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CASE REPORT

Prepartum relapses or treatment resistance: a case of unipolar mania

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ABSTRACT

Because of treatment resistance and risks to be considered in the choice of treatment, peripartum psychotic and manic episodes constitute treatment challenges. For perinatal psychosis, there is also the consideration of a substantial subgroup showing the phenomenon of relapse, defined as the recurrence of symptoms after a brief period of symptom reduction. We report prepartum relapses of psychotic manic episodes in a 30-year-old female patient with a 15-year history of bipolar disorder. After 4-month medication-free period due to pregnancy, the patient, who had been in remission for 8 years with a combination of risperidone, valproic acid, and lithium, suffered multiple relapses that could not managed with electroconvulsive therapy and antipsychotic medication. Later, her symptoms only managed with lithium addition to her treatment. In this report, we discuss the treatment of bipolar disorder in pregnancy in the context of prepartum relapse and treatment resistance.

Keywords: Bipolar disorder, ECT, lithium, pregnancy, relapse

INTRODUCTION

According to the DSM-5, manic episodes starting during pregnancy or within one month after birth are defined with the qualifier "peripartum onset" (1). Some experts in perinatal psychiatry have chosen to define episodes beginning in the prepartum period, during pregnancy, as "prepartum attacks." When attacks set on during pregnancy or postpartum, most clinicians are still correlating the reason for the short-term return of symptoms with a premature reduction of the drug doses or noncompliance, although already 200 years ago Esquirol (2) demonstrated the phenomenon of relapse, defined as a return of symptoms after a short period of improvement lasting no more than two months. Of the 223 perinatal psychosis cases in the literature showing a relapse phenomenon, 107 were reported prior to the introduction of the first antipsychotic drug, chlorpromazine, in 1950, which shows that these cases cannot have been caused by noncompliance or treatment resistance but indicate the presence of relapses (3). In this case presentation of a patient requiring hospitalization due to recurrent manic episodes during pregnancy, we want to discuss, based on the patient's attack pattern, if these manic episodes during pregnancy are an example of relapses or a condition to be explained with treatment resistance. In this context, it seems appropriate to review the definitions of remission, relapse, response to treatment, and recovery.

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The definition "in full remission" is used for a patient not showing any manic symptoms for the past two months (1). Patients, who in the past fulfilled the criteria of mania completely and still show manic symptoms that do not fully match the criteria for manic episode, or whose symptom-free period has lasted for less than two months, are defined as being "in partial remission." When a patient in partial remission develops a clinical course that again corresponds to the criteria of manic episode, this phenomenon is defined as "relapse" (1). These situations are established with the Young Mania Rating Scale (YMRS) according to the criteria formulated by the International Society for Bipolar Disorders (ISBD) (4,5). A drop in the YMRS score of 50% or more is considered an indication for a symptomatic response, while a reduction of 50% or more for each of the basic symptoms of mania according to the DSM is seen as a syndromal response (1,4). Leucht et al. (6), rather than evaluating treatment response according to one threshold as being present or not, suggested that a gradual assessment might be more beneficial. Thus, they proposed 4 categories of responses: below 25%, 25-49%, 50-74%, and 75-100%, which were included in the ISBD manual (4,6). A YMRS score below 5 is defined as remission. Recovery or sustained remission is specified as having a YMRS score below 5 for a period of 8 weeks. The absence of a significant reduction in the YMRS score is called "refractoriness." Symptoms outside the criteria for bipolar disorders, such as anxiety, panic attacks, irritability, hopelessness, avoidance, or cognitive dysfunction are kept outside these definitions (7).

We present a patient who had been in full remission with regular treatment and gradually phased out her medication due to a planned pregnancy. She was followed without drugs for 4 months but then had to be hospitalized 3 times, in February, March, and April of the same year, with bipolar mania. Lithium was added to her therapy, and after reaching a blood level of over 0.80mmol, she achieved full remission. Assessing the treatment process of our patient as an example of resistance to treatment during pregnancy, we might consider the manic episodes setting on peripartum as an example of the relapse phenomenon.

