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Postpartum Psychosis: A Review of Pharmacological Therapy Options

Postpartum Psikoz: Farmakolojik Tedavi Seçeneklerinin Derlemesi

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ABSTRACT

Postpartum psychosis is a severe postpartum mental health emergency characterized by mood swings, abnormal thinking or behavior, and confusion. Factors such as hormonal and psychological changes in the mother during pregnancy and the postpartum period, stress and a psychiatric disorder play an essential role in the development of postpartum psychosis, together with a genetic predisposition. Although this condition is most common in patients who have been or will be diagnosed with bipolar disorder, it may also occur less frequently in women with psychosis, schizophrenia, or major depression with schizoaffective disorder. In some patients, this situation may remain isolated in the postpartum period and not progress to any mood-destroying or psychotic disorders in the future. In a group of patients, this psychosis may manifest itself in the future. This psychiatric emergency can cause serious harm to both the mother and the baby, so postpartum psychosis should be recognized and treated as quickly as possible. There is no single guideline for the treatment of postpartum psychosis. Therefore, the treatment must be meticulously chosen by the clinicians according to the clinical characteristics of each patient. According to the data obtained from many clinics in recent years, it has been seen that the most effective treatments are antipsychotics, lithium, mood stabilizers, antidepressants, benzodiazepines, and electroconvulsive therapy (ECT). Therefore, facilitating and accelerating the clinician's choice among these options will significantly contribute to managing postpartum psychosis. This review presents an analysis of current pharmacological treatment modalities in the treatment of postpartum psychosis.

Keywords: Postpartum, Pregnancy, Psychosis.

ÖZET

Doğum sonrası psikoz, duygudurum dalgalanmaları, anormal düşünce veya davranışlar ve konfüzyon ile karakterize, doğum sonrası gelişen ciddi bir ruh sağlığı acili durumudur. Gebelik ve postpartum dönemde annede gelişen hormonal ve psikolojik değişim, stres, sahip olunan bir psikiyatrik rahatsızlık gibi faktörler, genetik yatkınlıkla birlikte doğum sonrası psikozun gelişiminde önemli bir rol oynar. Bu durum en sık bipolar bozukluk tanısı almış veya alacak hastalarda görülmekle beraber, psikoza sahip, şizofreni ya da şizoaffektif bozukluğu olan majör depresyonlu kadınlarda da daha az sıklıkta ortaya çıkabilir. Bir kısım hastada bu durum postpartum dönemde izole kalabilir ve ileride herhangi bir duygudurum bozan veya psikotik rahatsızlıklara ilerlemez ve hastalık başka bir atakla seyretmezken bir grup hastada bu oluşan psikoz kendini ileride de gösterebilir ve şizofreni gibi psikotik rahatsızlıklar dâhil kişinin yaşamını etkileyen bir duruma evrilebilir. Bu psikiyatrik acil durum hem anneye hem de bebeğe ciddi zararlar verebilmektedir, bu nedenle postpartum psikoz, klinisyenler tarafından en hızlı bir şekilde tanınmalı ve tedavisi en kısa sürede uygulanmalıdır. Doğum sonrası psikozun tedavisinde tek bir kılavuz yoktur. Dolayısıyla hastalara uygulanacak tedavinin, klinisyenler tarafından her hastanın klinik özelliklerine göre titizlikle seçilmesi önem arz etmektedir. Son yıllarda birçok kliniklerden elde edilen verilere göre en efektif tedavilerin, antipsikotikler, lityum, duygudurum düzenleyiciler, benzodiyazepinler ve elektrokonvülsif tedavi (EKT) olduğu görülmüştür. Bu nedenle bu seçenekler arasından klinisyenlerin seçim yapmasının kolaylaştırılması ve hızlandırılması, bu denli ciddi bir acil durum olan doğum sonrası psikozun yönetilmesine oldukça katkı sağlayacaktır. Bu derleme, doğum sonrası psikoz tedavisinde güncel farmakolojik tedavi modalitelerinin bir analizini sunmaktadır.

Anahtar Kelimeler: Doğum sonrası, Gebelik, Psikoz.

