is an acute and severe psychiatric illness with onset within weeks after delivery, and a high risk of suicide and infanticide. Most women with PP experience severe mood symptoms, including mania, mixed episodes, or depression with psychotic features. Impaired cognition, irritability, and agitation are also common. The specific timing of PP strongly suggests a biological basis, because the postpartum time period is characterized by profound endocrine, immune, neuroanatomical and physiological changes in the brain. Genetic studies show a unique risk architecture, partly shared with bipolar disorder. PP stands out as one of the most distinct clinical phenotypes in psychiatry due to its characteristic rapid onset, severity, phenomenology, treatment response, and prognosis. Despite this, as of August 2025, PP does not have a distinct diagnostic classification in the DSM. This expert consensus panel, in close collaboration with patient organizations and key interested partners, recommends classifying PP as a distinct category within DSM-5 and ICD 11. We recommend classification within the bipolar disorders chapter of the DSM because 1) most women with PP have prominent affective symptoms; 2) treatment response to lithium and ECT is excellent; 3) in half of cases, first-onset PP is also the first onset of bipolar disorder; 4) pregnant women with bipolar disorder are at very high risk of PP; and 5) the genetic risk architecture for PP is distinct but overlapping with bipolar disorder. This consensus statement summarizes scientific evidence that PP is a distinct mental illness within the bipolar spectrum; correct classification will improve detection and treatment.

Introduction

Postpartum psychosis (PP) is an acute and severe episode of psychosis, mania, or psychotic depression after childbirth. PP occurs after 0.1-0.2% of deliveries in women without a mental illness history, and this incidence is at least 10 times increased compared to other periods in a woman's life (1-5). PP is considered a psychiatric emergency and, in most cases, requires hospitalization of the mother. Untreated, PP is associated with high risks of suicide and infanticide (6-11). However, if detected and treated in time, PP responds well to treatment (12-14), and most women return to their premorbid functioning (15). In addition, the long-term prognosis of PP is better than those of psychosis or mania with onset at other times (16, 17).

The diagnosis, "Postpartum Psychosis," is not currently in the Diagnostic and Statistical Manual (DSM). We suspect that the name itself is partially the reason for this, because it suggests a primary psychotic disorder. This is misleading, because there is strong evidence that PP falls within the bipolar spectrum. First, the majority of women with PP present with mania, a mixed episode, or psychotic depression, and only a subset experience delusions, hallucinations, thought disorder, confusional state without a medical cause or catatonia in the absence of prominent mood symptoms (6, 8, 10, 11) . Second, the most effective treatments - lithium and electroconvulsive therapy (ECT) - are standard treatments for severe affective disorders including bipolar disorder (12-14). Third, follow-up studies indicate that women who experience a first PP episode have a 50% risk for developing a bipolar disorder course (but not schizophrenia) (8, 16, 17). Finally, women with bipolar disorder face an exceptionally high risk of PP, with their risk surpassing that of women with other severe mental illness disorders, including psychotic disorders (18).

PP stands out as one of the most distinct clinical phenotypes in psychiatry. PP has been demonstrated to have a genetic basis (19, 20), and the significant hormonal and immune changes after delivery are thought to trigger the illness (21-23). In this consensus statement, we summarize the neurobiological evidence, including phenotypic and genotypic characteristics of PP, and offer hypotheses on why childbirth triggers PP. Finally, we posit that the lack of accurate diagnosis and misinformed treatment has contributed to increased morbidity. We therefore argue that new diagnostic criteria for PP in the DSM are required to enhance identification of the illness, elucidate underlying biology, and improve patient outcomes.

1. PP has distinct phenotypical characteristics

1.1 Onset of severe psychiatric symptoms after delivery

PP has a distinct onset, phenomenology and risk profile compared to other disorders in psychiatry and should therefore be included as a distinct disorder in DSM 5. During the first few weeks postpartum, women face a tenfold increased risk of developing first-onset psychosis or mania compared to any other time in their lives (2). Most women with PP experience severe mood symptoms, including mania, mixed episodes, or depression with psychotic features (6, 8, 10) . Only a minority of women present with delusions, hallucinations, thought disorder or confusional state in the absence of prominent mood symptoms. Cognitive impairment, irritability, agitation and

aggression are also common symptoms, and untreated PP is therefore associated with high risks of harm to self and/or others (10, 11). Epidemiological studies suggest that the onset of PP is within the first 12 weeks postpartum (1-5). Prospective clinical studies report that the majority of patients have an acute onset of symptoms within the first 2 weeks postpartum, median day 8-10 (8, 11, 24, 25) (26). It is critical that clinicians working with postpartum patients have a clear understanding of the period of risk and phenomenology so that they can provide a timely diagnosis. While the symptoms are severe, they are happening in the context of being newly at home with an infant and numerous psychosocial and physical adjustments. As such, earlier/prodromal signs are often missed or normalized by healthcare providers.

