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CASE REPORT



Neurodevelopmental and growth follow-up of the baby exposed to antipsychotics during pregnancy and lactation: a case report

Ömer Faruk Uygur  and Hilal Uygur 

Department of Psychiatry, Necip Fazil City Hospital, Kahramanmaraş, Turkey

ABSTRACT

Clozapine is an antipsychotic drug for the treatment-resistant schizophrenia. Although clozapine is superior to other antipsychotics, it is less common in psychiatric prescriptions due to clozapine. Little is known about the use of clozapine during pregnancy and lactation, or its effect on the mother, foetus and baby. Pregnancy category of clozapine is considered to be of relatively reliable category B, while it is recommended to be avoided during breastfeeding. Switching from clozapine to other antipsychotics during breastfeeding may lead to psychotic exacerbations. In this case, low dose of clozapine may need to be added to the antipsychotic treatment initiated during breastfeeding. However, data on the safety of combination antipsychotics during breastfeeding are limited. Psychiatrists, obstetricians and pediatricians should closely monitor with team spirit on such cases, thus drug exposure and side effects of infant are minimized while the mother's mental health is maintained. We aimed to present the growth and neurodevelopmental outcomes of infant exposed to clozapine during pregnancy and exposed to clozapine plus olanzapine during the lactation period.

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Introduction



Schizophrenia begins at an average of 25 years old, a childbearing age in women. They are now more integrated into society and can become pregnant [1]. According to the results of a retrospective study in Canada between 2002 and 2011, three of every 1000 pregnant women were schizophrenia [2]. The main treatment for women with schizophrenia on perinatal period, as in other life cycles, is antipsychotics, especially the second-generation antipsychotics (SGA). Foetal exposure to untreated schizophrenia is associated with increased risk of stillbirth, preterm birth, low birth weight, congenital malformations and elevated rates of infant death [3,4]. On the other hand, exposure to antipsychotics during pregnancy is associated with an increased risk of major malformation, congenital heart defect, preterm birth and low birth weight [5]. The above situation is the first challenge for clinicians. The second starts after birth. Many mothers wish to breastfeed their babies, they abstain from continuing their treatment because they think drugs can harm their babies. Therefore, safety data on the antipsychotics during the perinatal period are essential to minimize infant exposure and adverse effects while maintaining optimum maternal mental health.

None of the studies related to drugs used during the perinatal period due to ethical issues meet the gold standards such as randomized, placebo controlled,

double-blind, cross-research. Therefore, every case report on the use of antipsychotics in the perinatal period contributes significantly to the accumulation of knowledge on this subject. In this article, we aimed to the present growth and neurodevelopmental outcomes of infant exposed to clozapine during pregnancy and exposed to clozapine plus olanzapine during the lactation period. We have followed prenatal and post-natal total 21 months of woman with schizophrenia who was in remission with clozapine treatment. To the best of our knowledge, this report was the first follow-up case in which clozapine and olanzapine were used together during breastfeeding.

Case

A 35-year-old woman, with a diagnosis of schizophrenia for 9 years according to the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (SCID-5). She was treated initially with risperidone 6 mg/d, and later on with amisulpride 800 mg/d. However, treatment was switched to clozapine 300 mg/d due to resistant auditory hallucinations. She remained remission with clozapine treatment. First pregnancy happened at 25 years of age before schizophrenia diagnoses. After 7 years of first birth, one unplanned pregnancy happened during clozapine treatment without regular

CONTACT Ömer Faruk Uygur  drofuygur@hotmail.com  Ömer Faruk Uygur, Kahramanmaraş Necip Fazil City Hospital, Department of Psychiatry, Kahramanmaraş, 46050 Dulkadiroğlu, Turkey