CASE

A 30-year-old female patient with diagnosis of bipolar disorder for 15 years and a history of two hospitalizations for treatment had been free from attacks for 8 years under treatment with risperidone (8mg/day), valproic acid (1000mg/day), and lithium (1200mg/day). Married for 1.5 years, she had no child and no previous history of pregnancy. She was a high school graduate and homemaker. As far as we could establish from her history and medical records, she had suffered 6 manic episodes but no depressive episode; therefore, her symptom pattern might be defined as "unipolar mania." In her general state of health, she had a history of vitamin B12 deficiency and hypothyroidism developing after lithium treatment. In her family history, there were no incidents of potential clinical interest.

As the patient's general state was good while she was followed for bipolar disorder with a treatment of risperidone 2mg/day and valproic acid 1000mg/day between 2004 and 2012, it was decided to reduce the treatment doses, and the patient had another manic episode.

Since 2012, she has been followed with a combination of lithium 1200mg/day, valproic acid 1000mg/day, and risperidone 2mg/day in full remission. In 2016, while planning a pregnancy, she gradually phased out first lithium, then valproic acid and risperidone. After being followed for 4 months without medication, 9 weeks into the pregnancy the patient presented to our emergency service complaining of insomnia, increased pressure of speech, aggressiveness, and mistrustfulness. She was admitted to the psychiatry department with a diagnosis of manic episode with psychotic features. Before admission, the patient and her family were informed about the treatment. As the patient's decision-making capacity was impaired, informed consent for the planned treatment was received from her husband and a sibling. During hospitalization, the patient scored 42 points on the Young Mania Rating Scale (YMRS). In the mental state examination, her affect was euphoric, she showed delusions of reference and delusional jealousy; hallucinations were not found, she had no insight.

After admission, the patient was assessed by specialists for gynecology and obstetrics, and after recording state and week of pregnancy, a treatment plan was worked out. On admission, the patient had been administered haloperidol 20mg/day and biperiden 5mg/day IM, and on the same day, quetiapine 100mg/day was added. Levothyroxine 50μg/day, which had been started because of a history of hypothyroidism and was still used, was continued, thyroid function tests were in the normal range. On day 15 of her

hospitalization, risperidone 3mg/day was started, as it had proven useful in the past; the dose of haloperidol was reduced to 10mg/day, and the following day, haloperidol IM was completely stopped, the dose of quetiapine increased to 400mg/day, and risperidone raised to 6mg/day. At the end of 3 weeks of inpatient treatment with quetiapine 400mg/day, risperidone 6mg/day, and biperiden 4mg/day, the patient's manic symptoms had not even slightly receded; therefore, electroconvulsive therapy (ECT) was planned. After consultation with specialists for internal medicine and gynecology and obstetrics, it was recorded that there was no contraindication for ECT. Seven sessions of ECT under anesthesia and muscle relaxation were given. Bilateral ECT with bifrontotemporal placement of the electrodes was applied. The patient's pseudocholinesterase level was 8857 IU/L; propofol 60mg was used as an anesthetic agent and suxamethonium chloride 30mg as a muscle relaxant during ECT. A Thymatron System IV machine (Somatics, LLC, Lake Bluff, IL) was used for the ECT. The induced seizure durations were 146, 98, 48, 79, 31, 40, and 36 s, respectively. After the ECT sessions, the patient was not confused. During the ECT, the patient's ongoing pharmacotherapy was continued. On day 42 after admission, the patient was discharged with partial remission, treatment with risperidone 6mg/day, quetiapine 400mg/day, biperiden 2mg/day, and levothyroxine 50μg/day. While she did not meet criteria for mania, the elevation of her mood continued (YMRS score: 8).

Three days after discharge, the patient, then in gestation week 15, presented again with irritability, increased pressure of speech, increased focus on religion, and mistrustfulness. In the mental state examination, she was alert, fully orientated and cooperative, in the interview she exhibited a hostile and grandiose attitude, speech was pressured, associations were loose, affect irritable, mood euphoric, psychomotor activity increased, delusions of reference, delusional jealousy, and erotomanic delusions were present, no hallucinations, and she had no insight (YMRS score: 46). After admission to the department, a consultation with a specialist for gynecology and obstetrics was arranged for the patient. Fetal ultrasound findings were appropriate for the gestation week, no hemorrhage or uterus contractions were found. The quetiapine dose was increased to 600mg/day, risperidone 6mg/day and biperiden 4mg/day, and in addition, lithium 900mg/day and haloperidol 10mg/day were started. Seven ECT sessions under anesthesia were given. The type of ECT administration was the same as during the previous hospitalization, the durations of the seizures were 145, 71, 28, 118, 50, 39, and 66 s, respectively. After ECT, the patient was not confused. The severe clinical picture at admission improved significantly, but a slight mood elevation and concomitantly a light increase in talkativeness continued. On day 26 after admission, the patient was discharged with partial remission (YMRS score: 7), treatment with haloperidol 10mg/day, risperidone 6mg/day, quetiapine 800mg/day, biperiden 2mg/day, lithium 900mg/day, and levothyroxine 50μg/day. During control in the outpatient clinic, a lithium blood level of 0.34mmol/L was measured and the lithium dose increased to 1200mg/day.