One argument against including PP as its own distinct entity in the DSM is that a "peripartum" specifier already exists for mood disorders. However, the "peripartum" specifier in the DSM refers to the time period during pregnancy and up to 4 weeks postpartum. Importantly, PP occurs exclusively "postpartum", i.e., in the period after childbirth (not in pregnancy). We have found no evidence supporting an increased incidence of psychosis or mania nor bipolar recurrence (27) during pregnancy, with a population-based study demonstrating reduced incidence of psychosis and mania during pregnancy (2). The distinct timing of acute postpartum onset strongly points to an underlying biological mechanism linked to the transition from pregnancy to the postpartum period.

1.2 Treatment algorithms specific for postpartum psychosis

Another reason why we believe PP qualifies as a full and separate category in DSM 5 is that treatment approaches to PP are distinct from other disorders in psychiatry. First, PP is a psychiatric emergency, and inpatient admission is recommended for diagnostic evaluation, treatment, and safety of mother and child (28, 29). The ideal treatment setting is a mother–infant joint admission unit, or a specialty psychiatric unit for perinatal women (although such units are not widely available worldwide) (30-32). Second, the risk of an underlying medical cause differ from those outside of the postpartum period and all patients should be evaluated for an underlying medical cause. Laboratory testing should include a comprehensive metabolic screen and a complete blood count to evaluate for an infectious process (e.g. mastitis, endometritis). The postpartum period is further known for exacerbation of autoimmune diseases, for which autoimmune thyroid disease is the most common, thus thyroid screening is recommended in all patients. Assessing for Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis and other neurological causes through a lumbar puncture, EEG and MRI should be considered, especially in patients with impairments in cognition or speech, dyskinesia, parkinsonian side effects to medication, catatonic symptoms or autonomic instability (33).

Third, there is evidence that the best treatment approach, while generally aligned with that of recommendations for acute and maintenance phases of treatment for acute mania with psychosis outside of the postpartum, is not exactly the same. The main treatment goals for women with PP are to (1) treat the current episode and (2) prevent recurrence of postpartum and non-postpartum episodes. Accordingly, management should focus on full recovery in the first year postpartum. Treatment recommendations are based on results from naturalistic cohort studies and expert consensus groups due to a lack of controlled trials (14) (34). The largest study to date

demonstrated the efficacy of a stepwise sequence of short-term benzodiazepines, antipsychotics, and lithium, finding a 98% remission rate for patients who were hospitalized for PP (12). This study further demonstrated that lithium alone is protective against relapse within one year. The second-largest study described a significant remission rate using ECT in patients with PP, of whom many had symptoms of catatonia (13). Remission with antipsychotics has been described in case reports, but antipsychotic monotherapy was associated with increased relapse risk within one year in a cohort study (12). Therefore, lithium is the preferred initial treatment for PP, and adjunctive treatment with benzodiazepines and/or antipsychotics is useful for treatment of agitation, mania, and psychotic symptoms associated with the illness. ECT should be considered for catatonia, suicidal risk and psychotic depression. Overall, postpartum episodes respond well to ECT, and response is better during the postpartum period as compared to episodes that occur outside the postpartum period (35).

The management of postpartum psychosis is also unique, as there are lactation considerations and the need for sleep preservation in the mother. Sleep disruption, fatigue, and stress affect mood state; in addition, the risk of skipped or infrequent feedings and difficulty with infant latch puts mothers at risk for mastitis. Moreover, some psychotropic drugs that are excreted in breast milk, including lithium, may require careful infant monitoring. Education about the risks of breastfeeding with pharmacotherapy for both the mother and her partner is an important part of the treatment plan (34, 36).

In summary, the most effective PP treatments are lithium and ECT, both of which are also used for severe affective disorders outside the perinatal time-period. These treatments have been efficacious not only in postpartum women with manic, mixed, or psychotic depressed episodes but also in women with PP without affective features. Treatment with antipsychotic monotherapy is emerging and needs further investigation (12).

1.3 Deleterious consequences such as suicide and infanticide if undetected and untreated

Unrecognized and untreated PP can have tragic consequences, including maternal suicide and infanticide (37, 38) (39). Making PP a distinct disorder will facilitate detection by clinicians, patients and families.

