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CASE REPORT

Schizophrenia relapse after stopping olanzapine treatment during pregnancy: a case report

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Abstract: Women with schizophrenia have a high risk for symptom exacerbation or relapse during pregnancy and thereafter. Relapses are more frequent when antipsychotics are discontinued. This paper describes the case of a 28-year old woman with schizophrenia who continued treatment with olanzapine during the first trimester. Olanzapine, a second-generation antipsychotic, was administered at a therapeutic dose from week 1 of gestation until week 13 when she reported the pregnancy to her psychiatrist. Despite the psychiatrist's recommendation to continue treatment, the patient stopped olanzapine at 20 weeks. She was hospitalized at week 36 for a schizophrenia relapse and was transferred to the obstetrics department where she gave birth by Cesarean section to a normal child. This case is important, illustrating the perils of unplanned pregnancy during antipsychotic treatment and abrupt discontinuation. Ultimately, clinical decisions should be made on a case-by-case basis, weighing the risks to the mother in terms of symptom exacerbation and relapse if antipsychotic treatment is discontinued, and the potential risk to the fetus regarding possible teratogenic effects of continued antipsychotic treatment.

Keywords: relapse, pregnancy, schizophrenia, olanzapine

Introduction

Information regarding the safety of antipsychotic drug use during pregnancy is limited, creating a strong ethical dilemma.[1] Most data are available from observational studies and isolated case reports.[2] Prescribing psychotropic medications during pregnancy is a complex issue. It involves the assessment of the risk of leaving a severe psychiatric illness untreated with the attendant risk of complications to the mother and, thereby, indirectly to the newborn baby, versus the potential risk of teratogenic/embryo-lethal effects on the developing fetus.[3,4] Most second-generation antipsychotics have been used since the 1990s. Olanzapine is placed among category C drugs by the US Food and Drug Administration (ie, "Risk cannot be adequately ruled out. Animal studies have shown an adverse effect [ie, teratogenic or embryo-lethal], but there are no adequate human studies"), and there is no unequivocal evidence of harm to the fetus.[5]

The present case report focuses on a female patient diagnosed with schizophrenia who was undergoing treatment with olanzapine and valproic acid during the first and half of the second trimester of pregnancy, and who was psychiatrically hospitalized for a schizophrenia relapse 16 weeks after having stopped olanzapine. The day after the admission, she gave birth by a Cesarean section to a healthy male child. The patient provided written consent for the anonymous publication of her case.

Case report

This report is about a 28-year old female patient, married for 2 years, a university graduate, and diagnosed with schizophrenia from 19 years old. She had four previous

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psychiatric hospitalizations in Romania and abroad, and had a suicide attempt at age 21, overdosing on olanzapine. The last psychiatric admission was in 2012, again for a schizophrenia relapse. During that hospitalization, the patient was treated with olanzapine 20 mg/day, diazepam 40 mg/day and valproic acid 900 mg/day, with fast remission of the psychotic symptoms. At discharge, the patient was recommended to continue treatment with olanzapine 10 mg/day and valproic acid 1,000 mg/day, as well as ongoing outpatient care. Since the patient was married and sexually active, she was advised at every meeting with the psychiatrist regarding contraceptive methods and the risk of psychotropic treatment for a potential pregnancy.

In April 2013, the patient presented to the psychiatrist, requesting counseling and psychiatric treatment. The psychiatric evaluation at that time revealed marked irritability, insomnia, and persecutory delusions. The patient also shared for the first time with a health professional that she was 13 weeks pregnant, and that she had continued the treatment with both olanzapine 10 mg/day and valproic acid 500–1,000 mg/day until the day before the consultation. Considering the current status and the patient's wish to continue with the pregnancy, the decision was made to continue olanzapine treatment, but to discontinue valproic acid due to its potential to cause neural tube defects.[6] The plan and further evaluations were accompanied by discussions with the patient's gynecologist and primary care physician. Further psychiatric evaluations showed an improvement in the patient's status with continuation of olanzapine 10 mg/day.

At week 21 of the pregnancy, however, during psychiatric evaluation, the patient affirmed that she stopped taking olanzapine 1 week ago because "she felt well'' and because she did not like the associated weight gain and daytime sedation. She was psychiatrically stable 1 week after having discontinued olanzapine and was periodically evaluated at the outpatient department, while the pregnancy progressed normally, documented by ultrasound measurements.

In October 2013, at 36 weeks of pregnancy and 16 weeks after having stopped taking olanzapine, the patient was admitted to the psychiatric emergency unit, presenting with marked psychomotor agitation, incoherence, persecutory delusions, insomnia, mood lability, and marked dysphoria. Biological investigations showed mild anemia (hemoglobin 11.9 g/dL, haematocrit 34.8%), macrocytosis, mild hypercholesterolemia (221 mg/dL), and an aspartate aminotransferase (serum glutamate oxaloacetate transaminase) of 34 U/L with normal fasting glucose value. She was treated with diazepam 40 mg over a period of 12 hours, and then transferred to an obstetrics hospital where she gave birth by Cesarean section to a boy. At birth, the health status of the new born child, including glucose levels (80 mg/dL), was normal (insulin was not assessed). In the obstetrics department, she was treated with haloperidol short-acting injectable 5 mg/day and diazepam as needed for severe agitation and psychotic symptoms according to the psychiatrist's recommendation and to the hospital protocol, with mild improvement of symptoms. Lactation was suppressed with bromocriptine 5 mg/day and she was discharged after 1 week.

