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A Review of Postpartum Psychosis

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Abstract

Objective—The objective is to provide an overview of the clinical features, prognosis, differential diagnosis, evaluation, and treatment of postpartum psychosis.

Methods—The authors searched Medline (1966–2005), PsycInfo (1974–2005), Toxnet, and PubMed databases using the key words postpartum psychosis, depression, bipolar disorder, schizophrenia, organic psychosis, pharmacotherapy, psychotherapy, and electroconvulsive therapy. A clinical case is used to facilitate the discussion.

Results—The onset of puerperal psychosis occurs in the first 1–4 weeks after childbirth. The data suggest that postpartum psychosis is an overt presentation of bipolar disorder that is timed to coincide with tremendous hormonal shifts after delivery. The patient develops frank psychosis, cognitive impairment, and grossly disorganized behavior that represent a complete change from previous functioning. These perturbations, in combination with lapsed insight into her illness and symptoms, can lead to devastating consequences in which the safety and well-being of the affected mother and her offspring are jeopardized. Therefore, careful and repeated assessment of the mothers' symptoms, safety, and functional capacity is imperative. Treatment is dictated by the underlying diagnosis, bipolar disorder, and guided by the symptom acuity, patient's response to past treatments, drug tolerability, and breastfeeding preference. The somatic therapies include antimanic agents, atypical antipsychotic medications, and ECT. Estrogen prophylaxis remains purely investigational.

Conclusions—The rapid and accurate diagnosis of postpartum psychosis is essential to expedite appropriate treatment and to allow for quick, full recovery, prevention of future episodes, and reduction of risk to the mother and her children and family.

CASE HISTORY

Ms. A. is a 27-year-old physician who delivered her baby 7 days before evaluation at a teaching hospital. She underwent an uncomplicated delivery, and her baby boy was full term and healthy. This was a planned pregnancy, and the family was excited about the birth. Within 2 days of delivery, she told her husband that she thought he was poisoning her food and that the baby was staring at her strangely. She thought she smelled horses and heard them galloping out-side her bedroom. She could not fall asleep even when her mother came to the house to care for their newborn and allow the patient to rest. At home, Ms. A. was able to sleep only 2–3 hours nightly. Her husband noticed that she would gaze out the windows in their apartment for hours without explanation. She had not bathed for 6 days.

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She required much help in simple tasks, such as diapering her baby. She expressed guilt about being a terrible mother and felt she did not deserve to have her family. She told her husband that she heard voices commanding her to go with her infant son to the subway and jump in front of the train; these hallucinations terrified her and became stronger after she returned home from the hospital. The husband became very concerned and brought his wife to the emergency room.

THE CLINICAL PROBLEM

Postpartum psychosis (PP) occurs in 1–2/1000 childbearing women within the first 2–4 weeks after delivery.[1–7] The onset of PP is rapid.[8] As early as 2–3 days after childbirth, the patient develops paranoid, grandiose, or bizarre delusions, mood swings, confused thinking, and grossly disorganized behavior that represent a dramatic change from her previous functioning. PP is far less common than postpartum depression which affects 10%–13% of new mothers,[9] and the maternity blues, which affects 50%–75% of postpartum women.[10] However, the combination of frank psychosis and lapsed insight and judgment in PP can lead to devastating consequences in which the safety and well-being of the affected mother and her offspring are jeopardized.[11] Therefore, it is critical to quickly identify and treat the symptomatic patient.

Although the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV),[12,13] allows for classification of PP as a severe form of major depression or the onset/recurrence of a primary psychotic disorder, such as schizophrenia, the preponderance of data suggests that PP is an overt presentation of bipolar disorder after delivery.[14] Among patients who develop PP immediately after childbirth, 72%–88% have bipolar illness or schizoaffective disorder, wheras only 12% have schizophrenia.[15,16] Puerperal hormone shifts,[17] obstetrical complications,[18,19] sleep deprivation,[20] and increased environmental stress are possible contributing factors to the onset of illness.

The intention of this paper is to inform physicians and health professionals about PP so they will be able to recognize the symptoms, medically evaluate and appropriately (and expeditiously) refer the patient for psychiatric intervention, and educate the patient and her family about this illness.

CLINICAL ASPECTS OF PP

Clinical features

Brockington[15] described the classic picture of a mother with PP: "… an odd affect, withdrawn, distracted by auditory hallucinations, incompetent, confused, catatonic; or alternatively, elated, labile, rambling in speech, agitated or excessively active."[15] The woman's strange beliefs may focus on childbirth themes and concern for the baby's altered identity or a sense of persecution from the baby/changeling.[15] Wisner et al.[11] reported that women with childbearing-related onset of psychosis frequently experienced cognitive disorganization and unusual psychotic symptoms. These were often mood-incongruent delusions of reference, persecution, jealousy, and grandiosity,[4,6,11] along with visual, tactile, or olfactory hallucinations that suggest an organic syndrome.[12] The mean age of onset in PP is 26.3 years,[21,22] which is a time when most women are having their first or second child.[23] Compared with women with chronic mental illness, patients with PP usually have attained higher functional levels before the onset of illness.

The baseline risk for PP is 1:500; however, the risk rises to 1:7 for women with even one past episode of PP.[1] In fact, women with bipolar disorder or schizoaffective disorder have a >50% risk for another episode of PP.[15,24–27] Jones and Craddock[27] found that PP affected

74% of mothers with bipolar disorder and a first-degree relative who had PP, compared with only 30% of bipolar women without any family history of PP. Patients who stop their mood stabilizer treatment, specifically lithium, are much more likely to experience a recurrence of bipolar disorder or PP after childbirth compared with those who remain on antimanic treatment (70% and 24%, respectively).[28] The mothers who cease antimanic treatment suddenly have an added risk for relapse. Sleep loss, such environmental stressors as marital discord, and the precipitous drop in hormone levels that occurs shortly after childbirth are other factors linked to PP.[20,29] Primiparity, socioeconomic status, and ethnicity are less compelling risk factors.[2,21,30–32] Therefore, physicians must watch carefully for the emergence of symptoms suggestive of PP in new mothers with bipolar illness and in those women with a personal or family history of PP (Tables 1 and 2).