Suicide is a leading cause of maternal mortality, with US maternal mortality review committees finding all such death preventable (40). While efforts to address perinatal suicide have focused on screening and addressing perinatal depression, PP incurs the highest risk for suicide. Studies in the UK, Europe and India have also 1) identified suicide as one of the major causes of death among new mothers and 2) documented a highly increased suicide risk within the first postpartum year in women with PP (41, 42) (43). (44). In a systematic review on long term follow-up after first onset PP, three studies reported on suicide rates ranging from 4-11% (16).

Another tragic outcome of PP is infanticide. In cases of infant harm or infanticide, a diagnosis of a specific mental illness is needed for the insanity defense in criminal court. Currently, women

face criminal charges in several countries, including the U.S, where the judicial approach to infanticide and child harm is particularly punitive.
Perhaps unsurprisingly, early life trauma in the form of childhood sexual abuse and a family history of violent death have been linked to infanticide (45). However, independent of these social risk factors, studies have underscored PP as a risk factor for infanticide (38, 39). Because of extensive media attention for infanticide cases, all mothers with acute onset of severe mental illness postpartum are at risk for out-of-home placement of their children. Children whose mothers develop a new-onset mental illness in the postpartum period face nearly the same risk of out-of-home placement as those whose mothers have a long-standing mental illness (46).

Suicide, out-of-home placement of children, and infanticide in women with acute PP can be prevented because the disorder carries an excellent prognosis when evidenced-based treatment is provided in a timely manner (47).

1.4 Short- and long-term prognosis is distinct from other disorders

The unique prognosis of PP has implications for management of the disorder and the education that we provide to patients and families, providing more additional evidence for why PP should be a distinct disorder in DSM. A clinical cohort study reported functional recovery in 74% of 78 patients with PP admitted for inpatient hospitalization (15). Although women experienced significant functional impairment during the acute episode, three-quarters reported recovery in areas such as work, relationships, recreation, and overall life satisfaction by nine months postpartum. Similarly, a retrospective cohort study found that 74% of women were symptom-free one year after delivery. (48). Together, findings suggest a generally positive prognosis for women with acute PP who receive evidence-based treatment with most returning to their prior level of functioning within one year postpartum.

Also, the long-term prognosis of first onset PP is different compared with the prognosis of patients with first onset mania or psychosis at other time-periods. A recent meta-analysis found that half of women with a history of PP experience episodes exclusively after childbirth with no episodes outside the postpartum period (16). A more recent prospective cohort study of 106 women with PP reported an even higher proportion- ~68%-whose risk of mania or psychosis was confined to the postpartum period only (17). Remarkably, the phenomenology of the index episode was not predictive of the disease course. Surprisingly, none of the women who initially presented with schizophrenia- like symptoms were later diagnosed with schizophrenia. Consistent with previous longitudinal studies, nearly all non-postpartum recurrences during follow-up fell within the bipolar spectrum (16).

1.5 Prevention

Urgent distinct classification is urgently needed because PP can be prevented in women at high risk of PP. The most robustly established risk factors for PP are a personal history of bipolar disorder (estimated risk of 17%, 95%CI 13-20%) and a history of PP (estimated relapse risk of 29%, 95%CI 20-41%) (49). Relapse risks are higher for women with bipolar I disorder compared to bipolar II disorder, and at highest risk might be women with a history of both PP and bipolar 1 (49, 50). Women with a history of bipolar disorder and/or PP should have specialist care during

pregnancy and be seen by a psychiatrist. These women should have a pre-birth planning meeting during pregnancy with their partner, family, friends, mental health professionals, midwife, obstetric clinician, and/or family medicine clinician to compose a PP prevention plan. The care plan should include strategies to ensure sufficient rest and sleep once the baby is born and a plan for monitoring mental state and pharmacological treatment response. Pharmacological prophylaxis immediately after delivery is highly effective in preventing PP, with the strongest evidence for lithium (47) (49, 51).

2. Familiality and genetic vulnerability

Several studies have suggested an overlap in the familiality between PP and bipolar affective disorder. Danish population-based studies documented that a family history of psychiatric disorders, especially bipolar disorder, is an important risk factor for postpartum psychiatric disorders in general. (54) (55). (52). A recent study using population-based health registers in Sweden showed that the relative recurrence risk (familial risk) of PP in full siblings was ~11 (53) with an absolute risk of ~1.60% This study further showed that when both PP and bipolar disorder were present in a sister, the combined odds ratio increased to ~14.