After discharge, she continued treatment with haloperidol 10 mg/day, valproic acid 1,000 mg/day, and tryhexifenidyl 4 mg/day with worsening of psychotic symptoms due to partial non-compliance.

One month after the birth, the patient was re-admitted to the psychiatric hospital for restlessness, insomnia, and persecutory and grandiose delusions. During this admission, the patient was initially treated with haloperidol 10 mg/day, but she started to present parkinsonian symptoms despite lowering the dosage and adding anticholinergic medication. The patient refused re-initiating treatment with olanzapine due to previous increased body weight and severe daytime somnolence. The psychiatrist decided to restart amisulpride, based on a good therapeutic response a few years ago and less risk for weight gain and sedation. The decision was agreed upon by the patient and her husband. Biological investigations showed a mildly lower value of hemoglobin (11.7 g/dL), but a normal value of hematocrit and no morphological abnormalities of the red blood cells. Blood glucose and cholesterol values were within normal range. The treatment recommended at discharge was amisulpride 600 mg/day, valproic acid 1,500 mg/day, diazepam 10 mg/day, and tryhexiphenidyl 2 mg/day. After discharge, the patient was monitored as an outpatient and continued with the treatment as recommended.

Since April 2014, the patient has remained in clinical remission. Both she and her husband declared that the infant, at 6 months of age, has been developing normally so far, both physically and psychologically. No formal assessment by a pediatrician was available.

Discussion

In the case of second-generation antipsychotics, there are no routine treatment recommendations for their use during pregnancy, and it is difficult to reach definitive conclusions regarding their safety for the developing child. Our case report describes a female patient with schizophrenia who continued treatment with olanzapine during pregnancy from

week 1 until week 20 when she stopped all medications herself. Subsequently, she relapsed at week 36 when she was hospitalized for 12 hours in the psychiatric hospital and then transferred to the obstetrics department where she gave birth to a healthy boy by Cesarean section. The newborn baby was normally developed for his age. The patient and baby were discharged after 2 weeks.

Clinicians must weigh the relative risks of medications administered during pregnancy and the associated risk of relapse if pharmacologic treatment is discontinued. The relapse of this patient with schizophrenia within 4 months of stopping her antipsychotic was an expected event. A recent meta-analysis of six trials showed that 77% (range: 57%–91%) of first episode schizophrenia patients who are randomized to discontinue antipsychotics relapsed compared to 3% of the patients randomized to continue antipsychotics.[7] According to a large meta-analysis, placebo controlled discontinuation trials demonstrated that relapses start early after replacing antipsychotic treatment with placebo, with 37.2% of patients experiencing a relapse within the first 3 months.[8] For women who are required to continue antipsychotic treatment during the first trimester, the lowest effective dose of a medication must be used, and agents with the lowest teratogenic potential should be selected. The US Food and Drug Administration classify medication risk during pregnancy into five categories to inform clinicians about the risks of fetus exposure. Categories include A (no risk in well-controlled human studies), B (no risk in animal studies), C (adverse effect on the fetus in animal studies, but no adequate studies in humans and potential benefits may warrant use of the drug in pregnant women despite potential risks), D (adverse effect on the fetus in animal studies and human investigational or marketing experience, but potential benefits may warrant use of the drug in pregnant women despite potential risks), and X (adverse effect on the fetus in animal studies and human investigational or marketing experience, and risks clearly outweigh potential benefits).[5]

Based on the available evidence of risks and benefits, the American Congress of Obstetricians and Gynecologists recommends continuing pharmacotherapy during pregnancy because severe psychiatric episodes are generally thought to be caused by discontinuation of medication, and an ill mother also affects the health of the fetus.[9] Various outcomes have been reported after olanzapine exposure during pregnancy. Olanzapine was found to be associated with low birth weight in a dose-dependent manner. Outcomes from 23 prospectively ascertained olanzapine-exposed pregnancies showed a 13% rate of spontaneous abortion, 5% stillbirth, 0% major malformations, and 5% prematurity, all within the range of normal historic control rates.[10] Another study of 18 pregnancies yielded similar results, suggesting that olanzapine is relatively safe when used during pregnancy.[11] There is also one case report suggesting that the use of olanzapine during pregnancy is associated with neonatal hypoglycemia due to hyperinsulinemia,[12] but in this case report glycemic levels were normal, while insulin levels had not been taken.

In another case report, the authors documented major complications, such as microcephaly and congenital anopthalmia after olanzapine exposure during the entire pregnancy.[13] Kirchheiner reported a case of a woman with schizophrenia who gave birth to a healthy child after she was treated with olanzapine from the 18th week of gestation through to delivery.[14] Treatment planning is critical for minimizing the risk to the mother and fetus while limiting the morbidity from active psychiatric illness. In order to assist patients in making the best choices for the health of the mother and fetus, clinicians must be familiar with the latest reproductive safety research of any medications used to treat the disorder.

Conclusion

More studies are needed to determine the effects of antipsychotics, including olanzapine, on pregnant women and the developing fetus. Schizophrenia relapse during pregnancy may expose the mother and fetus to high risk if the antipsychotic is stopped. Antipsychotics should be used in pregnant women only if the risk–benefit assessment justifies the potential medication-related risk to the infant.

Disclosure

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