EPIDEMIOLOGY AND PREVALENCE

Postpartum psychosis is seen in women who gave birth to 1-2/1000 children in the first weeks following birth.[1] Although it usually occurs 2-4 weeks after birth, symptoms may begin 2-3 days after delivery.[2] While almost all of the patients were women, it was observed that fathers could also have postpartum psychosis.[3] In one study, the mean age of women with the disease was found to be 26[4], while in another study, it was stated that 57% of the patients were between the ages of 20-30, and there were not any patients over the age of 40. In addition, the onset of the disease in 46% of the patients followed the first birth, and in 32%, the disease appeared within the first two weeks after birth.[5] Another study shows that about 87% of women who have experienced a postpartum episode of psychosis in the past have also experienced a psychotic episode in the future.[6]

ETIOLOGY

In a study conducted in the United Kingdom, psychiatric admissions due to psychotic or mood disorders in the first month after birth were found to be approximately 22 times higher than psychiatric admissions to hospitals before pregnancy.[7] For this reason, it can be said that the disease is based on many factors, including the psychosocial factors that develop during and after pregnancy. The circadian rhythm, thought to be only one of these factors, is complex in newborns, and this complexity is believed to interact with the mother's emotions.[8] Many studies on genetic factors draw attention.[9,10,11] The impact of the possible contribution of rapidly declining estrogen in the postpartum period may play a role in etiology as well.[12] In addition, it has been shown that causes such as cesarean delivery, excessive antepartum hemorrhage, postpartum hemorrhage, eclampsia and preeclampsia, puerperal sepsis, birth canal injuries, placental abruption, and uterine rupture are also risk factors.[13] Recently, it has been said that the COVID-19 pandemic has increased the incidence of the disease, with or without SARS-CoV-2 infection.[14]

DIFFERENTIAL DIAGNOSIS AND COMORBIDITIES

Patients may experience delusions, mood swings, confusion, and disorganized behavior. In a cohort study, the phenotypic characteristics of 130 postpartum psychosis cases were determined and collected in 3 different profiles. It was determined that 34% of the cases had mania or agitation (anger was more common than elevated mood); depression or anxiety was prominent in 41%, and 25% of the patients had an atypical or mixed profile.[15] These mental impairments can cause the patient to look very different from her previous life. This difference should be recognized as quickly as possible since it has been shown that suicide is the most common cause of maternal death in the perinatal period, and it has been noted that suicide often occurs postpartum.[16] It is observed that many psychiatric diseases may occur in the puerperal and post-puerperal periods. Here, clinicians must identify the most common psychiatric conditions and distinguish them from postpartum psychosis due to the high risk of suicide.[17] At the beginning of these differential diagnoses, maternal sadness and postpartum depression are the main ones. Maternal sadness can be defined as a temporary mood change that occurs mainly between the first and tenth days after childbirth and is characterized by crying crises, a mild depressive mood, and

anxiety.[18] In a study conducted, it was found that the prevalence of maternal sadness was 39% in over 5000 people.[19] Another common postpartum mental disorder is postpartum depression. Postpartum depression and non-perinatal major depression share the same diagnostic criteria: depressive mood for more than two weeks, loss of interest, anhedonia, difficulty sleeping, poor appetite, decreased concentration, psychomotor agitation or retardation, fatigue, feelings of guilt or worthlessness, and suicidal thoughts. The following table shows the symptomatic differences between postpartum depression and psychosis.[20]

Table 1. *The differences between postpartum depression and postpartum psychosis.*

Postpartum Depression	Postpartum Psychosis
Depressive mood	Mania
Loss of interest and pleasure in all or most activities	Mood variability
A significant weight loss or gain	Delusions
Insomnia or excessive sleepiness	Hallucinations
The presence of psychomotor agitation or retardation	Bizarre behaviors
Exhaustion or loss of energy	Severe depression
The feeling of worthlessness	Confusion
Decreased ability to concentrate	
Recurring thoughts of death	

On the other hand, the most critical risk factor for postpartum psychosis is the mother's history of bipolar disorder. Postpartum psychosis occurs in approximately 20%-30% of women with bipolar disorder.[21]

It should be remembered that metabolic disorders can also cause this condition, and it is known that laboratory tests should also be used in differential diagnosis. The conditions that should be considered in the psychiatric differential diagnosis are listed below.[22]

ASSESSMENT TOOLS AND SCREENING

Women applying for medical care during pregnancy or postpartum should be screened for existing mental health problems, a history of psychiatric treatment, and whether there is a family history of mental illness. Patients whose screening for any of these is positive should be evaluated for a history of further mania or hypomania, psychotic depression, or psychotic disorders. Patients with a personal or family history of one of these conditions should be trained and monitored in the first weeks of postpartum. More intensive monitoring and prophylactic treatment should be considered in patients with a history of bipolar or schizoaffective disorders. Women with a history of bipolar disorder or postpartum psychosis are at an extremely high risk of postpartum relapse. Additionally, they are at higher risk for a possible future psychiatric episode compared to the average population.[23] Although lithium prophylaxis has shown effectiveness in reducing postpartum relapse, the timing of prophylaxis is controversial, given the balance of risks and benefits for mother and baby.[24]