Most research into genetic biomarkers of PP has been limited to candidate gene studies and lacked replication. More recently, studies have emerged that apply the use of single measures of genetic vulnerability (Polygenic Risk Scores; PRS) to mental illness during the postpartum period. A UK-based study showed that women with first-onset PP had similar bipolar disorder and schizophrenia PRS to women with bipolar disorder, which were significantly higher than those of general population controls. (19) While women with bipolar disorder also had higher rates of major depression PRS than controls, women with first onset PP did not differ from controls in their polygenic liability to major depression. A subsequent investigation using whole genome sequencing data from the All of Us Research Program and Swedish national registers estimated PP heritability at 55% (95% CI, 42-68%) through family-based methods, comparable to bipolar disorder heritability estimates (44-90%) [20]. Whole genome sequencing-based heritability was estimated at 37% (SE, 16%) for autosomal variants, with X chromosome variants contributing disproportionately (14.2% ± 8.3%) relative to chromosomal size. Rare coding variant analysis identified DNMT1 (DNA methyltransferase 1) and HMGCR (3-hydroxy-3-methylglutaryl-CoA reductase) as potential risk genes. Comparative genomic analysis showed significant overlap of PP with risk genes for bipolar disorder, schizophrenia, and several autoimmune conditions [20]. These findings reveal both shared pathways and unique genetic contributions to PP, supporting its classification as a distinct entity within the bipolar disorder spectrum but findings all need to be replicated in independent datasets.

3. Triggers of postpartum psychosis

3.1 Socio-Demographic, Cultural, and Environmental Factors

PP occurs across the world. Clinical descriptions of PP are available from the Western world as well as Africa (56), the Middle East (57), and Asia (6, 58). While most studies from non-western cultures have consistently reported similar phenomenology of symptoms such as affective lability,

confusion, and perplexity as that found in the West, studies from India have reported much higher rates of catatonic symptoms (7). Evidence on the role of other demographic factors in the onset of PP is limited, and results have been inconsistent. While multiple studies found an increased risk for PP in single and older women (4, 59, 60), other studies have not (17, 61). Education level has not been associated with an increased risk of PP (11, 59). Some evidence suggests that complications during delivery may elevate the risk of PP, and hospital admission (62, 63). A few studies have found that primiparity is associated with PP, but this finding is not consistent (64). Personality traits, cognitive style of functioning, and temperament have not been associated with PP (65).

3.2 Sleep loss and stress

Sleep deprivation has been associated with an increased risk of PP, consistent with evidence that sleep disruption can trigger mania and psychosis outside the context of childbirth (66, 67). Notably, a recent study found that women with bipolar I disorder who identified sleep loss as a trigger to manic episodes were twice as likely to have experienced PP during their lifetime (68).

Evidence related to the role of stressful life events and childhood adversity in PP is inconsistent. Although some studies have not identified an association between psychosocial stressors and the onset of PP, other research has found that women with PP report more stressful life events and higher levels of stress compared to healthy postpartum women (69). Furthermore, studies have shown changes in the hypothalamus-pituitary-adrenal (HPA) axis in patients compared to controls. For example, in women with PP, elevated cortisol levels at 15 weeks postpartum have been reported compared with healthy postpartum controls (69) as well as differential expression of the glucocorticoid receptor α/β gene (21, 22). In women at risk of PP, a history of childhood maltreatment predicted a psychiatric relapse postpartum (70). Moreover, a study that measured diurnal cortisol levels in pregnancy found that women at risk of PP who went on to relapse following childbirth had higher daily cortisol levels than women at risk who remained well (70).

3.3 Sex steroids

A reproductive mood disorder can be conceptualized as an abnormal brain response to times of normal hormonal change that occur during the reproductive years in women, including during the premenstrual, postpartum, and perimenopausal time-periods (71, 72). Several studies have demonstrated that it is the change in reproductive hormone levels that triggers psychiatric symptoms among individuals sensitive to hormonal fluctuations (73) (74, 75), rather than abnormal hormone levels. In women with bipolar disorder, reproductive hormonal changes clearly triggers mood symptoms (51). In addition to the postpartum period, both premenstrual exacerbation and increased risk during menopause have been reported (76, 77).

3.4 Immune dysfunction

A postpartum flare pattern, similar to that seen in PP, is well recognized in various autoimmune disorders (e.g. thyroiditis, multiple sclerosis, rheumatoid arthritis), whereas pregnancy is typically protective for these conditions (78, 79). The postpartum period is marked by immune activation and endocrine changes, which trigger these autoimmune disorders. Involvement of the immune system in bipolar disorder is suggested by biomarker studies (80-82). Microglia, the

immune cells of the brain, go through specific adaptations during and,after pregnancy, play a crucial role in orchestrating maternal postpartum behavior and neuroplasticity (83-85) and postpartum hormonal changes (86). It is hypothesized that some patients are especially sensitive to physiological immune adaptations in the postpartum period. Alternatively, immune system dysregulation may contribute to PP. Abnormalities in monocyte and T-cell function and tryptophan breakdown have been demonstrated in women with PP compared to controls (21, 87. (88). Patterns of comorbidity further support evidence for immune dysfunction. A small study reported that women with PP are at high risk of thyroid autoimmune disease, a finding that needs replication (89). In addition, CNS-autoantibodies such as anti-N-methyl-D-aspartate receptor (NMDAR) have been found in 4 out of 96 consecutive patients admitted with PP (33, 90).

