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Switching from paliperidone palmitate 3-monthly long-acting injection to oral aripiprazole in a pregnant woman with schizophrenia: a case report and short review

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Summary. Treatment with long-acting injection (LAI) antipsychotics, such as paliperidone palmitate, has improved the quality of life in terms of symptoms and prevention of relapses in patients with schizophrenia. Although there are plenty of evidences about the efficacy and safety of paliperidone palmitate 3-monthly injection (PP3M) in adults with schizophrenia, literature appears lacking about the use of LAIs during pregnancy. We hereby describe the clinical case of a pregnant woman affected by schizophrenia (DSM-5-TR), taking pharmacological treatment of PP3M. Considering the inadequate evidence regarding the use of PP3M in pregnancy in agreement with the patient, we switched PP3M to an oral therapy with aripiprazole. The switch to oral aripiprazole allowed the patient to improve her sense of autonomy and strengthen the therapeutic relationship. To our knowledge, this is the first case report monitoring an entire pregnancy of a women affected by schizophrenia in treatment with PP3M injection and oral aripiprazole. No obstetrical or fetal complications were reported. As the research in this field is very demanding, it would be precipitous to derive final conclusions from the current case report, but we hope to build a growing number of data that would allow us to make more appropriate and safe therapeutic choices in such a vulnerable phase as the peripartum.

Key words. Antipsychotics, aripiprazole, LAI, paliperidone palmitate, pregnancy.

Switching da paliperidone palmitato trimestrale ad aripiprazolo orale in una donna incinta affetta da schizofrenia: caso clinico e rassegna breve.

Riassunto. L'uso dei farmaci iniettabili a lunga durata d'azione (LAI), come il paliperidone palmitato, ha migliorato la qualità di vita in termini di riduzione dei sintomi e prevenzione delle ricadute nei pazienti schizofrenici. Malgrado ci siano molte evidenze sull'efficacia e la sicurezza della formulazione di paliperidone palmitato trimestrale (PP3M) negli adulti con schizofrenia, i dati sul potenziale uso in gravidanza sono scarsi. Descriviamo di seguito il caso di una donna in gravidanza affetta da schizofrenia (DSM-5-TR) in trattamento con PP3M. Data la scarsa presenza di evidenze concrete in letteratura, è stata presa la decisione terapeutica, in accordo con la paziente, di passare ad aripiprazolo orale, un antipsicotico con un profilo di maggiore sicurezza in gravidanza. Il passaggio all'aripiprazolo ha permesso di migliorare il senso di autonomia della paziente e di rafforzare la relazione terapeutica. A nostra conoscenza, questo è il primo caso riportato che monitora l'intera gravidanza di una donna affetta da schizofrenia trattata con PP3M e aripiprazolo orale. Non sono state riscontrate complicazioni ostetriche e fetali. Sebbene la ricerca in quest'area sia impegnativa e sarebbe precipitoso trarre conclusioni definitive, speriamo di avere a disposizione un numero sempre maggiore di dati che ci permettano di fare scelte terapeutiche più appropriate e sicure in una fase vulnerabile come quella del peripartum.

Parole chiave. Antipsicotici, aripiprazolo, gravidanza, LAI, paliperidone palmitato.

Introduction

Schizophrenia is a chronic neuropsychiatric disorder affecting more than 21 million people across the globe[1] and it is associated with a decreased life expectancy, decreased quality of life, and social and familiar decline[2]. It is estimated that half of women with schizophrenia have the desire to become pregnant[3]. Pregnant women represent an exceptionally vulnerable population in which attention and monitoring of drug therapy is a must due to the possible detrimental consequences on the child and on the mother-child relationship[4,5]. It was established that women diagnosed with schizophrenia have an increased risk of relapse in the perinatal periods[6]. In recent years, the usage of long-acting injectables (LAIs) medications such as paliperidone palmitate, the major active metabolite of risperidone, improved the quality of life by reducing symptoms and preventing relapses[7]. In these regards, adherence to treatment and therapeutic relationship are prerequisite for the therapeutic success[8,9]. Real-world studies on LAIs safety for both the fetus and the mother and on the overall effectiveness in pregnancy, are sparse. Paliperidone palmitate 3-monthly (PP3M) formulation is the only available LAI antipsychotic providing an extended 3-month window of stable plasma drug

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concentration, enabling only four injections per year (approved by the US FDA in 2015 and by the European Medicines Agency in 2016[10]. Although there is extensive evidence about the efficacy and safety of PP3M formulation in adults with schizophrenia, data regarding the potential use in pregnancy are inadequate. Accordingly, the label reports that PP3M should not be used during pregnancy unless clearly necessary. Nonetheless, recent studies are reassuring about a possible use during pregnancy[11]. Here we describe a case of a pregnant woman suffering from schizophrenia who was under PP3M treatment and subsequently switched to oral aripiprazole (figure 1).

