

CASE REPORT

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Pregnancy in Parkinson's Disease with Levodopa and Pramipexole Exposure

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ABSTRACT Parkinson's disease is a common neurodegenerative disease that rarely occurs in young people. Therefore, cases where pregnancy and Parkinson's disease occur together are very rare and pregnant patients receiving anti-Parkinsonian therapy are rarely presented as case reports in the literature. We report a case of a 36-year-old pregnant woman with a 5 year history of early onset Parkinson's disease who was exposed to levodopa/benserazide plus pramipexole treatment during the first 8 weeks, and levodopa/benserazide treatment until the 37th gestational week. The patient was followed up by the perinatology specialist at regular intervals throughout her pregnancy. No fetal anomaly was detected in the follow-ups. She gave birth to a healthy baby girl by an uncomplicated cesarean delivery. Evidence based data on the most appropriate treatment of Parkinson's disease in pregnancy have not been found in the literature. Larger studies are needed on this subject.

Keywords: Levodopa; pregnancy; anti-Parkinson agents; Parkinson's disease; pramipexole

Parkinson's disease is a neurodegenerative disease that usually occurs in old people. Approximately 5% of patients are below 40 years of age.¹ Therefore, the co-existence of pregnancy and Parkinson's disease is rare. It is a progressive condition that manifests with motor function defects.² Postural instability appears much later in the course of the disease.³ Today, Parkinson's disease is recognized not only as a motor system disorder, but also as a complex condition with various clinical features that include neuropsychiatric and other non-motor symptoms with motor complaints.⁴

Studies on the pharmacological treatment of early-onset Parkinson's patients during pregnancy are generally limited to case reports. While most of them include levodopa treatment, fewer cases have been reported in patients who used dopamine agonists, antimuscarinics, catechol-O-methyl-transferase (COMT) inhibitors and mono-amine oxidase-B (MAO) inhibitors during pregnancy.⁵⁻⁷ All these anti-Parkinsonian

drugs are considered Pregnancy Category C by the Food and Drug Administration.⁸

CASE REPORT

We report the case of a 36-year-old woman with a 5-year history of Parkinson's disease. She had a previous cesarean section. In 2016, she visited neurology outpatient clinic with bilateral hand tremor and numbness in both hands. In her examination, bradymimi, hypophony, cogwheel rigidity of the left arm and jaw tremor were detected. Palmomental reflex was also positive. No significant bradykinesia in the lower extremities and Kayser-Flischer ring on eye examination were detected. The serum ceruloplasmin level, the copper level in the urine and brain magnetic resonance imaging were normal. She had no history of tobacco, drug or alcohol use. She was diagnosed with Parkinson's disease and pramipexole 3 mg daily and rasagiline 1 mg daily were prescribed. In the 6th month of this treatment, when the patient's com-

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plaints increased, the dose of pramipexole was increased to 3.75 mg daily and rasagiline was continued at the same dose. After 1 year, when she stated that she wanted to get pregnant, the dose of pramipexole was reduced to 3 mg/day, rasagiline was stopped and levodopa/benserazide 100/25 mg was added to treatment 3 times a day by the neurologist. On the follow-up examination 10 days later, bradykinesia, resting tremor in the right hand, and cogwheel rigidity in the left arm were observed, the pramipexole dose was increased to 4.5 mg daily and continuation of levodopa at the same dose was recommended. While she was pregnant for 8+5, she realized her pregnancy and applied to hospital and the neurologist stopped all her medications. But after 2 weeks, resting tremor in bilateral hands and difficulty in walking started to increase, she restarted levodopa/benserazide at 100/25 mg three times a day. She continued to receive it until the 37th week of pregnancy.