Fifteen days after discharge, in gestation week 21, the patient presented again with complaints of insomnia, pressured speech and increased anger, irritability, and mistrustfulness. She was readmitted to hospital with a diagnosis of manic episode with psychotic features (YMRS score: 44). A lithium blood level of 0.54mmol/L was determined and the lithium dose increased to 1500mg/day. The quetiapine dose was raised to 800mg/day, the haloperidol dose to 20mg/day. Risperidone 6mg/day and biperiden 4mg/day were continued with the same dose as before. A level 2 ultrasound performed in gestation week 22 found no pathologies in the fetus, whose development was appropriate for the stage of pregnancy. At control, a lithium blood level of 0.81mmol/L was found, and the patient was discharged with full remission on day 17 after admission, treatment with lithium 1500mg/day, haloperidol 20mg/day, quetiapine 800mg/day, biperiden 2mg/day, levothyroxine 50μg/day (YMRS score at discharge: 2). Fifteen days after discharge, the patient came for follow-up, being euthymic, and the treatment was continued unchanged.

The patient gave birth at an external center in the town where she lived. One day before delivery, the lithium blood level had reached a toxic dose (>1mmol/L) and the patient developed tremor of the hands and symptoms of nausea; therefore, lithium was discontinued and hemodialysis was performed. The baby was delivered by Cesarean section in gestation week 31 with a weight of 1500g and a length of 41cm. Apart from the low birthweight, the baby was healthy. No congenital goiter, hypotonia, lethargy, or cardiac arrhythmias were observed. Because of the early delivery and low birthweight, the baby was followed for 4 weeks in neonatal intensive care before being

discharged to the family. As the mother continued her pharmacotherapy after the delivery, it was made sure that she would not nurse the baby, who would be brought up on formula. The care of the baby would be divided between the mother and the maternal grandmother.

After the delivery, the external center where the patient had given birth let her continue the therapy with haloperidol 20mg/day, quetiapine 800mg/day, and risperidone 6mg/day, adding valproic acid 1000mg/day as a mood stabilizer. This treatment achieved a continuous euthymic state. Quetiapine and haloperidol were phased out. At 1-year follow-up after giving birth, the patient was able to maintain a euthymic state with the use of valproic acid 1000mg/day, risperidone 6mg/day, biperiden 4mg/day, and levothyroxine 50μg/day. The last valproic acid blood level measured was 84μg/mL.

DISCUSSION

Our patient had been in full remission with lithium and valproic acid. Planning a pregnancy, she had discontinued the use of her current medication, developing long-lasting manic episodes presenting with relapses that were difficult to control. It is known that discontinuing mood stabilizers because of pregnancy while in a euthymic state increases the relapse risk twofold and the duration of attacks is 5 times longer than in patients continuing their medication (8). As the use of lithium and valproic acid is to be avoided especially during the first trimester, recommended choices include to phase out lithium before conception and continue treatment with an antipsychotic agent or to renounce pharmacotherapy altogether (9-11).

In the normal population, the risk of perinatal psychosis is between 0.1 and 0.25%, but in case of bipolar disorder, a risk of 50% has been reported. For a long time, it has been accepted that typical antipsychotics used in pregnancy present only a low risk for the fetus (12). Therefore, these substances are generally used as first-line treatment in pregnant women (13). Regarding second-generation antipsychotics, data are mainly available for olanzapine and clozapine, and it is known that all second-generation antipsychotics carry a risk, at various levels, to develop gestational diabetes (14). It is reasonable to continue treatment with an antipsychotic previously used by the patient successfully; for this reason, we chose risperidone, which had been beneficial for the patient before.

