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Recommendations of the Polish Psychiatric Association regarding the treatment of affective disorders in women of childbearing age. Part II: Bipolar disorder

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Summary

In the article, the recommendations of the Polish Psychiatric Association regarding pharmacological treatment of women with bipolar disorder during pregnancy and postpartum period were presented. The issue pertains to every twentieth woman wanting to get pregnant. Before planned pregnancy, it is advisable to obtain a several-month stabilization of psychiatric state, to establish treatment with one mood-stabilizing drug (except for valproate and carbamazepine) or gradual discontinuation of drugs in case of mild course of illness and lack of recurrences in recent two years. In the first trimester of pregnancy, the dose of the mood-stabilizing drug should be reduced (lithium carbonate to 500 mg/day). Depression during pregnancy can be treated with quetiapine or lamotrigine or with antidepressant drug added to a mood-stabilizing drug. Atypical antipsychotics drugs with mood-stabilizing properties can be used in case of (hypo) manic or mixed states. Following the delivery, it is advisable to introduce a mood-stabilizing drug as soon as possible to prevent postpartum psychiatric disturbances. In the treatment of postpartum depression, quetiapine can be used or an antidepressant drug added to a mood-stabilizer. Considering breastfeeding, it should be remembered that the infant/maternal ratio of serum drug concentration is low for valproate, olanzapine, quetiapine, sertraline and paroxetine, and high for lithium and lamotrigine. In the case of postpartum psychosis, a hospitalization and antipsychotic treatment are needed.

Key words: bipolar disorder, pregnancy, perinatal period

Introduction

In recent years, there has been a significant increase in research on treatment of women with bipolar disorder (BD) during pregnancy and confinement. Although there is still a number of controversies and uncertainties, current research results and clinical experience seem to indicate that with proper functioning at all stages of the reproductive period there is a high probability that a woman with bipolar disorder can go through pregnancy, give birth to a healthy child and function properly in the postpartum period.

Epidemiological data indicate a significant prevalence of bipolar disorder. According to the American National Comorbidity Survey Replication, the risk of developing bipolar I disorder, bipolar II and bipolar spectrum disorder over time is 1.0, 1.4 and 2.4%, respectively [1]. Because this illness occurs with equal frequency in both sexes, usually begins in the period of early adulthood and proceeds in the reproductive period, it can be assumed that this problem affects every 20th women wanting to become pregnant. Recently, Merrill et al. [2] have evaluated mental state of women who had their first visit during pregnancy using *the Mood Disorder Questionnaire* (MDQ) and *the Edinburgh Postnatal Depression Scale* (EPDS). It turned out that 5.1% of women had positive results in the MDQ, and two-thirds of women in this group obtained positive results in the EPDS. This may indicate that the probability of the presence of bipolar disorder affects every 20th pregnant women, and in one third of cases these disorders remain undiagnosed when only screening for depression is used.

A number of studies indicate that bipolar disorder alone can be a source of pregnancy-related problems. The latest meta-analysis, conducted by Rusner et al. [3], showed that women with BD have an increased risk of gestational hypertension and antenatal bleeding, also premature labor, induction of delivery and Caesarean section occur more often. Moreover, women with BD more often give birth to newborns with lower birth weight. It is worth noting that the above observations occur in both women who take mood stabilizers and those who do take such medications, and bipolar disorder is not associated with an increased risk of malformations [4].

Pregnancy may, in turn, affect the course of bipolar disorder. The former view that pregnancy may be a protective factor for the course of BD is no longer valid. Viguera et al. [5] compared recurrences after discontinuation of lithium in pregnant and non-pregnant women with BD, and reported similar frequency in both groups. In another study, Viguera et al. [6] observed a high risk of an active affective episode during pregnancy in the case of discontinuation of treatment with mood stabilizers. In women who had been euthymic at the time of fertilization and who discontinued treatment with mood stabilizers, the risk of relapse was 2-fold higher and the duration of an episode was 5-fold longer compared with women who continued treatment with mood stabilizers during pregnancy [6]. Recently, Salim et al. [7] have carried out a systematic review of 11 papers that assessed the incidence of BD recurrence during