The patient was followed up by the perinatology specialist. At the 12th gestational week, the first-trimester combined test was applied. In sonographic measurements; fetal crown-rump length (CRL) was 53 mm, nasal bone was present, nuchal translucency thickness was 0.94 mm, and intracranial transparency was 1.6 mm. Biochemical markers associated with aneuploidy were normal. Maternal age-related risk was above the cut-off value (1:163). Thereupon, amniocentesis was performed at 20+3 weeks of gestation and conventional karyotype and fish analysis were performed on the amniotic fluid. The cytogenetic results were negative. Detailed fetal anatomical ultrasound examination was also performed at 21 weeks of gestation and no fetal anomaly was found. In the evaluation of fetal echocardiography performed in the same session, the cardiac position and axis, 4-chamber view without and with color Doppler, 3-vessel and trachea view with color Doppler were evaluated normal. Routine ultrasound examinations were performed at the 30th and 34th gestational weeks, and no fetal growth restriction and no additional anomaly were detected. She visited our emergency department with abdominal pain when she was 36 weeks and 4 days pregnant. After uterine contractions were observed in non-stress test, she was given a delivery decision. The patient gave birth to a

healthy baby girl by an uncomplicated cesarean section. The baby's zero-minute Apgar score was evaluated as 8. General and neurological examination of the baby revealed no abnormalities and the routine blood tests were normal. Postpartum treatment for Parkinson's disease was arranged by the neurologist as levodopa/benserazide 100/25 mg three times a day and rasagiline 1 mg daily. It was recommended that the patient take their medication immediately after breastfeeding and not breastfeed for 2 hours after taking the medication. Currently, the patient is neurologically stable. Her baby girl is 16 months old and healthy. Informed consent was obtained from the patient for this case report and data collection was carried out with her consent.

DISCUSSION

In the case report series that compiled the effects of levodopa used for dopaminergic treatment in pregnant women on pregnancy outcomes, spontaneous abortion was reported in 6.12%, while congenital anomaly including patent foramen ovale and patent ductus arteriosus was found at a rate of 2.02%.⁵ In addition, it is difficult to determine the live birth and anomaly rates precisely because there are fewer studies reporting pregnancy outcomes related to the use of dopamine agonists, antimuscarinics, COMT inhibitors, and MAO inhibitors during pregnancy. Spontaneous abortion was observed in 4 cases with pramipexole treatment alone.⁸ While levodopa appears to be safe and the most efficient medication in pregnancy with early-onset Parkinson's disease, data are also inadequate on safety of COMT inhibitors and MAO inhibitors. In the literature, a single case report has been reported in which levodopa, benserazide, and selegiline were used together during pregnancy and no complications developed.⁹ Two studies in the literature indicate that pramipexole has been used in pregnancy in monotherapy without adverse effects on fetal development.^{10,11} Studies in animal models indicate that the use of levodopa alone or in combination with deipo-decarboxylase inhibitors (carbidopa or benserazide) creates teratogenic risks at higher doses. In seven cases where levodopa was used as monotherapy, there were no reports of a teratogenic effect.^{11,12} In the literature, no increase in teratogenic

risk was shown in seven cases where levodopa was used alone. In addition, two pregnancies using levodopa resulted in miscarriage, while fetal osteomalacia was reported in one pregnancy with levodopa and benserazide.^{13,14}

In the literature, cases that received levodopa/benserazide and pramipexole treatment for restless leg syndrome during pregnancy have been reported.⁵ The median dose of levodopa/benserazide was reported as 100/25 g daily and no fetal anomalies or poor obstetric outcomes were encountered. All patients using pramipexole were exposed during the first trimester. The median dose of pramipexole administered was reported as 0.08-1 mg daily. While 68% of pregnancies resulted in live birth, spontaneous abortion was observed in 15%.⁵

The efficacy and safety profile of pramipexole during pregnancy and lactation was reported in three women affected by Parkinson's disease or restless legs syndrome, respectively.¹⁵ Pramipexole was associated with spontaneous abortion in 3 cases (co-exposure with isotretinoin in one case), while levodopa was associated with ventral septal defect in twin neonates (co-exposure with selegiline and entacapone).¹⁵

A patient with Parkinson's disease using levodopa/benserazide in all trimesters and pramipexole treatment during the first 8 weeks of pregnancy was described. Since Parkinson's disease is rare at young ages, pregnant patients receiving anti-Parkinsonian therapy are rare in the literature. More studies are needed to establish evidence-based management and standardized guidelines for recommended medical treatment during pregnancy with Parkinson's disease.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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