

## RESEARCH ARTICLE

# Obstetric and Neonatal Outcomes in Epilepsy-Complicated Pregnancies: The Impact of Levetiracetam Monotherapy

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### Abstract

**Introduction:** To evaluate the impact of levetiracetam monotherapy on obstetric and neonatal outcomes in pregnant women with epilepsy.

**Methods:** The present retrospective cohort study included pregnant women with epilepsy followed at our center from the first trimester onward. Patients with seizures during pregnancy, polytherapy use, and multiple gestations were excluded. Patients were divided into a non-medicated group and a levetiracetam monotherapy group. Demographic, obstetric, delivery, and neonatal outcomes were compared.

**Results:** A total of 74 patients were included in the study; 22 (29.7%) were assigned to the non-medicated group, and 52 (70.3%) were included in the levetiracetam group. No statistically significant differences were observed between the groups in maternal age, obstetric history, duration of epilepsy, gestational age at delivery, and APGAR scores. Neonatal birth weight was significantly lower ( $p = 0.042$ ) and neonatal intensive care unit (NICU) admission rates were significantly higher in the levetiracetam group ( $p = 0.047$ ).

**Conclusion:** Levetiracetam monotherapy was associated with lower neonatal birth weight and higher NICU admission rates, without significant differences in other major perinatal outcomes. These findings suggest that levetiracetam may represent a relatively safe treatment option during pregnancy with appropriate patient selection and close monitoring; however, larger prospective studies are needed.

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## Introduction

Epilepsy represents a common neurological disorder in reproductive-aged women and complicates approximately 0.3–0.5% of pregnancies.<sup>1</sup> Due to both the disease itself and the potential maternal and fetal effects of antiepileptic drug use, epilepsy is considered a high-risk condition during pregnancy. Therefore, the management of epilepsy throughout pregnancy requires a careful balance between seizure control and fetal safety.<sup>1,2</sup>

During pregnancy, epileptic seizures are associated not only with seizure-related maternal trauma and an increased risk of hypoxia, but also with adverse perinatal outcomes in the fetal compartment, including placental abruption, fetal hypoxia, spontaneous abortion, and preterm labor.<sup>1–4</sup> In addition, the use of antiepileptic drugs during pregnancy, particularly in the early gestational period, has been associated with an increased risk of major congenital anomalies and adverse neonatal outcomes.<sup>5–7</sup> These reported risks are known to vary depending on the type and dosage of the antiepileptic drug used, as well as whether monotherapy or polytherapy is administered.<sup>7–9</sup>

Recently, clinical practice has shifted from older antiepileptic drugs toward newer options, particularly levetiracetam and lamotrigine, which are considered to have more favorable safety profiles.<sup>6,7,9</sup> Levetiracetam, one of the most commonly used antiepileptic drugs, has been shown to be better tolerated by patients and to have a relatively low risk profile with respect to major congenital malformations.<sup>10,11</sup> However, data regarding prenatal exposure to levetiracetam remain limited.<sup>12–15</sup> In the present study, we aimed to evaluate the impact of levetiracetam use on perinatal outcomes in pregnancies complicated by epilepsy, beyond the risks associated with the disease itself.

## Material and Methods

This single-center study employed a retrospective cohort design. The study population comprised pregnant women with a diagnosis of epilepsy who were followed at the Perinatology Clinic of Ankara Bilkent City Hospital between March 2025 and December 2025 and who delivered at the same center. The patient data were retrospectively collected using the hospital's electronic medical record system and archived files. The study protocol was reviewed and approved by the relevant institutional ethics committee prior to the initiation of the study (approval number: 2-26-1983). All study procedures were performed

in compliance with the ethical standards outlined in the Declaration of Helsinki.

Singleton pregnancies in women aged 18–45 years whose antenatal follow-up and delivery were both conducted at our center and who were evaluated by the neurology clinic during pregnancy were included in the study. A confirmed diagnosis of epilepsy established by a neurologist prior to pregnancy, along with the availability of relevant medical records, was required for inclusion. Only patients who had been receiving levetiracetam from the preconceptional period onward and whose pregnancy follow-up was entirely carried out at our center were included in the analysis. Patients' antiepileptic therapies were managed and adjusted by neurologists. The principal criteria required for discontinuation of antiepileptic drug (AED) therapy were a seizure-free period of at least two years, absence of epileptiform activity on electroencephalography (EEG), and no evidence of structural cerebral lesions. In patients who did not meet these criteria, antiepileptic treatment was continued during pregnancy.

Patients who received polytherapy or had multiple gestations were excluded to avoid potential confounding effects on fetal outcomes. In addition, patients with a history of epileptic seizures during pregnancy were not included in the analysis to avoid potential confounding effects of seizures on fetal outcomes. The administered doses of levetiracetam ranged from 500 to 1500 mg and were within the optimal therapeutic range in all patients.

Patients were divided into two groups based on antiepileptic drug use during pregnancy: those who did not use antiepileptic medication (non-medicated group) and those who used antiepileptic medication (levetiracetam group). Demographic characteristics, obstetric history (gravidity, parity, number of abortions, and number of living children), duration of epilepsy, and pregnancy and delivery-related data (gestational age at delivery, birth weight, mode of delivery, and APGAR scores) were recorded for both groups. Neonatal outcomes included admission to the neonatal intensive care unit (NICU), preterm birth, low birth weight (defined as a birth weight <2500 g), and a first- or fifth-minute APGAR score <7.