In the first year after childbirth, suicide risk increases 70-fold, and suicide is the leading cause of maternal death up to 1 year after delivery.[42] Of 1000 women with PP, 2 complete suicide.[42] These women often used more irreversible and aggressive means (self-incineration, jumping from heights) compared with most reports that indicate women generally complete suicide nonviolently (overdose).[43] Therefore, it is critical that physicians and health professionals gauge the safety of their patient by inquiring about suicidal ideation —thoughts of dying, feelings of life not worth living, active plans to take her life, access to weapons, and past suicide attempts. Suicidal ideation must be taken seriously, and patients with recent or active suicidal plans should be referred to an emergency setting.

Homicidal behavior rarely occurs in PP.[11,39,44,45] Among women hospitalized for PP, 28%–35% described delusions about their infants, but only 9% had thoughts of harming the infant.[7] Women with PP, however, are more likely to express homicidal ideation than women with nonpsychotic childbirth-onset illness, such as postpartum depression.[11] The cognitive disorganization that occurs with PP may result in a mother's neglect of her infant's needs and unsafe practices.[7,46] It is important to ask the patient with PP about homicidal thoughts or plans and to enlist the help of psychiatric and social service supports to prevent harm to herself or other family members.[47,48] Infanticide and neonaticide are separate and distinguishable entities. Spinelli[49] investigated 16 cases of neonaticide and found the women suffered from dissociative symptoms. These patients denied their pregnancy and the pain of childbirth; they often experienced dissociative hallucinations, brief amnesia, and depersonalization. The mothers may avoid all antenatal obstetrical visits, deliver at home without any medical attention, and abandon the newborn after giving birth. Neonaticide is more difficult to prevent, as it involves denial of pregnancy.

Prognosis

Longitudinal data indicate a good prognosis for most women who experienced PP arising from bipolar illness; 75%–86% remained symptom free after a single episode of PP.[33,50] For women with schizophrenia, 50% remain well after one episode of PP, >33% have recurrent PP, and 5% have a refractory illness with numerous puerperal and nonpuerperal recurrences.[33] Women who sought help within 1 month of delivery had more favorable outcomes and were less likely to suffer long-term disability than women with late-onset PP, that is, after 1 month postpartum (13% and 33%, respectively).[25,51] Compared with women with new onset of non-PP, the patients with first episode PP had higher levels of confusion and disorientation but required only half the time to achieve treatment response[40] (Table 1).

In summary, the defining characteristic of PP is an illness that occurs shortly after childbirth. PP is marked by symptoms of mood lability, cognitive disorganization, delusional beliefs, and hallucinations that resemble a clinical picture of delirium but is most likely an overt presentation of bipolar illness. Predictors of recurrence include a personal or family history of PP, bipolar disorder, and cessation of antimanic treatment. All patients should be asked

about the presence of suicidal and homicidal symptoms. The overall prognosis is positive, especially when symptoms emerge <1 month postdelivery.

SCREENING FOR PP

The woman with known bipolar disorder and a personal or family history of PP is at substantial risk for PP. She and her family should be informed of the symptoms to recognize, that is, mood swings, confusion, strange beliefs, and hallucinations, especially in the first 2–4 weeks postchildbirth, and to contact her physician if these symptoms arise. Even before delivery, the at-risk patient is encouraged to consult with a psychiatrist to help her consider treatment options or treatment prophylaxis at delivery to avoid illness.[14] Physicians are strongly urged to ask about symptoms of PP in the high-risk patient at her 6-week obstetrical follow-up visit. The Edinburgh Postnatal Depression Scale (EPDS)[52] and the Mood Disorder Questionnaire (MDQ)[53] are useful tools to screen for depression and mania/hypomania. The EPDS is a self-rating instrument that uncovers the presence of persistent low mood, anhedonia, guilt, anxiety, and thoughts of self-harm. The MDQ explores for past and current symptoms of high, hyper or irritable mood, excess energy, racing thoughts, pressured speech, and symptoms that are linked with mania/hypomania. When the patient reports confusion, threats to harm herself or others, difficulty caring for her children, or poor self-care, the physician must consider these as red flags and arrange a psychiatric referral quickly.

EVALUATION AND DIFFERENTIAL DIAGNOSIS

PP is considered an emergency that necessitates an urgent evaluation, psychiatric referral, and possible hospitalization.[54] The initial evaluation requires a thorough history, physical examination, and laboratory investigations to exclude an organic cause for acute psychosis (Table 3). Important tests include a complete blood count (CBC), electrolytes, blood urea nitrogen (BUN), creatinine, glucose, vitamin B_{12}, folate, thyroid function tests, calcium, urinalysis and urine culture in the patient with fever, and a urine drug screen. A careful neurological assessment is essential; this includes a head CT or MRI scan to rule out the presence of a stroke related to ischemia (vascular occlusion) or hemorrhage (uncontrolled hypertension, ruptured arteriovenous malformation, or aneurysm).[55] The stroke patient is differentiated from the patient with PP by a history of hypertension or preeclampsia, evidence of fluid/electrolyte imbalance, and complaints of severe headache, unilateral weakness, sensory deficits, and even seizures with the neurological event.[56]