pregnancy. The percentage of women with relapses in these studies ranged from 4 to 73%, with a median of 24%. It was found that depressive episodes were the most common, followed by mixed episodes, while hypomanic or manic episodes were observed much less frequently. In papers that reported on the use of treatment, a lower rate of relapse was found in women who continued to use mood stabilizers. In women who discontinued medications, relapses were more frequent in the case of sudden discontinuation. The number of previous episodes of the illness was also important – the risk of relapse was higher when the number of such episodes was four or more. Bergink et al. [8] stated that relapses were more frequent in women whose previous episodes were not related to the postpartum period. Larsen and Saric [9] conducted, on the basis of 8 papers published between 2000 and 2016, a meta-analysis of the risk assessment of BD relapse associated with discontinuation of mood stabilizers. Most of the papers reported a significantly lower number of relapses in people who continued to use mood stabilizers. The results of these papers also seem to indicate that there is a group of women who, despite not using mood stabilizers, maintain a stable mental state during pregnancy.

In the case of women with BD, there is a high risk of postpartum depression and other affective disorders in the postpartum period. The research conducted as part of the nationwide DEP-BI program, including 643 women, showed that the risk of postpartum depression is 2.48-fold higher in BD than in cyclic depression [10]. Jaeschke et al. [11], in the study among 434 women, found postpartum depression in 15.2% of women (they scored ≥13 points in the EPDS). Women with postpartum depression were significantly more likely to obtain a positive 'bipolarity' result in the MDQ (38%) compared with women without depression (21%).

Wesseloo et al. [12], in a review covering 5,700 deliveries in 4,023 patients with BD, showed that the risk of postpartum psychiatric disorders was 35%. It was significantly higher in patients not continuing mood stabilizers during pregnancy (66%) than in women continuing such treatment (23%). Recently, Di Florio et al. [13], on the basis of the clinical course in 887 women with BD having children, have attempted to determine the risk of postpartum disorders depending on their prevalence in the previous period. In women with no previous history of postpartum disorders, the authors determined the likelihood of occurrence of such an episode at about 30%. However, in women who had a previous postpartum episode, the risk during the next pregnancy was over 50%.

First- and second-generation mood stabilizers during pregnancy and puerperium

Mood stabilizers are the basic medications used to treat bipolar disorder. Due to the chronology of introduction to psychiatric treatment, they can be divided into first- and second-generation medications. The first-generation includes lithium, valproates and carbamazepine, while the second-generation includes atypical neuroleptics (clozap-

ine, olanzapine, quetiapine, aripiprazole, and risperidone) and lamotrigine [14, 15]. A number of data on safety of these medications during pregnancy and postpartum, as well as on the effectiveness of these medications in prevention of affective relapses in pregnancy and the occurrence of postpartum disorders, has been collected.

Lithium

The first studies regarding the use of lithium during pregnancy appeared 45 years ago and concerned 118 women forming the so-called Register of Lithium Babies [16]. Since then, the most experiences have been collected in relation to this mood stabilizer. The main risk associated with the use of lithium during the first trimester of pregnancy was the increased risk of developing circulatory system malformations (including Ebstein's anomaly). In the latest analysis of this issue, carried out by Patorno et al. [17] on 1.3 million pregnancies, including 663 women using lithium in the first trimester of pregnancy, cardiovascular defects were found in 2.41% of women using lithium, in comparison with 1.15% for the rest of the group. The risk of these defects was 1.11 at lithium carbonate doses of 600 mg/day and less, 1.60 at doses of 600–900 mg/day and 3.22 at doses of over 900 mg/day.