The assessment tools for diagnosing postpartum psychosis are listed below.[25]

Table 2. *The differential diagnosis of postpartum psychosis.*

Condition	Tests	Additional Information
Bipolar 1 relapse	Family history, mood history	Current and past history of low and high mood plus family history
Unipolar major depression with psychotic features	Clinical evaluation	Begins after childbirth
Obsessive-compulsive disorder and schizophrenia or schizophreniform disorder	Treatment history, drug incompatibility	
Hyperthyroidism-thyroid storm	Thyroid function tests, complete blood count/erythrocyte sedimentation rate/ /differential, lumbar puncture	Graves' disease, fever due to infections such as sepsis, meningitis, encephalitis
Diabetic ketoacidosis	Fasting blood sugar, hemoglobin A1c, history of glucose tolerance during pregnancy	
Substance abuse	Drug screening for drugs abuse	
Uremia	Kidney function tests, blood urea nitrogen, creatinine	
Hepatic encephalopathy	Liver function tests, aspartate aminotransferase, alanine aminotransferase, hepatitis screening, alkaline phosphatase, direct/indirect bilirubin, lipase	A screening if there is a history of exposure or disease
Vitamin B12 deficiency	Clinical evaluation, blood tests	
Thiamine deficiency	Clinical evaluation, blood tests	
Hypercalcemia	Blood tests	
Pregnancy-related hypertension and stroke	Computed tomography/magnetic resonance imaging	Rule out stroke
Preeclampsia or eclampsia		
Metabolic or nutritional reasons	Electrolyte tests	
Immunological causes such as systemic lupus erythematosus	Clinical evaluation, blood tests	
Certain drugs	Clinical evaluation, drug history	Corticosteroids, antivirals (acyclovir and interferon), antibiotics (gentamicin, vancomycin, isoniazid), anticholinergic drugs, and stimulants such as amphetamine, ephedrine, and theophylline

Table 3. *The assessment tools for diagnosing postpartum psychosis.*

Important Assessment Tools
Full physical examination
Neurological examination
Comprehensive metabolic panel
Complete blood count
Urinalysis
Urine toxicology
Thyroid stimulating hormone, free T4, and thyroid peroxidase antibodies
Ammonia level
Brain imaging (if there are neurological symptoms)
Limbic encephalitis testing (if there are neurological symptoms)

TREATMENT

The importance of early and effective treatment is critical[26]; the earliest treatments produce the best results.[27]

Breastfeeding: Medications used to treat postpartum psychosis can be passed to the baby through breastfeeding. However, adequate clinical observations regarding the drugs' effects on the baby have not been made. At this point, what needs to be done is to create a drug selection by making a profit-loss ratio. Only a few prospective studies have been identified evaluating the use of haloperidol, chlorpromazine, and olanzapine during breastfeeding for antipsychotics. Olanzapine and quetiapine are categorized as acceptable for breastfeeding, while chlorpromazine, haloperidol, risperidone, and zuclopenthixol are categorized as suitable for breastfeeding under medical supervision. Aripiprazole, asenapine, chlorprothyxene, clozapine, droperidol, fluphenazine, flupenthixol, iloperidone, lurasidone, paliperidone, perphenazine, pimozide, trifluoperazine, thiothixene, and ziprasidone are currently not recommended in breastfeeding.[28] Most clinical guidelines do not recommend breastfeeding in women treated with lithium. It is extremely important for clinicians to inform and advise women about the risks and benefits of using lithium during pregnancy, if possible, before pregnancy.[29]

Of the antidepressants; sertraline, paroxetine, and nortriptyline are currently considered to be the drugs that may be preferred by breastfeeding mothers due to their low amounts in milk and high clinical experience in their use. MAO inhibitors and doxepin should be avoided, while bupropion, fluoxetine, nefazodone, venlafaxine, and some new drugs (levo-mylnacipran, vilazodone vortioxetine), which have little information about their use, should be used with caution in the postpartum period.[30] Benzodiazepines, on the other hand, can be used safely in mothers because they pass relatively little into milk.[31]