The primary psychiatric diagnosis to consider with the case of early-onset PP is bipolar disorder. Wisner et al.[16] found that 95% of PP cases fulfilled Research Diagnostic Criteria (RDC) for cyclic mood disorders at 5-year follow-up. Of these cases, 50% were misdiagnosed at first presentation. Other studies replicated this finding and indicated a high likelihood of a primary cyclic mood illness (43%–66%).[3,8,21,57] This is not surprising, as PP and bipolar psychosis or mixed episodes share common symptoms of elation, dysphoria, mood lability, confusion, and heightened sensitivity to sleep deprivation.[4,6,8,11,20,31,58–61] Women with a past or family history of bipolar illness are more likely to have BD that precipitates an episode of PP. These patients require antimanic drug treatment. Choices include lithium, such antiepileptic drugs as valproate or carbamazepine, and atypical antipsychotic medication, such as olanzapine, quetiapine, ziprasidone and the newer agent, aripiprazole.

Patients with PP are differentiated from those with unipolar major depression by the presence of cognitive disturbance, delusional beliefs, and disorganized behavior. However, women with a past history of unipolar psychotic depression can relapse shortly after delivery with an episode of PP.[4,30,31,62] These patients often report low mood, distraught feelings

about their inability to enjoy their new baby, psychomotor slowing or pacing behaviors, anxiety, fatigue, poor concentration, and preoccupations with strange ideas and suspicions.[63–65] Without intervention, they are at risk for worsening symptoms, treatment resistance, and mortality.[63,65,66] These patients respond best to a combination of antidepressant and antipsychotic drug treatment or electroconvulsive therapy.

PP must be distinguished from obsessive-compulsive (OC) symptoms and obsessive-compulsive disorder (OCD). OC symptoms and OCD are characterized by intrusive thoughts and compulsive, irresistible behaviors. Intrusive thoughts often center on themes of contamination, causing harm to their children, offensive violent or sexual images, religious preoccupations, and urges for symmetry.[67] The compulsions include urges to clean, check, repeat, order, and hoard and such mental rituals as counting. Women with postpartum depression commonly experience comorbid OC cognitions (41%–57%).[67–69] OC or OCD is differentiated from PP by the preservation of rational judgment and reality testing; patients typically do not act on their aggressive thoughts. Rather, they avoid objects or places that provoke anxiety and suffer discomfort from their unwanted cognitions. This contrasts with patients with florid psychosis, who are unable to discern reality, feel compelled to act on their delusional beliefs, and cannot assess the consequences of their actions.[70] First-line treatment for OCD includes serotonin reuptake inhibitors (SRIs), with such agents as sertraline, fluoxetine, and fluvoxamine; the gold-standard drug is clomipramine (which is both an SRI and a nor-epinephrine inhibitor). Most patients require pharmacotherapy in combination with cognitive behavioral therapy. Patients with refractory illness may require augmentation with an atypical antipsychotic drug.

PP could be a presentation of a primary psychotic disorder, such as schizophrenia. Although women with known schizophrenia have a 25% risk for puerperal exacerbations,[46,71] many studies have indicated a low prevalence of schizophrenia in early-onset PP (3.4%–4.5%).[1] These patients respond best to pharmacotherapy with atypical antipsychotic drugs; if the physician suspects the presence of comorbid depression, the addition of an antidepressant medication is highly recommended. Mothers with schizophrenia also may suffer cognitive impairment. These women could benefit greatly by referral to in-home services for additional support and enhancement of parenting skills.

TREATMENT OF PP

Psychoeducation and psychotherapy

Once the diagnosis has been established, the physician should (1) educate the patient and her family about the illness, (2) rule out organic causes, (3) initiate pharmacotherapy and supportive therapy, and (4) repeatedly assess the patient's function and safety status.[72] Physicians will contribute greatly by informing patients and their families about the symptoms, treatments, expected outcomes, and strategies to prevent recurrence of PP. The process of psychoeducation is essential. It will enhance the therapeutic alliance; furthermore, it will strengthen the patient's decision-making process about treatment and her feelings of self-efficacy and mastery over illness.[73,74]

After stabilizing the patient and starting acute pharmacotherapy for PP, a careful discharge plan must be developed before the patient leaves the hospital. Referral to intensive outpatient therapy (or day program), along with closely spaced out-patient follow-up visits, is advisable for the first several weeks after discharge. These measures will facilitate the patient's return home and allow the physician or health professional to closely monitor treatment response, address problems with drug intolerance, and spot clinical worsening early. Treatment plans work best when they are individualized for each patient and include interventions that provided good response in the past. Sleep loss is a major precipitant of

mania and PP. Physicians could encourage patients and their partners to enlist the help of other family or friends or doula services to reduce the affected mother's burden and allow her to regain sleep and recover from illness. Patients and their families should be advised to contact their physicians quickly when symptoms recur.[75–77] At this point, the physician should explore the patient's adherence to treatment and evidence of problematic side effects and consider a dose adjustment or medication switch if necessary.

Supportive psychotherapy that begins prior to hospital discharge may incorporate parenting skills and early infant interventions to address maternal-infant bonding and infant development. In-home services could optimize both mother and infant outcomes. Other psychotherapy options, such as family-focused therapy, cognitive behavioral therapy, or interpersonal psychotherapy (IPT), are effective adjunctive treatments for postpartum mood disorders.[78] IPT, specifically, was adapted for women dealing with childbearing-related events and is structured to help women who are facing losses, role changes, or relationship tensions. These advanced forms of psychotherapy are recommended once patients have regained an organized level of thinking.