Recently, Munk-Olsen et al. [18] have compared 727 pregnancies associated with the use of lithium, with the remaining 21,397 cases – data obtained from 6 cohorts from Denmark, the Netherlands, Canada, Sweden, the USA, and the United Kingdom. Administration of lithium was not associated with any complications of pregnancy and delivery. The use of lithium in the first trimester of pregnancy caused a 1.71-fold higher risk of developmental defects, while such risk did not concern defects of the circulatory system. The latest analysis on the use of lithium during pregnancy confirms that this procedure prevents relapses during pregnancy and is not associated with obstetric complications during this period [19]. However, Munk-Olsen et al. [18] showed that in the group of women receiving lithium there was a 1.62-fold higher risk of re-admission within a month after delivery. In turn, prospective studies involving almost 100 children indicate that the use of lithium during pregnancy is not associated with neurodevelopmental disorders during childhood [20–22].

The use of lithium during pregnancy is an effective strategy for prevention of postpartum affective disorders. For women who have experienced such disorders in the past and do not receive lithium during pregnancy, it is recommended to include lithium immediately after delivery, having regard to the consultation on feeding the newborn baby, as breastfeeding is contraindicated in women receiving lithium. It is also possible to safely introduce lithium in the final stages of pregnancy – to prevent recurrence in the postpartum period. This procedure requires careful, frequent monitoring of lithium concentrations to protect the fetus against toxic concentrations [23].

Antiepileptic drugs – valproates, carbamazepine, oxcarbazepine, lamotrigine

Recent years have shown evidence of adverse effects of valproates in women of reproductive age and the risk associated with the use of these medications during pregnancy. Out of mood stabilizers, valproates contribute the most to the formation of polycystic ovary syndrome [24], are the most teratogenic during pregnancy [25] and, when used during pregnancy, cause the most severe neurodevelopmental disorders in the first stage of life [26]. The risk of teratogenic effects is very high and is estimated at 10%. Therefore, when using valproates in women of reproductive age, effective contraception should be used and a pregnancy test should be done prior to the inclusion of these medications. Recommendations of the Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency (EMA) aimed at avoiding exposure to valproates during pregnancy are mandatory as of 2018. These recommendations formalize the supervision of the physician over women of childbearing age treated with valproates. In many countries, including Poland, recommendations for avoiding the use of valproates during pregnancy have been issued. The first country that completely prohibited the use of valproates during pregnancy was France [27]. It can be added here that, almost half a century ago, French researchers were the first to show mood-stabilizing (French: *thymoregulatrice*) effects of valproates [28].

Carbamazepine is a mood stabilizer with enzymatic induction properties that reduce the level of simultaneously administered medications. This also applies to contraceptives in the oral form or implants, which may cause a decrease in their effectiveness [29]. Carbamazepine also has teratogenic effects and its use in pregnancy causes 1.37-fold increase in the risk of developing malformations. Such an effect is not exerted by carbamazepine analog –oxcarbazepine [30]. The latest analysis showed that the use of oxcarbazepine during pregnancy may be associated with an increased risk of autism in childhood [26].

Lamotrigine, a new-generation mood stabilizer, is increasingly used in the prevention of BD, and the last few years have indicated safety of its use during pregnancy. Wegner et al. [31] demonstrated that the use of oral contraceptives reduces the concentration of lamotrigine, which may impair its efficacy. Newport et al. [32] compared recurrences of the illness during pregnancy in 16 women who discontinued their usual mood stabilizers (lithium, lamotrigine or valproate) and 10 women who continued to use lamotrigine. Relapses occurred in 100% of women in the first group and in 30% of women in the second group, which may indicate the prophylactic efficacy of lamotrigine. The initial suspicion that the use of lamotrigine during pregnancy may contribute to cleft palate has not been confirmed on large material [33], as well as an overall risk of malformation with the use of this medication [30]. The latest meta-analysis of 21 studies on the use of lamotrigine during pregnancy, including a total of 1,412 patients, did not show any adverse events related to pregnancy and delivery related to lamotrigine monotherapy [34]. Wesseloo et al. [35] also found that using

lamotrigine during pregnancy to a similar extent as using lithium prevented the occurrence of postpartum disorders. Recently, Veroniki et al. [26] have shown an increased risk of autism when using lamotrigine during pregnancy.