Antipsychotics are the first choice pharmacological treatment in patients with psychosis. However, a study comparing the effectiveness of antipsychotics in patients with postpartum psychosis has not been conducted until now. Therefore, the choice of medication here depends on the physician's clinical experience. It is known that second-generation antipsychotics are preferred more than first-generation antipsychotics due to the fact that their extrapyramidal and anticholinergic side effects are less. Of the second-generation antipsychotics, older drugs studied for pregnancy and lactation, such as quetiapine and risperidone, are more reliable than

newly released antipsychotics. It is essential to know the side effects that may occur during the use of second-generation antipsychotics. The most common metabolic side effects are dyslipidemia, hypertension, and metabolic syndrome.[32]

Clozapine appears to be effective in the treatment of severe and refractory postpartum psychosis, data here are limited. If the response to second-generation antipsychotics is poor, clozapine may be started at 250 mg/day. In a study, a patient started on clozapine had symptoms regressed within five days and was discharged. After discharge, clozapine was discontinued at the patient's request, olanzapine maintenance treatment was started, and complete remission was observed within one year.[33]

Although new antipsychotics have been used recently, there is not enough current data on these antipsychotics (cariprazine, lumateperone, brexpiprazole, pimavanserin) in treating postpartum psychosis.

Additionally, neurosteroid treatments such as brexanolone have been tried in postpartum depression, but their use in postpartum psychosis has not been studied.[34]

In patients with psychosis and mild agitation, initial doses of risperidone (0.5 to 1 mg/day per day), olanzapine (2.5 to 5 mg/day), or quetiapine (50 mg/day at baseline to 50 mg twice daily) may be used. The drug can then be titrated to a therapeutic dose over the next three to four days (risperidone 2 to 4 mg/day, olanzapine 10 to 15 mg/day, quetiapine 300 to 800 mg/day). The dose should be adjusted to achieve remission while minimizing side effects.[35]

In treating postpartum psychosis, it is necessary to determine the underlying psychiatric illness of the mother and select treatments for it. Mothers with postpartum psychosis, bipolar disorder, major depression with psychotic characteristics, schizoaffective disorder, or schizophrenia may be at the bottom. If the bipolar diagnosis is considered in patients, a mood regulator should be added to the treatment. Benzodiazepines can be used for agitation. For women with postpartum psychosis with a depressive episode or a history of major depression with psychotic features, treatment with an antidepressant in combination with antipsychotic medication is recommended.[36] The side effects of antidepressants that may affect the baby are not certain. Most new antidepressants produce very low or undetectable plasma concentrations in breastfed infants. The highest infant plasma levels have been reported for fluoxetine, citalopram, and venlafaxine. Suspected side effects have been reported in several infants, especially for fluoxetine and citalopram.[37]

Lithium is the most commonly used mood stabilizer in treating and prophylaxis postpartum psychosis.[38] Clinicians should be careful about potential side effects when using lithium. There is no clear evidence that there are any contraindications to the use of lithium during breastfeeding. However, lithium should be considered when alternative therapies are unavailable due to the relatively high exposure of breastfed infants and limited short- and long-term safety data on infants exposed to lithium during breastfeeding. Lithium treatment's possible risks and benefits during breastfeeding should be adequately discussed with the mother.[39]