Pharmacotherapy overview

Acute pharmacotherapy is essential to manage the psychotic and mood-related symptoms of PP. The medication options include atypical antipsychotic agents and mood stabilizer or antimanic agents, such as lithium or antiepileptic drugs (AED).[51] Although monotherapy is preferable, certain women require more than one drug to achieve a desirable level of symptom control and illness remission.[12,79] Women often reach higher serum levels and prolonged adverse effects from fat-soluble drugs that have a high volume of distribution and a long half-life. For better treatment adherence, side effects can be minimized with lower starting doses that are titrated slowly to the response dose.

Breastfeeding

The mother's breastfeeding preference and the associated benefits and risks must be considered by the patient and her physician.[80,81] The American Academy of Pediatrics (AAP)[82] has provided helpful recommendations on breastfeeding and the use of lithium or AED. It is imperative to inform the pediatrician of the mother's choice to breastfeed; this permits the pediatrician to appropriately monitor the clinical state of the breast-fed infant. Likewise, mothers must be instructed to observe for behavioral changes indicative of infant toxicity, such as poor hydration, sedation, poor feeding, and weight gain, as well as signs of hepatic and hematological impairment. Mothers should be instructed to contact their pediatricians immediately when they notice these symptoms.[80] Infant drug serum levels are not obtained routinely in clinical practice, but breast milk exposure can be limited by (1) the use of the lowest effective dose, (2) the use of fewer drugs to achieve response, and (3) dividing daily doses to avoid high peak serum concentrations.

Lithium treatment and prophylaxis

Lithium is an important treatment option for the prevention and treatment of PP and a standard treatment for bipolar disorder. Results from small open trials suggest that women with past PP have better outcomes when lithium treatment begins immediately postdelivery.[83] Lithium that is started in the third trimester is more controversial. Retrospective reports and small case series indicate a lower likelihood for early postpartum relapse when treatment is resumed in the third trimester.[83,84] Unfortunately, one mother suffered a stillbirth after agreeing to lithium prophylaxis before delivery.[85] Among patients with bipolar disorder, the recurrence risk is substantially higher for women who stop lithium compared with those who continue prophylactic treatment (52%–58% vs. 21%).[28] If patients are taking lithium, they should be discouraged from abruptly discontinuing their medication.

To avoid the high relapse risk after delivery, bipolar patients should be encouraged to resume treatment immediately after childbirth.

Physicians and health professionals are advised to assess the renal and thyroid functions of patients who require lithium treatment for symptoms of PP. Drug levels and renal tests should be rechecked after 5 days of starting treatment. The target level of lithium is 0.4–1.0 mEq/L at 12 hours postdose; drug levels should be tested every 6–12 months after stabilization.[82] Physicians should monitor their patients for side effects, such as sedation, tremor, renal dysfunction, weight gain, and nausea and vomiting. The window between therapeutic and toxic serum levels is narrow. Patients must be instructed to avoid thiazides, non-steroidal anti-inflammatory agents, and angiotensin-converting enzyme inhibitors that alter fluid balance and interfere with the renal excretion of lithium.[86] Women with dehydration or sodium-depleting conditions are at particularly high risk of lithium toxicity. Physicians must watch carefully for symptoms of toxicity in women on lithium: excessive sedation, severe tremors, acute renal dysfunction, and intractable vomiting. Toxicity is confirmed by elevated drug levels. Lithium toxicity must be managed immediately by stopping the drug, fluid rehydration, and close monitoring of electrolyte balance and renal function.

Although lithium is not commonly prescribed for breastfeeding women, investigators have noted that the avoidance is based on minimal data from over two decades ago.[80,87] The drug concentrations in breastfed infants of mothers on lithium rise quickly to a toxic range in newborns and young infants with feeding problems, fever, or other fluid-depleting conditions. Because the lithium levels of breastfeeding infants reach one third to one half of the therapeutic blood concentration, the AAP advises strict caution in breastfeeding when taking lithium.[87,88] If a patient demands to breastfeed while on lithium, the primary care physician is advised to seek consultation with a psychiatrist who is experienced in managing perinatal psychiatric illnesses.

Antiepileptic drugs (AED)

Valproic acid (VPA) is an FDA-indicated drug for bipolar illness. The starting dose is 500–750 mg/day, and the dose is titrated according to symptom response and serum drug levels. It is advised to check levels within 1 week of initiating VPA. Periodic monitoring of serum concentration, liver function, platelet count, glucose, and lipid profile is suggested with worsened side effects, any dose adjustment, and at least once yearly while maintained on a stable regimen. Therapeutic levels range from 50 to 125 μg/mL; patients with higher levels have more side effects. Valproate levels are affected by enzyme-inducing AEDs, such as carbamazepine. Patients must be observed closely to ensure therapeutic efficacy. Side effects include nausea, weight gain, tremor, ataxia, diarrhea, abdominal pain, alopecia, hepatitis, thrombocytopenia, and, rarely, pancreatitis. Menstrual irregularity, anovulation, polycystic ovarian syndrome, and insulin resistance may be associated with VPA.[89]

Carbamazepine (CBZ) is an FDA-indicated drug for the treatment of mania. It is protein-bound and induces hepatic cytochrome P450 3A4 enzyme activity to triple its own clearance rate (and the metabolism of such drugs as oral contraceptives) within 2–4 weeks of initiation. Therapeutic doses range between 400 and 1600 mg/day. After starting CBZ, a blood test is necessary to verify a therapeutic level (4–12 μg/mL) has been reached. Serum levels, liver function tests, and a CBC are indicated two or three times per year in symptomatic patients and at least once yearly for patients on maintenance therapy. Side effects may include hepatitis, leukopenia, thrombocytopenia, rash, sedation, and ataxia. Treatment with CBZ and clozapine together is contraindicated because bone marrow suppression has been reported with this combination.