Atypical antipsychotic drugs – clozapine, olanzapine, quetiapine, aripiprazole, risperidone

Several reviews on the safety of the use of antipsychotic drugs with mood-stabilizing properties during pregnancy have been published. Ennis and Damkier [36] reviewed the risk of developing malformations due to the use of olanzapine, quetiapine, risperidone, and aripiprazole in the first trimester of pregnancy. The relative risk was 1.0, 1.0, 1.5, and 1.4, respectively, which may suggest some increase in the case of the last two drugs. A study performed by Cohen et al. [37] confirmed the safety of the use of quetiapine in the first trimester of pregnancy. Meanwhile, a paper by Cuomo et al. [38], discussing the use of aripiprazole during pregnancy, speaks for the relative safety of this procedure. On the other hand, Park et al. [39] indicate a two-fold increase in the risk of gestational diabetes in the case of using olanzapine and 1.5-fold increase in the case of quetiapine.

Very little data determining whether the use of antipsychotic drugs during pregnancy have properties to prevent the recurrence of the illness, especially depression, during pregnancy and postpartum affective disorders, are available. Uguz [40] described 6 cases of olanzapine administration during pregnancy at doses of 5–10 mg/day with no relapses during pregnancy, as well as 2 cases of quetiapine administration where one of the patients experienced manic episode in the postpartum period. It seems, however, that until more data are collected in this area, the NICE recommendation to prefer antipsychotic medications instead of lithium is premature [41].

Clozapine is used in the case of drug-resistant BD with severe mania with psychotic symptoms, and, in the case of good prophylactic efficacy, its use should also be considered during pregnancy. A review of studies on the use of clozapine during pregnancy has not shown an increased risk of malformations associated with the use of clozapine, however, there is a 2-fold higher risk of gestational diabetes. Clozapine also increases the risk of developing floppy infant syndrome and convulsions [42].

Peng et al. [43] compared the development of 76 children whose mothers received atypical antipsychotics with 76 children in the control group. There were significantly lower results regarding cognitive and emotional functions at the age of 2 and 6 months, while no such differences were found at the age of 12 months. Another study found worse neuropsychological outcomes and major sleep disorders 2 months after delivery in children whose mothers received clozapine during pregnancy compared with other antipsychotics, however, these differences disappeared when children were examined at the age of 12 months [44, 45].

Recommendations regarding the treatment of bipolar disorder in women of childbearing age

Recommendations for patients with bipolar disorder who want to get pregnant

When dealing with a patient with BD planning pregnancy, a comprehensive physical examination should be performed as well as a series of additional tests – complete blood counts, kidney function tests (urea, creatinine, electrolyte levels), as well as – thyroid, liver, glucose, vitamin B12, folic acid, iron, vitamin D level tests (similarly as described in Part 1). In obese patients (e.g., after antipsychotics), glucose tolerance should also be assessed as well as the nutritional status [46].

In women with bipolar disorder who want to get pregnant, one should strive to achieve at least a 6-month period of mental state stabilization. During this time, it should also be decided whether and which mood stabilizer will be used during pregnancy. In women using valproates or carbamazepine who, due to the severity of the illness, are recommended to continue treatment with mood stabilizers, switch to lithium, lamotrigine or atypical antipsychotic monotherapy should be considered. The same should be done in patients with severe forms of disorders receiving polytherapy with mood stabilizers. Because, as recently demonstrated by Kessing et al. [47], lithium monotherapy is more effective in preventing bipolar recurrences than monotherapy with any other first- or second-generation mood stabilizer, it can be considered as a first-choice medication. Patients stabilized on lamotrigine or antipsychotics should be informed about the benefits and risks of continuing these medicines during pregnancy. In women stabilized on lithium therapy, the possibility of reducing the dose of lithium carbonate to 500 mg/day or less in the first trimester of pregnancy should be discussed. In women with mild illness and a lack of relapse in the last 2 years, gradual discontinuation of mood-stabilizing medication within 1–2 months may be considered.