Case report

KD is a 30-year-old Caucasian woman diagnosed with schizophrenia, according to DSM-5 TR criteria, who has achieved a stable period of symptom remission over the past six years. During the last three years, the patient was under treatment with paliperidone palmitate 350 mg 3-monthly (PP3M) formulation at her local psychiatric center. She came to our attention at the University outpatient clinic SOS MAMMA[12] as she was pregnant. Anamnestic reconstruction reveals that she was diagnosed with schizophrenia at the age of 16. Psychotic onset was characterized by persistent visual and auditory hallucinations, bizarre and paranoid delusions, formal thought disorder, disorganized speech and behavior. She was hospitalized at the Acute Care Psychiatric Unit and after discharge the patient was referred to the local center. From the age of 16 to the age of 24 there were four relapses which required further hospitalizations. No history of substance and alcohol use disorder was recorded. Infant psychomotor development was normal, and she graduated from high school at age 19. She has been in a stable relationship since the age of 20. No other medical comorbidities were found. Of note, the mother suffered from severe postpartum depression.

Regarding pharmacological therapy, the patient was prescribed with antipsychotics with partial ben-

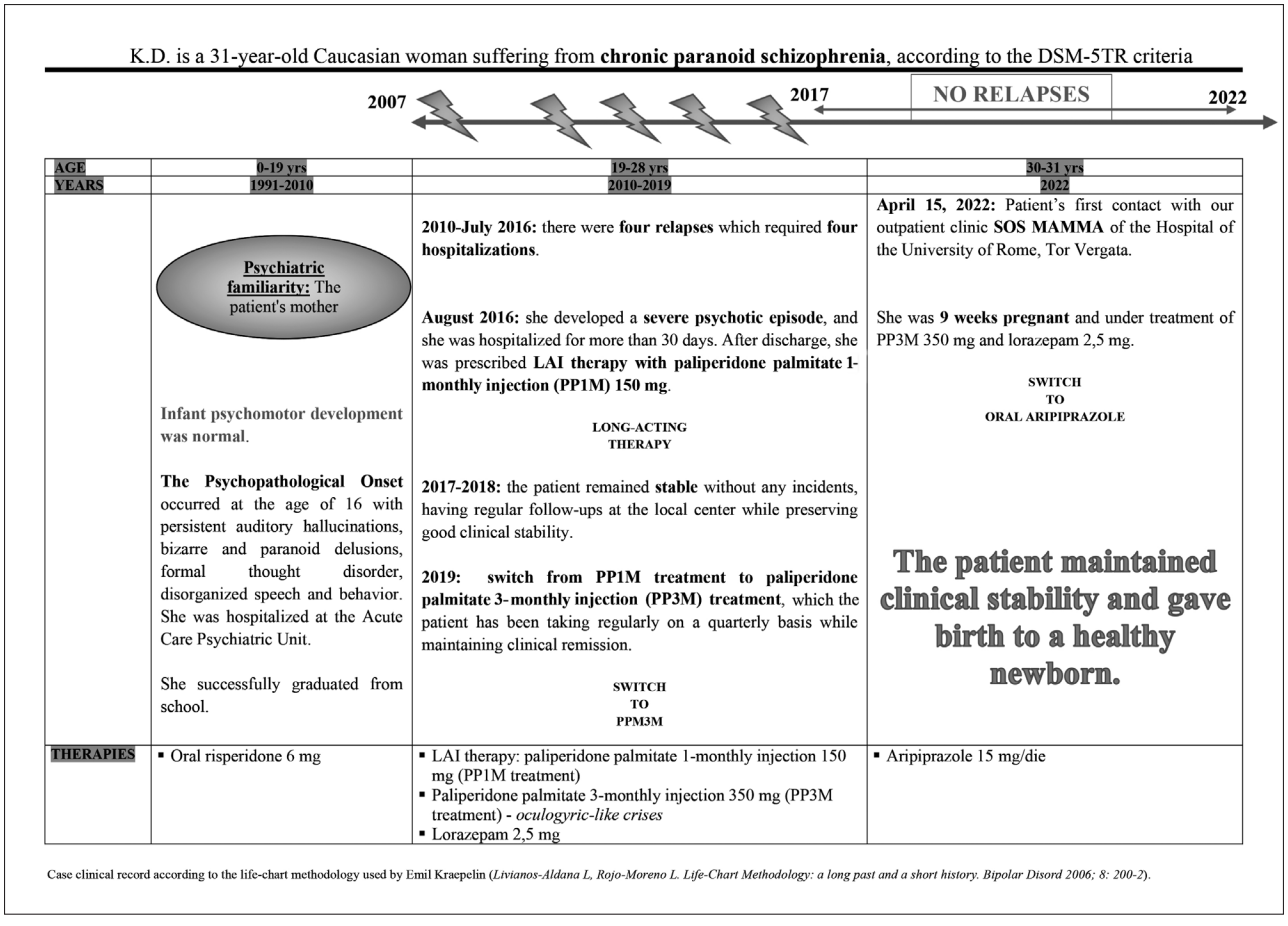

Figure 1. Patient's psychiatric and pharmacological history.

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efit due to recurrent discontinuation of medications. From the age of 25, she was prescribed LAI therapy with paliperidone palmitate 1-monthly injection (PP1M) 150 mg which resulted in remission of psychotic symptoms and satisfactory global functioning. Eventual agitation was treated with benzodiazepines. Furthermore, the patient developed eating disturbances characterized by alternating restrictive and binge eating behaviors and weight gain. However, the body mass index value indicated normal weight (range 18-24 kg/m^2). When she was 28 years old, she switched to PP3M 350 mg, which she assumed regularly while maintaining clinical remission.

When she informed her psychiatrist that she was nine weeks pregnant, he decided to turn to our university clinic which is specialized in perinatal depression and it is a hub of the Italian network for the management of psychiatric drugs in pregnancy and breastfeeding. An initial online consultation was carried out with the medical staff of SOS MAMMA made up of psychiatrists, psychologists, midwives, and residents. At that point, she was on lorazepam 2.5 mg and had the last administration of paliperidone palmitate 350 mg when she was 5 weeks pregnant. Two further face-to-face visits were performed followed by staff meetings to discuss the case. During these visits, two validated psychometric tests were administered: the Edinburgh Postnatal Depression Scale and the Brief