The AAP Committee on Drugs[88] views CBZ and VPA as drugs that are compatible with breastfeeding. Transient hepatic toxicity and cholestatic hepatitis[90,91] may occur in neonates exposed throughout pregnancy and breastfeeding. The infant of a woman who was treated during breastfeeding only developed a CBZ level 15% and 20% of the total and free maternal levels, respectively.[92] In a separate study of 6 mothers who took VPA during breastfeeding only, the mothers attained levels from 39 to 79 μg/mL, and their infants' serum levels were 0.7–1.5 μg/mL.[93] No adverse effects were described in the infants. The indicators of infant toxicity may include increased sedation, poor feeding, and signs of hepatic and hematological impairment.[80]

Other AEDs that are FDA approved for bipolar illness include oxcarbazepine for bipolar mania and lamotrigine for maintenance therapy of bipolar depression. The importance of a slow titration of lamotrigine to avoid potentially toxic dermatological side effects implies that lamotrigine is less likely to be a first-line agent for managing PP. However, patients with an established diagnosis of bipolar illness and good response to these drugs could choose to continue or resume either drug if their symptoms recur or as prophylactic treatment in pregnancy or after delivery.

Oxcarbazepine is prescribed in divided doses, with a dose range of 600–1200 mg/day. In the liver, it inhibits the enzymes, CYP2C19 and induces CYP3A4. The parent compound is rapidly and almost completely metabolized to the active metabolite (10 OH-CBZ), which undergoes hepatic glucuronidation and renal excretion. Adverse effects may include hyponatremia, hypersensitivity reactions, and lowered oral contraceptive efficacy; other common side effects are headache, dizziness, gait imbalance, fatigue, poor concentration, and memory changes. The breastfeeding data are limited, but one case report indicated that the amount of drug dropped rapidly in a breastfeeding infant. At 5 days after birth, the infant drug concentrations for parent drug and metabolite were only 12% and 7%, respectively, of the levels drawn shortly after birth.[94]

Lamotrigine is indicated for maintenance therapy in bipolar depression.[95] The importance of a gradual titration precludes the use of this drug for management of acute psychosis. It induces a nonserious rash in 7%–10% of patients and Stevens-Johnson syndrome, a potentially life-threatening condition, in 3 of 1000 patients. A serious rash is more likely with rapid dose escalations, in combination with valproate, and among adolescents.[86] At the onset of a rash, patients must stop this drug immediately and seek medical attention. Although the lamotrigine-associated rash is potentially life threatening in rare instances, the risk must be weighed against the benefit of preventing the recurrence of major puerperal illness.[96] Lamotrigine undergoes hepatic glucuronidation and renal excretion. This drug is transferred to breast milk readily, and the serum drug level decline is noticeably slow in neonates and infants. Therefore, this drug is not advised for breastfeeding mothers shortly after delivery, as are other drugs metabolized by glucuronidation, such as oxazepam, lorazepam, aspirin, acetaminophen, VPA, and olanzapine (OLZ).[97]

Atypical antipsychotic medications

The atypical antipsychotic agents, such as OLZ, risperidone, quetiapine, and ziprasidone, are indicated for treatment of acute psychosis, bipolar mania, and schizophrenia. The dose ranges are 2.5–20 mg/day OLZ, 2–6 mg/day risperidone, 25–700 mg/day quetiapine, 20–80 mg bid ziprasidone. The side effects commonly include somnolence, dry mouth, akathisia (internal sense of restlessness), and increased liver transaminases. Hyperprolactinemia occurs commonly with risperidone (88%) compared with conventional antipsychotics, such as haloperidol (48%) or OLZ (minimal if any).[98] The metabolic effects of atypical agents are considerable. Patients risk significant weight gain (above 7% baseline weight), elevated triglycerides, and new onset of metabolic syndrome or insulin intolerance.[99] Vigilant

monitoring of the glucose and lipid profiles is recommended. Patients on atypical antipsychotic agents must be encouraged to follow healthy eating patterns, diet modification, regular exercise, and dietary counseling to minimize the adverse metabolic effects. Although extrapyramidal side effects (EPS), such as tremors, rigidity, akathisia, bradykinesia, tardive dyskinesia, and dystonia, are reported infrequently with atypical antipsychotics, the risk for EPS is elevated in women, the elderly, and patients with affective disorders.

Women who were exposed to atypical antipsychotic drugs during pregnancy (60 women on OLZ, 49 on risperidone, 36 on quetiapine, and 6 on clozapine) delivered babies with low birth weight (LBW) at a rate that significantly exceeded the rate of LBW among nonexposed babies (10% and 2%, respectively).[100] Goldstein et al.'s follow-up of 20 cases of OLZ exposure in pregnancy indicated 4 adverse birth outcomes[101]: 1 stillbirth at 37 weeks' gestation to a mother with polysubstance abuse, premature ruptured membranes, gestational diabetes (GDM), thrombocytopenia, and hepatitis who took OLZ in the second and third trimesters; 1 cesarean section delivery at 30 weeks' gestation to a mother with GDM, preeclampsia, elevated liver transaminases, hypothyroidism, who took OLZ in all three trimesters, the baby survived but required 2 weeks of NICU care; 1 postterm baby born with fetal distress to a mother on OLZ for all three trimesters; and 1 postterm infant who aspirated meconium after a cesarean birth and was born to a mother who took OLZ only in the first trimester. In summary, patients with preexisting psychosis are at elevated risk in the puerperium. They must be referred and managed by the high-risk obstetrical team throughout the antepartum and postpartum periods. Both the mother and infant must be treated as high-risk patients after delivery.