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psychiatric examination. She continued clozapine during both pregnancy and breastfeeding period. The mother and her family did not report any negative effects of the treatment on the infant. When the third pregnancy was confirmed she contacted us and used 300 mg/d clozapine regularly. Written informed consent for publication was obtained from the patient and her family. We started following the perinatal period with an obstetrician. Ultrasound examinations were normal. Although no family history of diabetes she developed diabetes in the 18th week pregnancy that was successfully controlled with dieter. The dose was decreased to 100 mg/d gradually at the third trimester. The clinical observations indicated no psychotic exacerbation. She gave birth in the 38th week pregnancy by caesarean delivery while 100 mg/d clozapine was used. No perinatal complications were recorded and there was a good obstetric outcome. The Apgar-min 1/5 score was 7/9. No agranulocytosis, seizures, or other neonatal complications were observed. After birth the mother wishes to breastfeed her baby. We recommended to switch to another antipsychotic drug during the postpartum period. Because there is little published experience with clozapine during breastfeeding, and sedation and adverse haematologic effects have been reported in breastfed infants, other agents are preferred [6]. It was planned to switch to olanzapine because it had the highest number of olanzapine-related data on SGA exposure during breastfeeding and had a low rate in breast milk. The risks were explained and the mother and her family accepted olanzapine treatment. While clozapine was gradually stopped and olanzapine was increased to 20 mg/d but auditory hallucinations and agitation began. The mother and her family persisted on using clozapine despite the risks. Then clozapine was added to the olanzapine treatment and titrated up to 50 mg/d, which improved the clinical symptoms. She used olanzapine and clozapine combination during breastfeeding. The baby was regularly followed up by a pediatrician. No agranulocytosis, seizures and neurodevelopmental disorders were detected in the infant one-year follow-up after birth (Table 1).

Discussion

Clozapine is a gold standard drug approved by the FDA since 1989 in schizophrenia-treatment resistant patients. And also it is the only antipsychotic approved by the FDA to reduce the risk of suicidal behaviour [7]. In addition, clozapine is in category B, which can be considered relatively reliable in the pregnancy period [8]. Despite the evidence related to the effectiveness of clozapine and its relative reliability during pregnancy, prescription rates of clozapine were reported to be too low and delayed. This also shows that clinicians have developed a kind of phobia: clozapophobia.

The presence of this phobia was markedly reflected to data about clozapine usage rate in Turkey. For example, according to the Intercontinental Marketing Service reports for the years 2013–2014, clozapine was prescribed only 2.3% among all antipsychotics. This ratio increased to 2.8% in the first 10 months of 2015 and 2016. However, compared to European countries and especially 10% usage rates in China, the use of clozapine in Turkey remains far below than in many other countries. Undoubtedly, the most important obstacle holding clinicians back from the use of clozapine is the restrictions around blood monitoring [9,10]. In our case, we felt the fear of clozapine use, but the good cooperation with the patient and her family helped us overcome clozapophobia and encouraged to use clozapine during pregnancy.

Gestational diabetes mellitus, neonatal seizures, neonatal agranulocytosis, macrocephaly, shoulder dystocia, floppy infant syndrome, decrease foetal heart rate variability, atrial septum defect, gastroesophageal problems, and delayed peristalsis have been reported to have adverse outcomes in maternal exposure to clozapine during pregnancy [11–20]. On the other hand, some studies have reported that no adverse effects were found in the newborns [21–23]. Pregnancy period is not protective for schizophrenia, unlike may lead to relapse of a patient in remission. Additionally, when the current effective antipsychotic medication of patient is stopped or change with another antipsychotics increases the risk further [24]. In clozapine-treated patients, a switch in antipsychotic drug treatment is not recommended [25]. Therefore, we continued to use clozapine in our case during pregnancy. Gestational diabetes mellitus was observed and controlled with dietary. No abnormal data were detected in ultrasound examinations on foetus.

Based on the results of the research and case reports, it is possible to conclude that most SGA are not associated with undesirable results, are found to be safe in the breastfed infants, and that temporary, non-specific or mild side effects are observed. Therefore, the risk of untreated or inadequate treatment of a mother with schizophrenia outweighs the risk of having a small amount of drug to the baby. Case reports suggest that clozapine tends to accumulate readily in breast milk in a dose-dependent manner [26,27]. However, the relative infant dose for clozapine is a modest 1.4% of the weight-adjusted maternal dose [28]. Perhaps because of the well-known side effect profile of clozapine including haematologic toxicity and seizure, large cohort studies evaluating information regarding breastfeeding and neonatal side effect do not exist. In case reports, after exposure clozapine via breast milk one infant had agranulocytosis, one had somnolence. Another infant which exposed to clozapine during pregnancy and lactation had delay in speech acquisition without other neurocognitive or neuromotor

