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OLGU SUNUMU / CASE REPORT

Maternal and newborn outcomes following paliperidone palmitate use during pregnancy and puerperal period in two women with schizophrenia

Şizofreni tanısı olan iki kadında gebelik ve lohusalık dönemi boyunca paliperidon palmitat kullanımının anne ve yeni doğan üzerine etkileri

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Abstract
Use of long-acting antipsychotics in schizophrenia provides advantages in achievement of compliance to treatment and maintenance of treatment. There is limited information on use of Paliperidone Palmitate (PP) during period of pregnancy and puerperality. Here, it was reported that two cases with schizophrenia who used PP during period of pregnancy, at the term, had healthy and vaginal delivery and then continued to use PP for a while including period of puerperium. The assessment of infant development included pediatric and psychiatric examination, physical and neurobehavioral development measurements at 2, 6, 12, 18 and 24 months of age. In our cases, no specific risks for the mothers and their children can be attributed to the use of PP during monitoring period. A clear plan for a woman and her supports (partner and family as appropriate) for postpartum care is essential for ongoing monitoring and care. Although it was not reported that fetus exposed to antipsychotics had congenital malformation; it should be kept in mind that in the future these children can develop neurodevelopmental and neurobehavioral problems.
Key words: Schizophrenia, pregnancy; puerperality, infant, paliperidone palmitate.

Öz
Şizofrenide uzun etkili antipsikotiklerin kullanımı, tedaviye uyumu ve etkin tedavinin sürdürümünü sağlamada avantaj sağlamaktadır. Paliperidon palmitatın (PP) gebelikte ve lohusalık döneminde kullanımı ile ilgili bilgiler kısıtlıdır. Bu yazıda gebelikleri süresince paliperidon palmitat kullanılan, terminde, sağlıklı, vajinal yolla doğum yapan, sonrasında da lohusalık dönemi dahil PP kullanımına devam eden şizofreni tanılı iki olgu bildirilmiştir. Bebeklerin gelişiminin değerlendirilmesi 2, 6, 12, 18, 24. aylarda yapılan fiziksel, pediatrik muayene ve nörodavranışsal gelişim ölçümlerini kapsamaktadır. Vakalarda, izlem süresince anne ve bebek açısından PP kullanımına bağlı olarak belirlenmiş bir sorun saptanmamıştır. Doğum öncesi ve sonrası sürdürülen izlem ve bakımda anne ve yakınları için (uygun olan eş ve aile) net bir plan gereklidir. Antipsikotiklere maruz kalan fetuslarda konjenital malformasyon bildirilmemiş olmasına karşın ileriki dönemlerde bu çocuklarda nörogelişimsel ve nörodavranışsal sorunların ortaya çıkabileceği akılda tutulmalıdır.

Anahtar kelimeler: Şizofreni, gebelik, lohusalık, bebek, paliperidon palmitate.

INTRODUCTION

In patients with schizophrenia, chance of living out of treatment institution, marriage, and having child were increased by using antipsychotics. Percentage of use of contraceptive methods of these patients is lower compared to normal population, with higher risk of unplanned pregnancy[1]. It has been known that mental disorders are getting worse by period of pregnancy through neurochemical mechanisms and

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that patients are under more risk with respect to exacerbation of mental disorders[2,3]. Moreover, it is possible that patients cannot go their regular contraceptive controls due to positive, negative, and cognitive signs of disorder and thus this can bring along some risks for health of fetus and mother.

It is important for clinicians to decide treatment used in pregnancy period of cases with a serious mental disorder who intentionally or unintentionally become pregnant with respect to the impact of treatment used on fetus and mother. Consideration needs to be given to the risks of teratogenesis, obstetric complications, impairment of neonatal adaptation and adverse neurodevelopmental outcome. Studies identified found risks that included prematurity, low and high birth weight, neonatal withdrawal, abnormal muscle movements (motor restlessness, tremor, hypertonicity, dystonia and parkinsonism), atrium or ventricular septum defects, gestational diabetes, preeclampsia and caesarean delivery[4-7]. The two study found an association between in utero exposure to second generation antipsychotics and early delayed neuromotor performance[8,9]. Delayed cognitive, socioemotional and adaptive behavior scores on Bayley Scales of Infant and Toddler Development, third edition (BSID-III) was also found at 2 months of age, although reassuringly these differences were no longer significant by 12 months[8].