To date, only 28 cases of atypical antipsychotic exposure in breastfeeding infants have been reported.[80] Kirchheiner et al.[102] described one woman with schizophrenia who took OLZ 10 mg/day throughout the second and third trimesters and continued treatment while breast-feeding. Mother-infant levels were obtained at 2 and 6 weeks after birth. At both times, the infant levels were undetectable (<2 ng/mL), and maternal trough levels measured 39.5 and 32.8 ng/mL, respectively. The baby's growth dimensions, for example, head circumference, height, and weight, remained normal up to 11-months follow-up. Although the child had difficulty rolling over at 7 months, the delay had resolved by the 11-month evaluation. Infant risks depend not only on the breast milk-transmitted drug (from the passive diffusion of unbound drug) but also on neonatal intestinal absorption, distribution, and elimination characteristics. Therefore, the practice of tracking infant drug levels may be very appropriate for estimating the extent of drug exposure and disposition in breastfed infants.

Regarding breast milk exposure to risperidone, Hill et al.[103] described one bipolar patient who stopped all treatment in pregnancy and developed a postpartum psychotic depression within 2 months of delivery. She resumed taking risperidone and stopped breastfeeding, and plasma/breast milk samples were obtained to measure drug and metabolite (9-hydroxyrisperidone) levels. The infant drug exposure was calculated as a product of the average drug concentration in breast milk and the quantity of daily milk intake. They estimated the infant received 0.84% of the maternal risperidone dose, 3.5% of the metabolite, and 4.3% of the weight-adjusted maternal dose. These values fall well below the suggested level of concern (10%) for psychotropic drugs (antidepressants only).[104]

Lee et al.[105] obtained serial breast milk measures of one mother on 200 mg/day quetiapine in pregnancy who nursed her full-term infant. The average milk concentration over a 6-hour period was 13 μg/L, and the maximum concentration was 62 μg/L at 1 hour postingestion. Assuming that the infant consumed 150 mL/kg breast milk daily, they estimated that the infant ingested 0.09%–0.43% of the weight-adjusted maternal dose. With these reassuring data, the patient began nursing; a 4-month-old pediatric assessment indicated normal

development without clinically discernible adverse effects. No infant serum levels were available for this case.

Altogether, the data suggest that exposure to drug during breastfeeding is orders of magnitude less than the medication exposure in pregnancy, when the blood supply of the mother and infant are shared. Primary care physicians and pediatricians must observe the breastfed infants carefully for hydration status, excessive sedation, feeding difficulties, and failure to gain weight, which are possible signs of drug toxicity, and inform mothers to contact their physicians when they observe such symptoms.[80] Physicians who prescribe medications to breastfeeding mothers could limit infant drug exposure by choosing the lowest effective dose, avoiding polypharmacy, and dividing daily doses to reduce peak concentrations.

Electroconvulsive therapy

Prior to the advent of electroconvulsive therapy (ECT), significant mortality was associated with PP. Nine of 14 puerperal patients from 1927 through 1941 died during a psychiatric admission.[33] As ECT became a mainstream treatment, the mortality rate dropped considerably (down to 1 in 23 patients) between 1942 and 1961. Women with PP responded more robustly to ECT with much faster and more complete remission of mood and psychotic symptoms than did women with nonpuerperal psychosis.[106] In one case series, women with PP and psychotic bipolar depression experienced >50% improvement in mania, depression, and psychosis with bilateral ECT.[107] Such patients may also benefit, with greater reduction in suicidal ideation and decreased risk for hospital readmission (hazard ratio 0.678) than before treatment.[108,109] Therefore, physicians are encouraged to help their patients consider the diverse treatments available for managing PP. ECT appears to be an excellent option that provides swift symptom resolution in patients who have been admitted to hospital with acute, florid psychosis. ECT is an ideal choice for patients who have failed several drug trials, patients who cannot wait for the delayed onset of action of these drugs, patients with intolerable drug side effects, and patients who require quick effective symptom relief because of gross impairments in self-care, cognition, and judgment that threaten their safety and well-being.

AREAS OF UNCERTAINTY

Investigators have explored estrogen replacement as a novel treatment for puerperal mental illness. Estrogen is not recommended for the management of PP in general psychiatry or general practice settings; it is strictly an investigational drug in these cases. Findings from two earlier small studies suggest the possible efficacy of estrogen in the prevention and treatment of PP in carefully selected women who were hospitalized during the experimental treatment and were provided antithrombotic therapy.[110,111] The pretreatment estrogen levels of their subjects ranged close to the levels of menopausal women. Following estrogen therapy, these women experienced rapid and significant resolution of mood, psychosis, and cognitive symptoms; their treatment response correlated closely with a restoration of normalized estrogen levels that were appropriate for reproductive-aged women. Although these reports were compelling, a recent trial failed to replicate the findings.[112]