4. Structural and functional neuroimaging studies

Recent case reports and series of healthy women showed notable changes in the maternal brain during- and after pregnancy (91) including pronounced decreases in gray matter volume and cortical thickness and increases in white matter microstructural integrity during the perinatal period (92). To date, imaging studies during PP are scarce, and only three studies have explored brain structure or function in women at risk of PP (93-95). A structural Magnetic Resonance Imaging (MRI) study demonstrated that women who developed PP episodes postpartum had reduced gray matter volume and surface area in the anterior cingulate, superior temporal, and parahippocampal gyri compared to at-risk women who remained well (94). In the same sample, women at risk for PP showed increased- rather than decreased connectivity in the right dorsolateral prefrontal cortex (DLPFC) as well as increases in connectivity between the right DLPFC and ipsilateral middle temporal gyrus (95). Another fMRI study found that women at risk for postpartum psychosis, when performing an emotional task, show decreased executive network connectivity and altered emotional load-dependent interactions between executive, salience, and default-mode networks. Those who developed postpartum illness exhibit increased salience network modulation of the default-mode and executive networks, while women who remained well demonstrate greater executive network-driven modulation of the salience network. These findings suggest that disrupted connectivity within and between networks involved in goal-directed behavior- may represent a neural phenotype associated with vulnerability to PP (93).

5. Postpartum psychosis: a distinct diagnosis and proposed diagnostic criteria.

In recent years, an expert panel on PP was invited to collaborate with the American Psychiatric Association to refine and clarify the diagnostic criteria for this condition. Based on this work, we urge a change to the DSM classification of PP. Currently, the DSM does not include PP as a distinct illness. The only way to document PP within the DSM is to use the “with perinatal onset” specifier to another diagnosis such as bipolar I disorder or brief psychotic disorder. This risks clinicians missing PP as a distinct disorder, which is problematic because of its unique potential for highly negative consequences - including death - not only for one patient, but also for her child. There is substantial epidemiological and biological support for PP as a distinct disorder, and by classifying it as such, clinicians will be much better positioned to implement the unique

considerations for its management, including safety, ruling out of distinct medical causes, acute and maintenance treatment, and longer-term planning (especially for prevention of recurrent postpartum psychosis, and accurate diagnosis and treatment of emerging bipolar disorder).
PP has a specific onset, phenotype, phenomenology, risk profile and prognosis, leading to specific prevention and treatment recommendations. A distinct category in the DSM is warranted because PP does not fit into the currently available categories of mental illness, and the available specifier “with perinatal onset” inaccurately describes the timing of onset of the illness.

In summary, PP has a distinct clinical presentation, outcome, genetic risk and treatment response. Due to the risks to self and the infant, the rapid escalation of severity and its fulminant course, it is imperative that it is recognized, diagnosed, and treated as early as possible. To facilitate such care, we recommend including the following criteria for PP in DSM-5: the onset of at least one of the following states (at least one out of five) within 12 weeks of childbirth, lasting at least one week and present most of the day, nearly every day, or any duration if hospitalization is necessary. 1) Mania/Mixed State, 2) Delusions, 3) Hallucinations, 4) Disorganized speech or formal thought disorder, 5) Disorganized, confusional or catatonic behavior, 6) Depression with psychotic features. We recommend classification within the bipolar disorders chapter of the DSM because recognition of PP as part of the bipolar spectrum will improve clinical outcomes and facilitate evidence-based treatment. This is particularly important for women who present with postpartum depression with psychotic features or psychosis without mania, who are currently not recognized as having a bipolar spectrum disorder. A footnote could be placed in the psychosis chapter so that clinicians will be redirected to the bipolar chapter. We recommend that PP can be diagnosed in addition to other mental illness or as first-onset illness for those patients without psychiatric history.
We are committed to working further with the American Psychiatric Association and the DSM steering committee to find a solution that will facilitate diagnostic accuracy and the provision of timely and evidence-based treatment for PP. Doing so carries the potential to 1) improve the quality of treatment and outcomes for women with PP, and 2) prevent the tragic outcomes of suicide and infanticide.

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