Psychiatric Rating Scale. The patient scored 5 points on the EPDS, hence a negative score for peripartum depression, and 28 points at the BPRS. The patient expressed concern about taking LAI therapy during pregnancy and explicitly expressed her intention to interrupt it due to the potential damage to the health of the fetus. She reported oculogyric crises in the past and fear of excessive weight gain. We have provided her with appropriate information about therapy options and we agreed to stop paliperidone palmitate and to switch to oral aripiprazole (15 mg/die) based on a risk/benefit balance discussed with the patient and her psychiatrist. We outlined the pros and cons of initiating aripiprazole treatment during pregnancy. Since there was no evidence to suggest a risk related to LAI discontinuation, we approved discontinuation of LAI therapy and switched to oral therapy primarily for improved manageability and to consolidate the therapeutic alliance. Furthermore, aripiprazole has a lower risk of metabolic side effects and there is more data in the literature on its use in pregnancy[13] than PP3M. As the patient lives 90 km from our clinic, she continued to be assisted by the local center. We have scheduled a monthly follow-up and reaffirmed our availability in case of alarm signs.

The clinical course was favorable with good drug tolerance. During follow-ups, we observed a good clinical response with stable remission of psychotic symptoms in the absence of either metabolic side effects or excessive weight gain. Work and relational functioning remained stable. However, six days after starting aripiprazole she reported sedation which was completely resolved after 28 days. No other side effects have been reported. There were no oculogyric crises. Ultrasound checks were performed every month starting from the eighth week of pregnancy and showed no fetal abnormalities. The pregnancy progressed without any other complications. Shortly before labor, the patient had some bleeding without evidence of significant placental abruption. Delivery was performed by elective cesarean section at week 39, without complications. The infant was born with an APGAR score of 10/10, no malformations were detected, she weighed 3.390 kilograms (length 48 cm; head circumference 36 cm) and all newborn screenings resulted negative. The patient gained 13 kilograms in pregnancy and after delivery she decided not to breastfeed. Four months after delivery, no developmental abnormalities or congenital malformations of the child were observed (initial suspicion of plagiocephaly, later ruled out). At the 4-month postpartum follow-up, the patient regularly takes aripiprazole 15 mg/day with complete clinical remission and stability; therefore, we have chosen to maintain this treatment. She had no symptoms of postpartum depression: the Edinburgh Postnatal Depression Scale, EPDS, score was 1 and the score at the BPRS was lowered to 26.