APPROACH TO TREATMENT

There are no current treatment guidelines for the management of PP. In general, once medical causes for acute-onset psychosis have been excluded, the first-line drug treatment should be based on the underlying diagnosis. A patient with PP and a known cyclic mood illness or close family members with BD is most likely experiencing an episode of bipolar illness. She will benefit from treatment with an antimanic agent, such as lithium, an AED, or

an atypical antipsychotic drug. Women who have a primary diagnosis of schizophrenia and recurrent puerperal illness will benefit from a medication chosen within the class of atypical antipsychotic drugs. The choice of treatment also should be governed by the patient's history of past treatment response, the side effects profile, and the acuity of illness. For example, the postpartum patient with insulin-dependent diabetes, an acute onset of paranoid delusions, inconsolable crying and fitful bursts of unexplained laughter, and a twin sister with mixed episodes would require antimanic drug treatment with the fewest metabolic effects. In this case, initiation of 20 mg ziprasidone bid, which is an FDA-indicated drug treatment for psychosis and mania and the least likely to induce glucose intolerance, is an acceptable treatment option. A quick titration to a therapeutic dose range of 60–80 mg ziprasidone bid may be necessary to achieve symptom relief. If the patient fails to reach a timely response and displays deteriorating self-care or becomes desperately suicidal, she may require a more aggressive form of treatment, such as ECT. Once she has completed the course of 7–9 treatments of ECT over a 2–3-week period, she will need to continue on maintenance antimanic pharmacotherapy to prevent recurrence. Before release from hospital, the treatment team must work with the patient and her family to devise a discharge plan that will bolster her supports, incorporate close follow-up, and reduce stressors that contribute to relapse risk. For future pregnancies, her primary care physician is advised to collaborate with the obstetrician, endocrinologist, and other specialists providing her care in consideration of antimanic prophylaxis during pregnancy or after childbirth.

CONCLUSIONS

The core features of PP are an early and rapid onset, accompanied by profound confusion, delusional beliefs, mood swings, and inability to function that represent a major change from baseline. Patients with PP usually experience a brief illness, rapid treatment response, and the absence of long-term impairment. These are clinical clues that suggest an underlying affective disorder, most likely a bipolar illness.[1,3,4,8,11,21,22,32,113–115] The prognosis is optimistic in the setting of acute onset and lack of premorbid debility.[6] PP and puerperal-onset bipolar illness are distinct from more severe forms of BD that manifest with recurrent bouts of bipolar psychosis, mixed mania, and treatment-refractory bipolar depression and are associated with less promising outcomes.[65,116]

To move forward with our understanding of bipolar illness presentations and treatments for reproductive-aged women, we require data from prospective studies on the treatment response and outcomes of women with PP and comparisons with their healthy counterparts. The physical and neurodevelopmental outcomes of anti-manic and antipsychotic drug exposure in breastfed infants remain critical areas of research. Persistent mental illness has been linked with impairments in mother-infant bonding. The impact of untreated vs. treated maternal bipolar disorder on infant and childhood development is essential in our appreciation of risk for mental disorders in the progeny and how interpersonal relationships develop in children of parents with major mental illness. These remain highly significant but tremendously understudied topics.

Correlations among the symptoms of PP, gonadal hormone states, and neurotransmitter activity are also major areas of investigation that are necessary to explain the pathophysiology of PP and explore novel, efficacious treatments. Functional imaging of the frontal and mesolimbic structures with treatment holds promise for enhancing the understanding of the neurobiology that underlies PP. Ongoing investigations into the neurobiology, diagnosis, and long-term outcomes of PP will lead to better illness recognition and effective interventions and will be essential to unravel the mystery of this fascinating but tragic disorder. This will improve our understanding and treatment of mothers and families who suffer this highly debilitating yet treatable disorder.

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Table 1

Summary of Follow-Up Studies

Author	Sample size and description	Follow-up period (years)	Findings
Protheroe, 1969[33]	134	35	Average age at admission, 28.3 years Primiparous, 63% Incidence: Affective psychosis, 68% Schizophrenia, 28% Organic, 4/5% Recurrence: Affective psychosis, 33% Schizophrenia, 50% Organic, 4.5% PP[a] recurrence frequency, 33% Both PP and non-PP recurrence, 5%
Kadrmas et al., 1979[34]	157, with age-matched controls	3.4–5.9	PP associated with greater frequency of psychosis; less non-PP recurrences than controls
Platz and Kendell, 1988[35]	72 matched pairs, women with nonpuerperal illness	9	PP, fewer relapses, fewer suicides, less hospitalizations, shorter inpatient stays
Benvenuti et al., 1992[36]	30, no controls	4–18	63% relapse rate of PP 76% affective disorder (DSM III-R) 24% brief reactive psychosis or schizoaffective disorder No schizophrenia
Videbech and Gouliaev, 1995[32]	50	7–14	Bipolar illness: incidence >40% of all PP cases (50% had depression) Non-PP recurrences in 50% 60% readmission rate Schizophreniform disorder: incidence 12% Functional outcomes: Early onset PP (<1 month), 13% on disability insurance Late onset PP (>1 month), 33% on disability
Hunt and Silverstone, 1995[37]	36 bipolar women with PP; 22 bipolar women non-PP acute episode; 28 bipolar men with acute episode	2	Rate of affective episodes at 3 months after childbirth: 28% women, 14% men First episode bipolar disorder in puerperium: 33% women, 0% men Rate of PP in primiparous, 65% Rate of PP in multiparous, 37% Relapse rate of bipolar disorder in puerperium: 25%–40%
Pfuhlmann et al., 1999[38]	39	12	Unipolar psychotic depression, 28% Acute transient psychosis, 21% Cycloid psychosis (bipolar illness), 54% Pregnancy or puerperal relapse rate, 50% Nonpuerperal relapse rate, 11% Suicide rate, 4%
Robling et al., 2000[25]	64	23	Unipolar psychotic depression, 55% Bipolar disorder, 30% Schizophrenia/schizoaffective/other primary psychosis, 11% Recurrence rate of PP, 75%: 38% <3 relapses; 29% puerperal onset relapses Lower relapse rates associated with primiparity, PP onset <1 month after delivery, unipolar depression
Davidson and Robertson, 1985[39]	82	11.7	Unipolar psychotic depression, 52% Bipolar disorder, 18% Schizophrenia, 16% Personality disorder and depression, 8% Organic disorder, 2%
Rohde and Marneros, 1993[21]	86	26	Schizoaffective disorder, 49% Schizophrenia, 28% Affective disorder, 13% Functional disability in 33% of study population
Kirpinar et al., 1999[40]	64 matched pairs	11	Schizophrenia, 40%

Author	Sample size and description	Follow-up period (years)	Findings
			Schizoaffective disorder, 11% Bipolar illness, 20% Unipolar depression, 20%

[a] PP, postpartum psychosis.

