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Outcomes following exposure to lacosamide monotherapy during pregnancy and breastfeeding — a prospective case series

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ABSTRACT

Aim of the study. To evaluate the safety of lacosamide (LCM) monotherapy during pregnancy and breastfeeding.

Material and methods. Patients taking LCM monotherapy treated at the university epilepsy clinic were prospectively followed up during pregnancy, delivery, and breastfeeding. Data on seizure frequency, LCM dosage, pregnancy course, delivery and breastfeeding, birth outcome, congenital malformation, and development of newborns was collected.

Results. Four pregnancies in three patients with refractory focal epilepsy treated with LCM monotherapy were reported. One of these pregnancies ended in a miscarriage during the seventh week of gestation. The average daily LCM dose at the time of conception was 300 mg. Treatment with LCM was continued throughout pregnancy and breastfeeding. The dose of LCM was increased in two pregnancies: in one case following a seizure relapse, and in the other case as a preventive measure to avoid an increase in seizure frequency. Seizure frequency remained stable during pregnancy in two cases. All deliveries were carried out via caesarean section, with an average gestational age at birth of 37.6 weeks. The Apgar score was 10 in all newborns, and no congenital malformations were detected. At the age of 12 months, normal developmental milestones were reached. Infants were breastfed without any complications.

Conclusions and clinical implications. This case series adds to a growing body of evidence suggesting the relative safety of LCM monotherapy throughout pregnancy and breastfeeding.

Keywords: lacosamide, pregnancy, breastfeeding, malformations

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Introduction

Epilepsy is a chronic neurological disorder that affects around 15 million women and girls of reproductive age globally [1]. Many of these women require treatment with antiseizure medications (ASMs) not only before conception but also during pregnancy and breastfeeding [2, 3].

A growing body of evidence from observational studies and pregnancy registers has heightened awareness regarding the potential teratogenic effects of ASMs. Among these medications, valproate is associated with the highest reported risk of major congenital malformations when the foetus is exposed to it *in utero*. On the other hand, monotherapies involving lamotrigine, levetiracetam (LEV), and oxcarbazepine (OXC) appear to have a relatively safer profile [1, 4]. While third-generation ASMs are gaining popularity, the pregnancy-related data remains limited for most of them.

Lacosamide (LCM) is a newer ASM that has gained widespread use, having been approved for managing both focal and generalised epilepsy. Despite its popularity, there is a lack of substantial data regarding its safety during pregnancy and breastfeeding. As per the product's characteristics, LCM is not advised for use during pregnancy and breastfeeding.

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The aim of this case series was to assess the safety and effectiveness of LCM monotherapy throughout pregnancy and breastfeeding.

Material and methods

This study involved a prospective observation of three patients who received LCM monotherapy for the duration of their pregnancies at the epilepsy clinic of the Jagiellonian University of Krakow, Poland. The patients and their offspring were monitored for a minimum of 12 months after delivery.

Demographic and clinical information including age, age at epilepsy onset, seizure type and frequency, current and past epilepsy treatments, details of pregnancy, delivery, and breastfeeding, birth outcomes, newborn development, any congenital malformations, and information about previous pregnancies were all recorded.

The study protocol was approved by the local bioethics committee. Written consent was obtained from all patients to present anonymised data about pregnancy outcomes alongside clinical information.

Results

Four pregnancies in three patients with refractory focal epilepsy were prospectively followed up at the university epilepsy clinic. Clinical characteristics, pregnancy and foetal outcome are set out in Table 1.

Patient 1

Patient 1 is a 36-year-old woman with a history of febrile seizures and epilepsy since the age of four. Her seizure manifestations included focal seizures with altered awareness and bilateral tonic-clonic seizures, occurring 3–4 times per month.

Table 1. Clinical characteristics, pregnancy and foetal outcome. Pregnancies on lacosamide monotherapy are presented in italics

