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RESEARCH LETTER

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Lemborexant levels in maternal serum, cord blood, and breast milk during pregnancy and lactation: A case report

Poor sleep quality due to insomnia can be a risk factor for intrapartum and postpartum depression and mood disorders.[1] In addition, previous miscarriages often result in insomnia and anxiety disorders that affect the mental state of the next pregnancy.[2]

Lemborexant is an orexin receptor antagonist approved for the treatment of insomnia.[3] No safety studies have been conducted on pregnant or nursing women, and its safety in fetuses and infants is unknown. This study reports on the placental and breastfeeding transfer of lemborexant and the safety to the fetus and infant in a case in which lemborexant was used during pregnancy and lactation.

A 40-year-old woman weighing 63.8 kg became pregnant with her third child after her fifth pregnancy. She has no relevant family or psychiatric history. The patient had experienced the infant death of her previous child 5 years prior to this pregnancy and developed depression, anxiety, and insomnia. Three years later she became pregnant but miscarried, further exacerbating these symptoms.

Although multiple doses of benzodiazepines for depression and insomnia are not currently recommended, due to the intensity of the patient's symptoms she was given 0.25 mg of brotizolam and 0.5 mg of etizolam once a day before sleep before conception, and continued them until after delivery. At 12 weeks gestation, she was started on 10 mg of lemborexant once daily for her insomnia. After starting lemborexant, the patient did not add or increase the dose of psychotropic drugs, and her difficulty in falling asleep was resolved. No insomnia symptoms developed thereafter.

At 13 weeks, the patient underwent a cervical suture and cricothyrotomy for cervical incompetence, during which ampicillin-sulbactam was administered to prevent infection. At 17 weeks, she was started on progestin to prevent imminent preterm labor. She began taking 10 mg of esomeprazole for her reflux gastritis at 27 weeks gestation, which was continued until delivery.

At 37 weeks gestation, a 2889-g male infant was delivered by scheduled Cesarean section. The infant immediately cried after birth and his Apgar score (1/5 min) was 9/9. The infant was in good general condition and showed no abnormalities. No oxygen intervention was required. Elevated plasma bilirubin was noted, which resolved on phototherapy, and the infant was discharged on the eighth day of birth.

After obtaining ethics committee approval and written consent from the participant, lemborexant concentrations in maternal serum, cord blood, and breast milk were evaluated by liquid chromatography-tandem mass spectrometry.[4] The metabolites of lemborexant, M4, M9, and M10 show receptor binding rates similar to those of the main drug, but their blood levels are around 10% or lower, so they were not evaluated in this study.[5]

The results are shown in Table 1. Maternal serum concentrations of lemborexant were 37.8 ng/ml at 7.1 h after the last dose and ranged from 5.5 to 7.7 ng/ml at 10.9 h. In the present case, blood levels at 7 h after administration on postpartum day 6 were higher than in previous studies in healthy adults,[6] but no related adverse events (i.e., somnolence, headache, fatigue, nasopharyngitis)[7] were reported. Lemborexant is metabolized primarily by CYP3A,[6,8] and decreased clearance has been reported in patients with hepatic and renal dysfunction.[9] Although no strong inhibitors of CYP3A were used in the concomitant medications, and both hepatic and renal function were normal, the possibility of an effect on lemborexant blood levels due to concomitant use of drugs metabolized in the liver (etizolam, brotizolam, esomeprazole) cannot be ruled out.

The concentration of lemborexant in cord blood collected immediately after delivery (12.5 h after the last dose) was 1.1 ng/ml. Breast milk was collected over time starting on the second postpartum day. The concentration of lemborexant in breast milk from 8 to 19.6 h after administration ranged from 1.8 to 12.7 ng/ml. The daily infant dose via breast milk, calculated from the maximum concentration of lemborexant in breast milk in this study (12.7 ng/ml) and the average breast milk intake (150 ml/kg/day), was 1.91 μg/kg/day, which was lower than the dose per body weight in adults (0.04–0.16 mg/kg/day). The relative infant dose in this case was 1.21%. In this study, the transition of the concentration in breast milk after administration of lemborexant was not examined in detail, and the highest breast milk concentration was not evaluated.

Maternal administration of lemborexant from the second trimester of pregnancy may be safe and compatible with breastfeeding during the lactation period. Further studies are needed to evaluate to the safety of lemborexant during pregnancy and lactation.

TABLE 1 Lemborexant (LEM) concentrations in serum and breast milk samples after administration of oral LEM 10 mg

	Maternal serum		Umbilical cord blood		Breast milk	
Postpartum day	Time after LEM dose (h)	LEM concentration (ng/ml)	Time after LEM dose (h)	LEM concentration (ng/ml)	Time after LEM dose (h)	LEM concentration (ng/ml)
−5	10.9	7.7				
0			12.5	1.1		
1	10.9	5.5				
2					11.8	2.5
					14.2	2.2
					19.6	1.8
3					8.0	12.7
					12.0	4.9
6	7.1	37.8				

AUTHOR CONTRIBUTIONS

Jumpei Saito, Mariko Ishii, Noriko Sandaiji, and Koshi Yamaguchi carried out the data analysis and obtained informed consent. Mariko Ishii and Atsuko Murashima helped draft the manuscript. Naho Yakuwa, Tomo Suzuki, Haruhiko Sago, Yoshiyuki Tachibana, Akimasa Yamatani, and Atsuko Murashima contributed to designing the study, performed the literature review, and analyzed and interpreted the data. Jumpei Saito drafted the manuscript and made suggestions for revisions. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS APPROVAL STATEMENT

This study was approved by the ethics committee of the National Center for Child Health and Development. The participant provided written informed consent.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from the patient for publication of this case report.

CLINICAL TRIAL REGISTRATION

Not applicable.

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