Table 2

Summary of Family Studies

Author	Sample size and description	Follow-up period (years)	Findings
Protheroe, 1969[33]	134 98 probands with family 119 parents and siblings enrolled	35	Morbidity risks for PP[a]: both siblings and parents, 11.7%; siblings, 8.9%; parents, 14.7% Morbidity risk for family of bipolar patients, 10%–15% Morbidity risk for schizophrenia in siblings and parents of PP probands, 10.4% (similar to risk for first-degree relatives of schizophrenia patients)
Reich and Winokur, 1970[41]	35 females, 29 first-degree relatives	13–17	Morbidity risk for affective disorder in first-degree relatives, 23.5% Morbidity risk for affective disorder in first-degree relatives, 34.7% PP recurrence in proband, 50% PP recurrence in first-degree relatives, 30%
Kadrmas et al., 1979[34]	157 relatives of bipolar women with PP, 136 age-matched control relatives of patients with nonpuerperal bipolar mania	3.4–5.9	Affectively ill first-degree relatives: PP women, 19% Matched controls, 38% Female manic group, 36%
Platz and Kendell, 1988[35]	72, with matched controls	9	Morbidity risk for unipolar depression in first-degree relatives: PP, 7.7%; control, 12.2% Morbidity risk for bipolar disorder in first-degree relatives: PP, 1.6%; control, 3.4% Morbidity risk for puerperal disorder in first-degree relatives: PP, 4.9%; control, 4.2% Morbidity risk for admission in first- degree relatives: PP, 9.3%; control, 15.9%
Dean et al., 1989[24]	51 puerperal-only 33 puerperal and non-PP episodes 19 bipolar and only non-PP episodes	8.9	Mood disorder in 60% first-degree relatives Significantly more first-degree relatives of PP-only and both PP and non-PP groups received psychiatric treatment than bipolar group 10-fold risk for PP in first-degree relatives of PP-only group
Jones and Craddock, 2001[27]	152 women with BD I or S-affective disorder bipolar type (313 births)	Not stated	PP occurred in 26% women with BD I or schizoaffective disorder bipolar type PP occurred in 57% women with BD I and family history of PP

[a] PP, postpartum psychosis.

Table 3

Summary of Differential Diagnosis and Evaluation of PP

Differential diagnosis	Evaluation and laboratory tests
Psychiatric disorders	
Bipolar I disorder (BD I): Manic or mixed or depressed episode with psychotic features, postpartum onset	Careful exploration of present and past: mood symptoms, low mood and high or irritable moods; unusual beliefs, suspiciousness, grandiosity; obsessive-compulsive symptoms; suicidality and thoughts to harm others
Unipolar major depression with psychotic features	
Schizophrenia, single episode or schizophreniform disorder (first episode psychosis)	Past treatment response and recent history of stopping medications
	Family history of mood disorder or PP[a]
Obsessive-compulsive disorder (unlikely)	
Medical or organic causes	
Cerebrovascular	Careful medical history, with history of severe headache, preeclampsia during pregnancy, unilateral weakness, new onset sensory deficits, seizurelike behaviors; check blood pressure; consider head CT or MRI; consult neurologist urgently
Ischemic stroke (arterial or venous) secondary to preeclampsia or eclampsia, severe hemorrhage during delivery	
Hemorrhagic stroke secondary to uncontrolled hypertension, arteriovenous malformation, aneurysm, disseminated intravascular coagulation	
Normal pressure hydrocephalus	
Metabolic or nutritional	Serum electrolytes
Hyponatremia or hypernatremia	
Hypoglycemia or diabetic ketoacidosis	Fasting blood glucose, HbA1C in patient with insulin-dependent diabetes, type II diabetes, glucose intolerance during pregnancy
Uremic encephalopathy	BUN, creatinine in patients with history of renal dysfunction
Hepatic failure	Liver function tests in patients with history of hepatitis or known liver disease; AST, ALT, alkaline phosphatase, LDH, bilirubin (direct and indirect), lipase
Graves' disease (hyperthyroidism) or myxedema (hypothyroidism)	Thyroid function tests, total T4, T3, thyroid reuptake, TSH
Parathyroid disease (hypercalcemia/hypocalcemia)	Serum calcium levels
Vitamin B_{12}, folate deficiency	Serum B_{12}, RBC folate levels
Thiamine deficiency	Thiamine levels
Medications	Medical history; consider urine drug screen
Corticosteroids	
Narcotics: meperidine (Demerol)	
Sympathomimetics: amphetamine, theophylline, ephedrine, phenylephrine	
Antibiotics: gentamicin, sulfonamides, isoniazid, metronidazole, vancomycin	
Anticholinergics: atropine, benztropine, diphenhydramine, eye/nose drops	
Antivirals: acyclovir, interferon	
Benzodiazepines and barbiturates	
Immunological	Medical and family history, ESR; rheumatology consultation
Systemic lupus erythematosus	
Infectious	Complete blood count and differential, electrolytes, BUN, creatinine
Sepsis	

Differential diagnosis	Evaluation and laboratory tests
Meningitis or encephalitis	Possible lumbar puncture or CT of head
HIV	Serum HIV test

[a] PP, postpartum psychosis