	Patient 1		Patient 2			Patient 3	
	Pregnancy 1	Pregnancy 2	Pregnancy 1	Pregnancy 2	Pregnancy 3	Pregnancy 1	Pregnancy 2
Age at pregnancy [years]	36	37	31	34	36	30	35
Seizure frequency in 12 months before pregnancy	2–3/month	2–3/month FIA, BTC	0	0	Seizure-free	3–4 FIA/ month	1–2 FIA/ /month
Seizure frequency in pregnancy	2/month FA	2–3/month FIA, BTC	0	0	1 FIA, 10 FA	3–4 FIA/ /month	1–2 FIA/ /month
ASM during pregnancy	LCM	LCM	LEV 500 mg bid	LEV 1,000 mg bid	LCM	OXC 300 mg bid	LCM
LCM dose at conception [mg]	400	400			200		200
LCM dose at delivery [mg]	–	600			400		200
LCM dose at breastfeeding [mg]	–	400			300		200
Gestational age at delivery, weeks	Spontaneous abortion in week 7	36	Induced abortion due to malformations	38	39	37	38
Newborn sex	UNK	M	Probably M	F	F	F	F
Mode of delivery	–	cc	–	cc	cc	cc	cc
Birth weight [g] (percentiles)	–	3,410 (90)	–	3,250 (50)	3,810 (90)	3,400 (90)	4,050 (97)
Birth length [cm] (percentiles)	–	51 (90)	–	49 (50)	51 (50)	52 (90)	53 (97)
Head circumference [cm] (percentiles)	–	35 (90)	–	UNK	34 (50)	UNK	36 (97)
Apgar score	–	10	–	10	10	10	10
Malformations	–	No	–	No	No	No	No
Breastfeeding	–	Yes (12 months)	–	Yes	Yes (6 months)	Yes	Yes (7 months)
Child's development at last follow-up/age	–	Normal/ /12 months	–	No	Normal/ /12 months		Normal/ /4 years

ASM — antiseizure medication; bid — twice daily; BTC — bilateral tonic-clonic; cc — caesarean section; F — female; FA — focal aware; FIA — focal with impairment of awareness; LCM — lacosamide; LEV — levetiracetam, M — male; UNK — unknown

Her prior treatments had encompassed carbamazepine, lamotrigine, gabapentin, topiramate, and OXC. With a prescription of LCM at 200 mg twice daily (bid), there was a slight enhancement in seizure management, leading to a reduction in frequency to 2-3 seizures per month. In preparation for pregnancy, she began taking folic acid at a dose of 0.4 mg. Her first pregnancy had ended with miscarriage in the seventh week of gestation. An array comparative genomic hybridization (aCGH) excluded chromosomal aberrations of the miscarried embryo.

One year later, she became pregnant while on LCM 200 mg bid. Dydrogesterone was added by obstetricians for the support of early pregnancy. During this second pregnancy, the dose of LCM was gradually increased up to 300 mg bid, with stable seizure frequency. The dose of LCM was increased by 50 mg every two weeks from the second trimester of pregnancy. Due to premature rupture of membranes, she underwent a caesarean section, delivering a male infant at 36 weeks. The LCM dose was reduced by 50 mg every week after delivery to 200 mg bid. She breastfed up to 12 months, and no medical problems or developmental delays were detected when the child was aged 12 months.

Patient 2

Patient 2 is a 36-year-old woman with a history of epilepsy since the age of eight due to subependymal heterotopia. Her past treatments included valproate and levetiracetam (LEV). At 31 years old, while on LEV at 500 mg bid, she became pregnant. An ultrasound in the first trimester revealed bilateral cleft lip and palate, leading to a decision to terminate the pregnancy through induced abortion. At 34 years old, she had a successful caesarean section delivery of a healthy baby after experiencing a seizure-free second pregnancy while on LEV at 1,000 mg bid. Subsequently, due to seizure recurrence, her medication was switched to LCM at 100 mg bid, resulting in freedom from seizures. She planned pregnancy and was placed on folic acid 0.4 mg daily. The patient experienced several focal seizures during the third pregnancy (mostly in the last trimester) and the LCM dose was gradually increased by 50 mg every two weeks from the second trimester of pregnancy to 200 mg bid. She delivered a healthy baby girl at term and breastfed up to six months. The dose of LCM was decreased after the delivery by 50 mg every week to 150 mg bid. Normal developmental milestones were reached at 12 months postnatally, and no health problems were detected.

Since many cases of periventricular nodular heterotopia are associated with a mutation in the filamin A (FLNA) gene, the patient has been referred for genetic testing. The test results are not available yet. The X-linked FLNA mutation may carry a higher risk of malformation in future pregnancies with male foetuses.

Patient 3

Patient 3 is a 36-year-old woman with a history of meningoencephalitis at age 9 months complicated by right spastic hemiparesis and refractory epilepsy since the age of four. She experienced 2–4 focal seizures per month with impaired awareness, and occasional tonic-clonic seizures. She had undergone trials with numerous ASMs including carbamazepine, gabapentin, valproate, lamotrigine, LEV, topiramate, and OXC, but with limited success.