In bipolar disorder during pregnancy, one of the preferred choices is the treatment with antipsychotics, whereas some patients can only reach a state of well-being using mood stabilizers such as lithium. As our patient did not achieve full remission with antipsychotic treatment, we added lithium to the therapy. Although lithium is related with cardiac malformations such as the Ebstein anomaly (15), the risks are lower than those of other mood stabilizers and the patient had previously benefited from lithium, which was the reason of our choice. High-resolution ultrasound and echocardiography examinations performed in weeks 6 and 18 found no malformations in the fetus; in the newborn, despite an increased risk, no problems such as congenital goiter, hypotonia, lethargy, or cardiac arrhythmias were seen.

Although the patient had previously benefited from valproic acid, we did not use valproic acid during pregnancy because it is related with risks of spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis, as well as low head circumference in newborns (16,17).

It has been reported, that in bipolar disorder, the rates of preterm birth and low birthweight are high (18). While lamotrigine is safer to use during pregnancy than other mood stabilizers, its effect on manic episodes is limited; it is more effective in preventing depressive episodes, while effectiveness in the treatment of acute mania has not been observed (19,20). Accordingly, as the episodes for which our patient required treatment were entirely manic and she had no history of depressive episodes, we considered lamotrigine not to be a suitable choice of treatment; when it became necessary to start a mood stabilizer, we chose to use lithium, which is less risky during pregnancy than valproic acid and carbamazepine (21).

Due to lithium intoxication in the external center one day prior to delivery, lithium was discontinued and treatment after birth continued with valproic acid. At this point, it might have been an adequate choice to go back to lithium treatment, given that it had benefited the patient, but as she had entered a state of remission with valproic acid, we preferred to continue with this drug, which is safe in the postnatal period, considering the risk of changing treatment once more. In an update to NICE guidelines made in 2018, it is emphasized that babies having been exposed to valproic acid in utero have a malformation risk of 11% and a risk of developmental disorders of 30-40%; hence they recommend not to use valproic acid in the treatment of women of childbearing potential (22). Considering the

possibility that the patient might have another pregnancy, it is reasonable to use lithium instead of valproic acid or to replace a different mood stabilizer already started by lithium. The presence of hypothyroidism in the patient requiring the use of levothyroxine for normal thyroid functioning is not a contraindication for treatment with lithium. It is appropriate to include the patient (while in remission) and the family in making this decision, informing them about the risks involved in changing the medication of a patient in remission as well as the danger that may arise if a pregnancy begins during the use of valproic acid. In our case, considering the risks for a treatment worked out with great difficulties, we reached a firm commitment to use birth control and thus chose to continue with the established treatment. In the light of the research data and our clinical experience, we would recommend in similar cases continuing treatment with the agent that achieved remission, unless there is a reason to the contrary; in women of childbearing age, lithium should be chosen as a first-line mood stabilizer and in case of a positive treatment response, lithium therapy should be continued.

By definition, relapse means an increase in the symptoms of the same polarity; the beginning of an episode of opposite polarity, as in the transition from mania to depression, does not fit the definition of relapse. Furthermore, clinical symptoms in bipolar disorder can present fluctuations; therefore, to be persuaded of the long-term effectiveness of a given therapy, it is necessary to observe the state of wellbeing over 2-4 weeks. While the trend towards relapse of psychoses in the perinatal phase is an important characteristic, it is often overlooked, as is exemplified by the fact that to this day, only 9 cases of preterm-onset relapsing perinatal psychoses have been reported (3). Brockington (3) points out that in relapsing cases in the literature, the first peripartum attack is of short duration (median: 25 days) and multiple relapsing peripartum cases may constitute a separate group (3); in addition, he suggests that menstruation may play a role in cases showing postpartum relapse (23). On the basis of our case who suffered an aggravation of her symptoms shortly after achieving treatment response in the perinatal phase and required another hospitalization, we want to draw attention to the importance of frequent and efficient follow-up examinations of patients in this period after discharge because of potential relapses. The relapse phenomenon in peripartum psychosis and related factors continue to be unclear but appear to be promising topics for future research.

Contribution Categories		Author Initials
Category 1	Concept/Design	E.Y.
	Literature review	A.O.
	Data analysis/Interpretation	N.B.T, H.M.A.
	Case follow-up (if applicable)	E.Y.
Category 2	Drafting manuscript	E.Y., H.M.A.
	Critical revision of manuscript	N.B.T., A.O.
Category 3	Final approval and accountability	E.Y., N.B.T., A.O., H.M.A.
Other	Technical or material support	H.M.A.
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