The special situation concerns an unplanned pregnancy when the patient realizes that she is pregnant and asks for consultation. If the current medical record indicates the necessity to use medication, all the rules described above, i.e., replacement of valproates and carbamazepine with another mood stabilizer and setting up a monotherapy with mood stabilizer at the lowest possible dose in the first trimester, apply. Similarly, in women with mild illness and a lack of relapse in the last two years, gradual discontinuation of mood-stabilizer within 1–2 months may be considered.

Recommendations for treatment of patients with bipolar disorder during pregnancy

In patients receiving mood stabilizers, due to the crucial importance of the first trimester of pregnancy for the possibility of developing malformations, it is recommended to use a mood stabilizer at the lowest possible effective dose during this period. In the case of lithium carbonate, a dose reduction to 500 mg/day or less is recommended, which should not significantly reduce prophylactic effect. If possible, around the 20th week of pregnancy, an ultrasound scan may be performed to reveal possible fetal

defects. In the second and third trimester of pregnancy, the dose of lithium and other mood stabilizers may be increased depending on the evaluation of patient's mental state. In the case of lithium, a concentration of 0.5–0.8 mmol/l should be sought. The size of the fetus should be controlled in patients receiving antipsychotics – both reduced and increased fetal weights are observed. Any psychotropic drugs during pregnancy should be used in divided doses to protect fetus against high concentration of the drug.

As mentioned above, the most common type of affective episode during pregnancy in women with BD is depression. The greatest antidepressant effect among mood stabilizers is exerted by quetiapine and lamotrigine, therefore in women who do not receive treatment with mood stabilizers, inclusion of one of these drugs should be considered. In the case of lamotrigine, it should be remembered to increase the dose very gradually. There is also the possibility of using an antidepressant medication or adding it to the treatment with mood stabilizers despite the generally poorer efficacy of antidepressants in people with bipolar features [48]. The use of antidepressants during pregnancy has been discussed in the chapter on depression [49]. Similarly as mood stabilizers, antidepressants should be used in divided and the lowest effective doses. In patients receiving therapy with mood stabilizers, antidepressants may be discontinued after clinical improvement. In patients receiving antidepressant monotherapy, its length should depend on the assessment of the mental state and the course of pregnancy.

In cases of lack of antidepressant effect, the use of electroconvulsive therapy as the most effective way of treatment in drug-resistant depression may be considered, especially in the second trimester of pregnancy. A recent review by Leiknes et al. [50], however, indicates a number of adverse effects of ECT used during pregnancy and therefore this therapy should only be used in very severe and drug-resistant depressions.

In the case of (hypo)manic or mixed episode, antipsychotics should be used: olanzapine or quetiapine – as monotherapy or periodic addition to mood stabilizers. There is a case report regarding the effective use of high doses of quetiapine for this purpose [51]. In women who do not receive other mood stabilizers, it is advisable to continue antipsychotics to prevent postpartum affective disorders.

Recommendations for treatment of patients with bipolar disorder in the postpartum period

When using lithium, it is recommended to reduce the dose of the drug 1–2 weeks before delivery. Due to the higher risk of complications after childbirth, very careful observation of the newborn is also recommended [19].

In women who do not use mood stabilizers during pregnancy and have a history of postpartum episode, a mood stabilizer should be initiated immediately after delivery [12]. In this respect, there are no contraindications to the use of any first- and second-generation mood stabilizer, also valproates and carbamazepine, depending on previous experience with these drugs.

In general, postpartum depression in BD patients is usually treated as depression in BD. Sharma et al. [52] demonstrated the effectiveness of quetiapine monotherapy in patients with BD and postpartum depression. The addition of antidepressants to the treatment with mood stabilizers is used with similar frequency. In this respect, the most experience in efficacy and safety has been collected with regard to selective serotonin reuptake inhibitors (SSRIs). In the first episode of postpartum depression, there is a high probability that it is an episode in the course of bipolar disorder. In a retrospective study, Mandelli et al. [53] showed that half of women who experienced postpartum depression had a diagnosis of bipolar II disorder, one fourth – of bipolar I disorder and another one fourth – of cyclic depression. Because the features of bipolarity, e.g., assessed using the MDQ, predict worse outcomes when using antidepressants alone [48], it is recommended that antidepressants should be used together with mood stabilizers.