During her first pregnancy at age 30, she was on a regimen of OXC at 300 mg bid and delivered a healthy daughter via caesarean section. Subsequently, she attempted LCM at 200 mg bid, which resulted in an improvement in seizure management (1–2 focal seizures per month). Before her second pregnancy, OXC was discontinued and folic acid at 0.4 mg was added. The LCM treatment was sustained throughout the second pregnancy, with no deterioration in seizure control. For her second pregnancy, she delivered a healthy daughter at full term via caesarean section. The infant was breastfed for seven months postnatally. No medical issues or developmental delays were identified when the child reached the age of four years.

Discussion

Lacosamide is one of the most common newer ASMs used as add-on treatment and more recently as monotherapy. Despite its popularity, scant evidence exists regarding its safety while pregnant and breastfeeding. Initial insights are derived from isolated case reports and series, with a few concentrating on the alterations in LCM's pharmacokinetics during pregnancy. However, these reports offer only limited information concerning the progression of pregnancy and the subsequent neonatal outcome [5–8].

The UCB global safety database documented 16 instances of pregnancies involving LCM monotherapy. Among these, 14 pregnancies (87.5%) resulted in live births, and a single case of malformation (with unspecified details) was recorded [9]. Because the data has been published as a conference report, the information on maternal and neonatal outcome is limited. In the latest report from EURAP, 45 pregnancies involving LCM monotherapy were included. Unfortunately, this report did not offer additional insights into the obstetric and foetal outcomes [4]. No occurrences of malformations were detected in the offspring born to 64 mothers who were treated with LCM during pregnancy, as reported by the North American AED Pregnancy Registry [10]. Nevertheless, the aforementioned reports did not provide data regarding LCM doses or dose changes.

Lattanzi et al. [11] presented two cases where maternal exposure to LCM monotherapy occurred, and no instances of congenital malformation were observed. Additionally, the infants displayed normal psychomotor development, and breastfeeding proceeded without any complications.

In the most recent study, data concerning the usage of newer ASMs in pregnancy was retrieved from the German Embryotox Centre of Clinical Teratology and Drug Safety. Within this study, six cases of pregnancies where LCM monotherapy was administered were prospectively monitored. Notably, no significant birth defects were identified in the infants. It is important to note however, that the available

information was obtained from paediatric examinations conducted at around 4–5 weeks of age. Unfortunately, there is an absence of data regarding the subsequent developmental stages and breastfeeding in these cases [12].

Similar to other studies, infants born to our patients treated with LCM monotherapy during pregnancy had no major malformations. Furthermore, normal developmental mile-stones were reached at 12 months postnatally and no health problems were detected. All infants were breastfed, and none of them developed side effects from exposure to LCM via maternal milk. It can be assumed than the early miscarriage in Patient 1 was related to the inadequate secretion of progesterone. All babies were delivered via caesarean section. The premature rupture of membranes and seizures in pregnancy in Patient 1, and the spastic hemiparesis and seizures in pregnancy in Patient 3, could have been the cause of the caesarean section. However, in Poland, half of all pregnancies end with a caesarean section. There were no reported issues with neonatal adaptation or bradycardias.

The major strengths of this study include the long lasting exposure to LCM monotherapy prior to pregnancy, at conception, and during pregnancy and breastfeeding, the prospective evaluation of seizure frequency both before and during pregnancy, and a comprehensive postpartum follow-up extending over a prolonged duration.

One limitation was the small sample size. Furthermore, the serum concentration of LCM was not measured during pregnancies. Measurement of LCM level is not available at our laboratory.

Conclusions

This case series adds to a growing body of evidence suggesting the relative safety of LCM monotherapy throughout pregnancy and breastfeeding.

Clinical implications/future directions

Lacosamide could be safe during pregnancy and breastfeeding. Further studies are needed to confirm the safety profile of LCM, and assess its long-term effects on the psychomotor development of offspring.

Article information

Data availability statement: *All data is provided in the manuscript.*

Ethics statement: *Study protocol was approved by the local bioethics committee. Written consent was obtained from all patients to present anonymised data about pregnancy outcomes alongside clinical information.*

Authors' contributions: *MB: Conception and design of study, analysis and interpretation of data, drafting article, critical revision of article, final approval of version to be published; RD and KM: acquisition of data for work, final approval of version to be published; AS: revising article critically for important intellectual content, final approval of version to be published.*

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