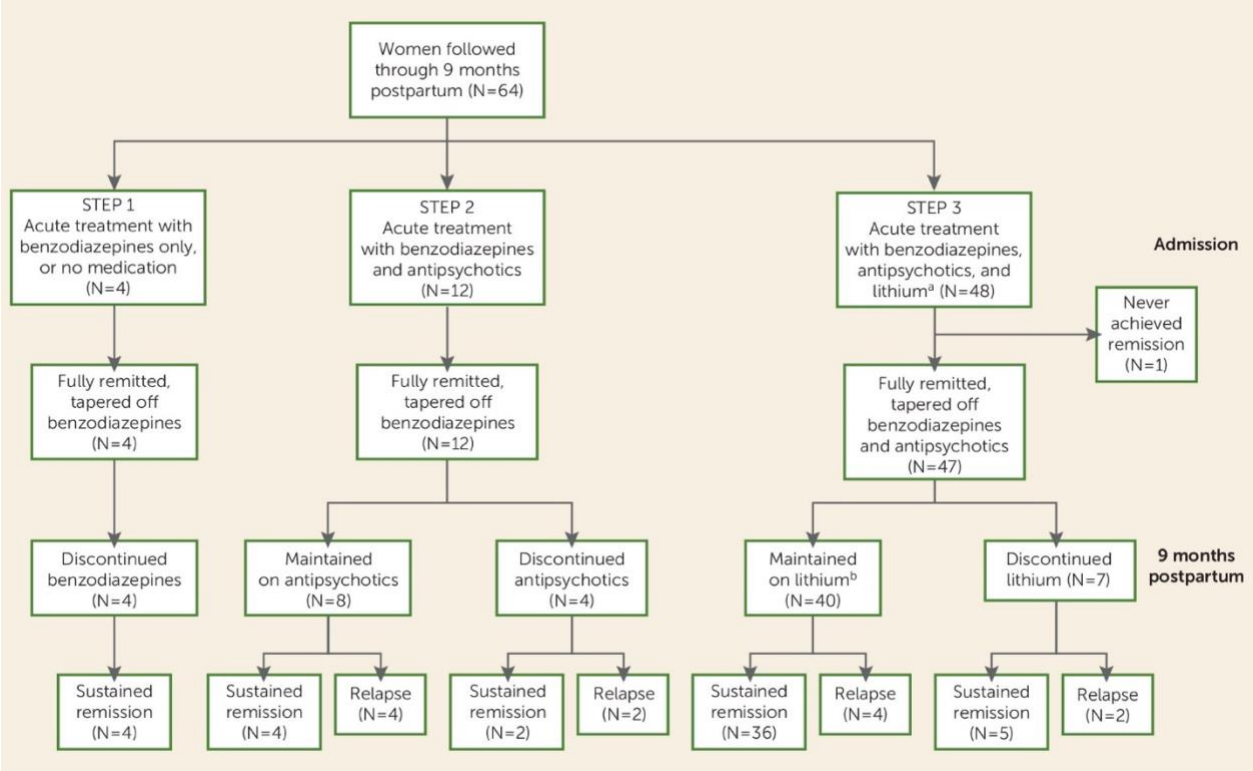

Figure 1. Treatment Outcomes in 64 Women With Postpartum Psychosis by Bergink et al.[40]

[a]One patient declined antipsychotic medication.

[b]Three patients were maintained on both lithium and an antipsychotic.

In 2015, Bergink et al.[40] developed a 4-step treatment protocol for female patients with first-episode postpartum psychosis. According to this protocol: In Step 1, lorazepam treatment was administered before sleep for 3 days. The aim here was clear that sleep hygiene played a role in the etiology of postpartum psychosis, as mentioned earlier. In patients with clinical improvement, the benzodiazepine dose was tapered and discontinued. In Step 2, antipsychotic treatment was added on Day 4 to patients with persistent manic or psychotic symptoms. The recommended antipsychotic treatment was initially 2-6mg/day of haloperidol. Patients who experienced side effects were switched to atypical antipsychotics. In a group of patients who had been using antipsychotics for 2 days or more, the first step was passed, and the same antipsychotic was continued. It was recommended to continue the treatment for 9 months in patients who responded to treatment. In the 3rd step, additional lithium treatment was started in patients who received a combination of benzodiazepine and antipsychotic therapy for 2 weeks and did not show sufficient clinical improvement. The lithium plasma level target was determined as 0.8-1.2 mmol/L. It was recommended to discontinue the antipsychotic treatment by gradually reducing the dose in patients with improvement and to use lithium as monotherapy for 9 months as maintenance. The maintenance therapy target plasma level was determined as 0.6-0.8 mmol/L. In the 4th step, ECT was recommended in patients who did not respond adequately to the combination of benzodiazepine, antipsychotic, and lithium treatment after 12 weeks. Before ECT, all drugs were recommended to be discontinued by tapering the dose.

DISCUSSION

Postpartum psychosis is an urgent psychiatric disorder for both mother and baby. This condition can cause irreversible damage; therefore, it is vital that the disease is recognized quickly and the treatment planned accordingly for each patient is started as soon as possible. The treatment model that Bergink et al. created can be used.[40] Otherwise, alternative treatment options are available. For instance: the first treatment to be selected in a patient with psychosis can be antipsychotics, preferably atypical. Initial doses of risperidone (0.5 to 1 mg/day per day), olanzapine (2.5 to 5 mg/day), or quetiapine (50 mg/day at baseline to 50 mg twice daily) may be used for the patient.[35] If the patient has underlying bipolar disorder, a mood stabilizer, preferably lithium, should be added to the treatment.[38] The addition of antidepressants may be considered in those with a history of major depression or those with depressive episodes.[36] According to the patient's current agitation, benzodiazepines may also contribute to treatment. In patients with psychosis who resist these treatments, electroconvulsive therapy may be considered the last.[41] In prevention, it has been shown that lithium and antipsychotics can be effective in high-risk patients.[38,40]

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