Table 1. Neurodevelopmental and growth follow-up of the baby during 12 months

Time	Weight (g)	Length (cm)	Head circumference (cm)	Congenital anomaly	Neurodevelopment
At birth	3570 g	51 cm	36 cm	No	Normal
3 rd month	4600 g	60 cm	40 cm	No	Normal
6 th month	6500 g	63 cm	43 cm	No	Normal
9 th month	8500 g	68 cm	45 cm	No	Normal Started to speaking
12 th month	9125 g %50–75 percentile	75 cm %50–75 percentile	46 cm	No	Normal Started to walking

deficit [29]. No adverse effects were reported in the two infants [29,30]. Due to potential serious risk for agranulocytosis and seizure in the exposed infant, the American Academy of Pediatrics notes concerns regarding infant exposure to clozapine in breast milk [31], and its use should be avoided during lactation [32]. Uguz [33] reported that a new safety scoring system for the use of psychotropic drugs during lactation, clozapine is not recommended owing to safety scores ≤ 3 [33]. Due to all these present risks we stopped clozapine in our case after birth.

According to the current literature, the first option for breastfeeding women with schizophrenia should be olanzapine [34]. So, we started olanzapine and gradually increased the dose during breastfeeding. No side effect was observed on baby. There are more data on olanzapine in SGA exposure during breastfeeding. The mean relative infant dose for olanzapine has been reported to be 1.6%, which is much low compared with the levels that are generally accepted to be clinically significant are 10% or more [35]. Considering the high relative infant dosage and the reported adverse effects in infants, the use of clozapine, lithium, and sulpiride is contraindicated during breastfeeding. Chlorpromazine and olanzapine could be considered the first-choice drugs for treatment of psychotic disorders in breastfeeding mothers because they have the lowest degree of excretion into human breast milk and scant adverse effects in breastfed infants [36]. Most of the data on side effects in infants exposed to olanzapine come from the manufacturer's pharmacovigilance database. According to these data, 102 women using olanzapine during breastfeeding (mean dose 7.4 mg) had some adverse effects including most commonly sleepiness, irritability, tremor and insomnia were reported in their babies [37].

Although the olanzapine dose in our patient was optimized up to 20 mg/d, the patient's auditory hallucinations and agitation began. Patient and her family persist on clozapine treatment. Therefore clozapine was added to the current treatment and titrated up to 50 mg/d, which improved the clinical symptoms. Limited information exists on polytherapy with antipsychotics during breastfeeding. More recently, two breastfed infants exposed to combined antipsychotics have been reported. In one, the mother utilized olanzapine and haloperidol during pregnancy and breastfeeding. Through 10 months of age, there were no neonatal side effects or developmental delays. The other mother

exposed the foetus to amisulpiride and aripiprazole during the first four weeks of gestation, and then after exacerbation of delusions while off medication, she started haloperidol and amisulpiride for the remainder of gestation and throughout 12 months of breastfeeding. No adverse neonatal side effects or developmental delays were noted in the infant at 15 months follow-up [38].

Our case is the first case about the usage clozapine and olanzapine combination during breastfeeding. The baby was regularly followed up by a paediatrician. No neurodevelopmental problem was observed at one-year-old follow-up and complete blood count values were within normal ranges. Additionally, according to the information obtained from the patient and her family, there was no problem in her two-years-old child who was exposed to clozapine during both pregnancy and lactation, and no neurocognitive or motor delays. Although it is a retrospective and patient-based information, it contributes significantly to the literature.

In conclusion, due to the limited data on clozapine during lactation, management of clozapine treatment during breastfeeding is difficult for schizophrenic patients who are in remission with clozapine treatment before pregnancy and who continue clozapine treatment during the perinatal period. On the other hand, olanzapine, which has a lot of knowledge about breastfeeding safety, is recommended during breastfeeding. Switching from clozapine to olanzapine during breastfeeding may lead to exacerbation of psychotic symptoms. An antipsychotic combination may be required in the treatment of this condition, and it may be necessary to make difficult decisions for both clinicians and patients and their families. However, as a result of good cooperation like in our case, increased metabolic risks and haematological side effects can be monitored for the combination of olanzapine and clozapine and both maternal and infant health can be maintained. Further large scale studies or case reports on the safety of these combinations in breastfed infants are needed.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Ömer Faruk Uygur  <http://orcid.org/0000-0003-2376-5113>
Hilal Uygur  <http://orcid.org/0000-0001-9438-8031>

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