Discussion

Antipsychotics cross the placenta with potential teratogenic risk to the fetus[14]. However, since the risk of major malformation is 3-4% in the general population, the background risk is never zero[15]. It is well-known that psychiatric disorders in pregnancy carry risk for women and newborns and consequently, antipsychotic use during pregnancy is a challenge that clinicians habitually have to handle balancing the benefits and potential risks. To date, there is no consistent data on the use of paliperidone during pregnancy and even less for the PP3M formulation. Intramuscularly injected and orally administered paliperidone were not teratogenic in animal studies, although reproductive toxicity was noted. Infants exposed to paliperidone during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery[16]. Paliperidone was detected in plasma up to 18 months after a single dose of PP3M[17]. Since the patient had received the last administration of PP3M long injection in the fifth week of pregnancy, she was exposed to the drug throughout the first trimester and beyond. A recent review of 13 case reports

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found that one child has reported multiple congenital anomalies and three children have manifested minor congenital anomalies[18]. There are few studies on the use of LAIs in pregnancy, so risk assessment is often done based on the safety profile of the oral formulation. Aripiprazole has a lower metabolic risk than paliperidone[19] and being overweight is a general risk factor in pregnancy. Our review of the literature revealed a stronger safety profile associated with the use of aripiprazole in pregnancy than paliperidone, although recent research appears more reassuring[20]. The potential benefits of aripiprazole for pregnant women diagnosed with bipolar disorder or schizophrenia have been documented to often outweigh the potential risks[19]. Our case report adds to the studies on the safety of aripiprazole in early pregnancy. Furthermore, since the patient was also exposed to paliperidone palmitate during pregnancy, we can state that paliperidone palmitate proved to be safe. Oral therapy is more manageable and, considering our patient's anamnesis, she showed a growing awareness of the disease and expressed to us the fear of taking long-acting therapy during pregnancy associated with the desire to be able to assume an oral drug in a more flexible way. The switch to aripiprazole has allowed to enhance the patient's sense of autonomy and to strengthen the therapeutic relationship. In fact, the sharing of the project with the treating psychiatrist was fundamental. To our knowledge, this is the first prospective case report monitoring the entire pregnancy of a woman with schizophrenia treated with paliperidone palmitate formulation quarterly (PP3M) and switched to oral aripiprazole. The positive outcome of our case indicates that, although there is no definitive evidence of reproductive safety, oral aripiprazole is an option for pregnant women with schizophrenia. It is essential that the expectant mother has clinical stability during peripartum so that a healthy mother-child relationship can be built. Choosing appropriate medications while taking all these aspects into consideration, represents a daily challenge that clinicians must face with the aim of guaranteeing, through treatment and the therapeutic relationship, the health of mother and child. Our study presents a few limitations. Firstly, we only administered two psychometric scales: the Edinburgh Postnatal Depression Scale (EPDS) and the Brief Psychiatric Rating Scale (BPRS), which are, nonetheless, validated psychometric scales[21,22]. Moreover, due to the patient living 90km away from our clinic, she continued to be followed by her local psychiatrist as well as a local gynecologist. For this reason, we do not have the original reports of the gynecologic/ultrasound examination. We were, however, in contact with them after every follow-up to make sure of the positive course of the pregnancy. Furthermore, we did not provide any follow-up data regarding the emotional and cognitive development of the baby, not allowing to determine if there have been long-term side effects on the baby's development.

Conclusions

In our case, it was imperative to maintain antipsychotic therapy throughout pregnancy in order to preserve the mother's long-standing psychopathological stability and maternal-fetal well-being. Based on the current evidence and the patient's medical history, we did a risk-benefit analysis and finally discontinued the LAI therapy and switched to oral therapy. Our decision was successful; however, it should be noted that in this case, the patient had oculogyric crises with the long-acting therapy and that aripiprazole was a more suitable option from a metabolic point of view. Furthermore, we did not find obstetric and fetal complications despite the fact that the mother was exposed to paliperidone palmitate during pregnancy. Although research in this area is challenging and it would be precipitous to derive final conclusions from the current case report, we hope to have an increasing number of data available that will allow us to make more appropriate and safer therapeutic choices in such a vulnerable phase as peripartum.

Consent for publication: the patient signed the written informed consent for the publication of the present case report.

Authors' contribution. CP: patient's information collection, manuscript drafting, literature review; EB: diagnostic interpretation, manuscript drafting, manuscript critical revision; IS, RS, GC: literature review, manuscript drafting; AS, CN: diagnostic interpretation, manuscript critical revision. All authors have read and approved the final manuscript.

Conflict of interests: the authors declare that they have no conflict of interests.

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