0.1% of women in the postpartum period may experience severe depression in the course of bipolar disorder, with psychotic symptoms, referred to as postpartum psychosis. This condition usually requires psychiatric hospitalization and treatment with antipsychotic drugs.

Recommendations related to breastfeeding in the postpartum period in women using first- and second-generation mood stabilizers were provided by Uguz and Sharma [54] and Uguz [55]. The largest amounts of the drug passing into breast milk were demonstrated in the case of lithium and lamotrigine, while the lowest in the case of valproates. In general, however, the side effects associated with the use of lithium and antiepileptic drugs in breastfeeding mothers are minor. The authors believe that both lithium and lamotrigine can be used during breastfeeding if they are the best-acting medicines for a given patient. These drugs should be used at the lowest effective daily dose, in divided doses, and taken after feeding [54].

Data on atypical antipsychotic drugs with mood-stabilizing properties indicate a low rate of transfer into breast milk in the case of olanzapine and therefore the safety of the use of this drug during breastfeeding. Quetiapine has similarly low rate, while aripiprazole and risperidone have slightly higher rate. Nevertheless, these drugs are not detectable in the child's blood. The highest number of side effects was noted in the case of clozapine. In general, however, up-to-date data regarding atypical antipsychotic drugs with mood-stabilizing properties are encouraging and indicate the possibility of their use during breastfeeding [55].

As mentioned above, postpartum depression in patients with BD is treated with SSRI antidepressants along with mood stabilizers. With regard to these drugs, the safety of sertraline and paroxetine is indicated [56].

Final remarks

The basic task of a psychiatrist regarding pregnancy, childbirth and the postpartum period in women with bipolar disorder is to discuss with the patient the potential benefits and risks associated with the use of pharmacotherapy during pregnancy [57]. The

experiences of the first author of these recommendations indicate significant benefits for the mother and the child that can be obtained with properly applied pharmacotherapy. Optimal results in this area are obtained with proper cooperation with a woman and her partner, as well as with the obstetrician who monitors the course of pregnancy.

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Table 1. **General principles of treatment of women of childbearing age with bipolar disorder**

Planning of pregnancy
Obtaining stabilization of mental state for several months
Determining one mood stabilizer; withdrawal of valproates and carbamazepine
Gradual discontinuation of medication in the event of a balanced mental state and no relapse in the last 2 years
Pregnancy
Reduction of the dose of a mood stabilizer in the first trimester Lithium carbonate in the first trimester ≤ 500 mg/day, in the second and third trimester – doses ensuring a concentration of approx. 0.6 mmol/l
Treatment of depression Quetiapine or lamotrigine in the case of therapy without mood stabilizers – continuation to prevent postpartum disorders An antidepressant added to a mood stabilizer In severe cases – hospitalization, consideration of electroconvulsive therapy
Treatment of mania/hypomania/mixed state Olanzapine or quetiapine – continuation to prevent postpartum disorders
Psychotropic drugs during pregnancy should be administered in divided doses Dose reduction or drug discontinuation in the last 2 weeks before delivery
Cooperation between a patient, partner, psychiatrist, and gynecologist
Postpartum period
Detailed observation of the newborn in the first days of life, especially when using lithium, clozapine
Introduction of a mood stabilizer as soon as possible to prevent postpartum disorders
Treatment of postpartum depression Quetiapine monotherapy An antidepressant added to mood stabilizer
Postpartum psychosis – hospitalization, antipsychotics
Breastfeeding Drugs with low rate of transfer into breast milk: valproates, olanzapine, quetiapine, sertraline, paroxetine Drugs with high rate of transfer into breast milk: lithium, lamotrigine – use only in the case of very good clinical effect, in divided doses, after feeding