Paliperidone palmitate (PP) is a second generation antipsychotic that is intramuscularly administered once a month. There is limited data on PP use in pregnancy, which is the longest-acting atypical antipsychotic. It is a treatment option in schizophrenic patients whose treatment compliance is poor as presented in our cases. There is no clinical study of PP use during pregnancy, and only one case report was seen in the literature10.

In this report, we aim to present two cases with the diagnosis of schizophrenia who become pregnant when using PP, and had healthy deliveries. Planned assessment of infants included Apgar score, body weight, height, pediatric and psychiatric examination, and the cognitive, language and motor composite scores of the BSID-III. The Bayley Scales of Infant and Toddler Development (Bayley-III) is a standard series of measurements used primarily to assess the development of infants and toddlers, ages 1–42 months. This measure consists of a series of developmental play tasks and takes between 45–60 minutes to administer and derives a developmental quotient rather than an intelligence quotient. Raw scores of successfully completed items are converted to scale scores and to composite scores. Average of composite scores is 100 and standard deviation is 15. It is a metric scoring system that takes values between 40 and 160. These scores are used to determine the child's performance compared with norms taken from typically developing children of their age (in months). The most the Bayley-III has three main subtests; the Cognitive Scale, which includes items such as attention to familiar and unfamiliar objects, looking for a fallen object, and pretend play, the Language Scale, which taps understanding and expression of language, for example, recognition of objects and people, following directions, and naming objects and pictures, and the Motor Scale, which assesses gross and fine motor skills such as grasping, sitting, stacking blocks, and climbing stairs. The Bayley-III Cognitive and Language scales are good predictors of preschool mental test performance. These scores are largely used for screening, helping to identify the need for further observation and intervention, as infants who score very low are at risk for future developmental problems.

Assessments were applied by the same child psychiatrist at 2 months, 6 months, 12 months, 18 months and 24 months old infants. The other risks mentioned in literature were screened for mothers and babies (regular blood samplings, ultrasonographic measurements for systems of body).

CASE

Case 1, 25-year, married, homemaker, Body Mass Index-prepregnancy (BMI): 26.3. First symptoms of disease were introversion, resorting to violence against her mother, attempt to suicide with drug, grandiose speaking including "I am the God-Prophet!" at the age of 18. A few oral antipsychotics were started during clinical monitoring but it was changed with PP due to non-compliance with treatment.

In the medical history of family, there were a twin sibling and a grandmother with a diagnosis of schizophrenia. She met DSM IV criteria for schizophrenia in psychiatric examination. The case did not use cigarette, alcohol, and substance and did not have any other medical condition. She unintentionally became pregnant when under PP

treatment for 1 year and after last PP injection at 22 weeks of pregnancy, she discontinued drug without consultation of clinician. At the 29 week of pregnancy, the case was again hospitalized with an acute psychotic attack. During the last month, she was admitted to our clinic due to her refusal to leave her room, displaying poor hygiene, and showing aggression when frustrated. Seven sessions of electroconvulsive therapy with anesthesia was applied. At postconception period, hemogram, functions of liver, kidney, and thyroid, and electrolyte values were found in normal range. The case who made a normal vaginal delivery at 40 weeks had a healthy male baby (body height: 51 cm, kilogram: 3.200, Apgar score: 1. minute: 9; 5. minute: 10). At postpartum week 1, she was restarted to PP treatment with a dose of 150 mg/month after taking informed consent from spouse and patient. She continued to breastfeed her baby and succeeded to maintain care of the baby. Physical development of infant has been described in Table 1. Neurobehavioral development was assessed with BSID-III[11]. Subscales of cognitive, motor and language developments were in normal ranges at 2, 6, 12, 18 and 24 months of age (Table 2).

Table 1. Physical development of infants according to months of age.

	Months of age	Infant 1 em: percentile	Infant 2 em: percentile
Head circumference	0	35.5; 75	34; 37.5
	2	39.5; 50	38; 25
	6	45; 75	43; 50
	12	49; 90	46.5; 65
	18	50.5; 90	47.5; 58
	24	50; 75	-
Height, cm	0	51; 75	49; 40
	2	57; 10	56; 25
	6	65; 15	67; 63
	12	73; 15	75; 50
	18	82; 35	80; 38
	24	89; 60	-
Weight, kg	0	3.2; 35	2.9; 14
	2	5.1; 30	4.8; 25
	6	8.6; 70	7.9; 65
	12	10,8; 70	10.1; 70
	18	13; 82	11.5; 70
	24	14.9; 90	-

*Percentiles for physical development of boys and girls are taken from Neyzi[18] . The interval between 3 and 97 percentile is considered as normal.

Table 2. Neurobehavioral development of infants according to months of age

	Months of age	Infant 1	Infant 2
BSID-III, cognitive scale	2	95	100
composite scores	6	95	97
	12	90	95
	18	100	98
	24	106	-
BSID-III, language scale	2	100	103
composite scores	6	94	97
	12	90	94
	18	95	96
	24	102	-
BSID-III, motor scale	2	100	103
composite scores	6	97	103
	12	95	97
	18	91	102
	24	96	-

BSID-III: Bayley Scales of Infant and Toddler Development, 3rd Ed.; Composite scores of BSID-III are given in the Table 2.. Scoring system takes values between 40 and 160. Average of composite scores is 100 and standard deviation is 15 in normal population.

Case 2, 32-year, divorced, homemaker, BMI-prepregnancy: 25.9. At the age of 21, two weeks after her first delivery, fears, not having ability to care baby, not eating, not having a bath, and sleeplessness started. She was hospitalized in psychiatry service. She met DSM IV criteria for schizophrenia in psychiatric examination. Two years after, she was divorced, and parental custody of child was given to the father. She was treated in psychiatry service for additional three times with 2-year intervals. In the medical history of her family, there was no psychiatric disorder. She did not use alcohol and substance and did not have any other medical condition. Her prominent symptoms were delusions of infidelity and auditory halusinations, apathy and social isolation. Treatment was changed with 150 mg/month PP due to non-compliance to oral antipsychotics. She unintentionally conceived a child out of wedlock when taking PP treatment for 2 years. 150 mg/month PP treatment was continued during pregnancy after taking informed consent from the legal guardian of the patient. At the postconception period, hemogram, functions of liver, kidney, and thyroid, and electrolyte values were found in normal range. At 41 week, she made a normal vaginal delivery and had a female child (body height: 49 cm, kilogram: 2.980, Apgar score: 1. minute: 9; 5. minute: 10). The case did not breastfeed her baby, 4 months after delivery she gave the baby to ward of state. Physical development of infant has been described in Table 1. Neurobehavioral development was assessed with BSID-III. Subscales of cognitive, motor and language developments were in normal ranges at 2, 6, 12 and 18 months of age (Table 2). The written consents about of both patients were obtained.

DISCUSSION

Psychopharmacological treatment of pregnant women requires particular interest, and it should be carefully evaluated that untreated mental disorders can lead to harmful conditions for both mother and baby. If a woman was successfully treated with a drug before pregnancy, it is recommended that the same drug should be continued during pregnancy[2]. This approach was also applied in presented two cases and psychotic exacerbation was not observed during pregnancy and puerperal period. Most frequently used antipsychotics during pregnancy are olanzapine, risperidone, and quetiapine[12-15]. It was not observed that these drugs directly lead to malformation of fetal limbs and organs[6-8]. It was found that there is a relationship between antipsychotic use during pregnancy and gestational diabetes[5], increased respiratory distress for newborn, and withdrawal symptoms[4]. In another study, infants that exposed to clozapine during the fetal period had lower adaptive behavior score at 2 and 6 month[16]. Once more, infants exposed to atypical antipsychotics had lower cognitive, motor, social-emotional, and adaptive behavior scores than control at the age of 2 months. The difference between two groups was disappeared when they come to age of 12 months[8].

In the literature, there is one case report for each of long-acting injectable risperidone and PP use during pregnancy[10,17]. In our cases, there was no development of gestational diabetes, preeclampsia, and postural hypotension. In the prenatal monitoring, we could'nt obtain any kind of congenital malformation or anomaly in both fetuses. Babies are still age of 27 and 20 months and babies has been still monitored. No particular risks for the mother and their children can be attributed to the use of PP during pregnancy in our cases. A clear plan for a woman and her supports (partner and family as appropriate) for postpartum care is essential for ongoing monitoring and care. This should include monitoring of maternal mental health, infant health and wellbeing, and the developing relationship between mother and baby. Although it was not reported that fetus exposed to antipsychotics had congenital malformation; it should be kept in mind that in the future these children can develop neurodevelopmental and neurobehavioral problems. Additionally, there is a need for further prospective, longitudinal follow-up studies that evaluate developmental characteristics of children.

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