Data analysis was performed using IBM SPSS Statistics software, version 29.0 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was applied to examine the distribution of continuous variables. Continuous variables that did not follow a nor-

mal distribution were presented as the median and interquartile range (IQR), and comparisons between groups were performed using the Mann–Whitney U test. Categorical variables were expressed as numbers and percentages, and comparisons between groups were conducted using the chi-square test or Fisher’s exact test when the expected cell count was less than five. A  $p$ -value  $<0.05$  was considered statistically significant in all analyses.

## Results

During the study period, a total of 132 deliveries occurred among pregnant women with a diagnosis of epilepsy at our center. Of these, 52 were excluded due to the occurrence of at least one epileptic seizure during pregnancy, and six were excluded because of polytherapy use. Consequently, a total of 74 patients were included in the analysis. Among these, 22 patients (29.7%) were assigned to the non-medicated group, while 52 patients (70.3%) were included in the levetiracetam group.

When the non-medicated and levetiracetam groups were compared, no statistically significant differences were observed in terms of maternal age, gravidity, parity, history of abortions, number of living children, duration of epilepsy, gestational age at delivery, or first- and fifth-minute APGAR scores. However, birth weight was significantly lower in the levetiracetam group (median: 2910 grams) compared with the non-medicated group (median: 3312.5 grams) ( $p = 0.042$ ) (Table 1).

Table 1. Clinical and obstetric characteristics of epileptic patients according to antiepileptic drug use

Variable	Non-medicated group (n = 22) Median (IQR)	Levetiracetam group (n = 52) Median (IQR)	p value
Age (years)	27 (8)	29 (8)	0.061
Gravidity	1.5 (2)	2 (2)	0.980
Parity	0 (1)	0 (1)	0.422
History of abortion	0 (1)	0 (1)	0.538
Number of living children	0 (1)	0 (1)	0.501
Duration of epilepsy (years)	10 (6)	14.5 (11.75)	0.148
Gestational age at birth (weeks)	39 (2)	38 (3)	0.293
Birth weight (g)	3312.5 (750)	2910 (505)	<b>0.042</b>
APGAR score at 1 minute	7 (0)	7 (1)	0.131
APGAR score at 5 minutes	9 (1)	9 (1)	0.604

Data are presented as median (interquartile range).

Comparisons between groups were performed using the Mann–Whitney U test.

A  $p$  value  $<0.05$  was considered statistically significant.

When obstetric and neonatal outcomes were evaluated, no significant difference was observed between the groups with respect to mode of delivery ( $p = 0.202$ ). There were also no statistically significant differences between the groups in terms of preterm birth, low birth weight, or a first-minute APGAR score below 7 (all  $p > 0.05$ ). All neonates had fifth-minute APGAR scores of 7 or higher. However, the rate of admission to the neonatal intensive care unit (NICU) was significantly higher in the levetiracetam group compared with the non-medicated group (30.7% vs. 9.1%;  $p = 0.047$ ). These obstetric and neonatal outcomes are summarized in Table 2.

Table 2. Comparison of obstetric and neonatal outcomes between non-medicated and levetiracetam groups

Variable	Non-medicated group (n = 22) n (%)	Levetiracetam group (n=52) n (%)	p value
Mode of delivery			0.202
Vaginal delivery	12 (54.5)	20 (38.5)	
Cesarean section	10 (45.5)	32 (61.5)	
NICU admission	2 (9.1)	16 (30.7)	<b>0.047</b>
Preterm birth	4 (18.2)	14 (26.9)	0.423
Low birth weight	1 (4.5)	6 (11.5)	0.666 <sup>a</sup>
APGAR score at 1 minute $< 7$	4 (18.2)	7 (13.5)	0.602

NICU: neonatal intensive care unit.

Comparisons between groups were performed using the Pearson chi-square test.

<sup>a</sup> Fisher’s exact test was used when the expected cell count was  $<5$ .

A  $p$  value  $<0.05$  was considered statistically significant.

## Discussion

The current study evaluated the effects of levetiracetam use in pregnant women with epilepsy on obstetric and neonatal outcomes. The findings demonstrated that neonatal birth weight was significantly lower and NICU admission rates were higher among pregnant women using levetiracetam. In contrast, no statistically significant differences were observed between the groups in terms of gestational age at delivery, mode of delivery, first- and fifth-minute APGAR scores, low birth weight, or preterm birth rates.

Although many pregnancies complicated by epilepsy result in favorable outcomes without major complications, these pregnancies are considered high-risk pregnancies due to an increased likelihood of obstetric and fetal complications. The occurrence of

convulsions during pregnancy not only increases the risk of maternal trauma but may also adversely affect the fetus through hypoxemia and asphyxia. In addition, higher rates of cesarean delivery and an increased risk of hypertensive disorders during pregnancy have been reported among women with epilepsy.<sup>1,3,16</sup> Furthermore, these pregnancies have been shown to be associated with spontaneous abortion, stillbirth, preterm birth, small-for-gestational-age neonates, low fifth-minute APGAR scores, and neonatal respiratory distress syndrome.<sup>3,5,17</sup>

Several studies have reported higher rates of spontaneous or iatrogenic preterm birth among pregnancies complicated by epilepsy.<sup>18</sup> In women with epilepsy, the risk of preterm birth has been shown to be associated with antiepileptic drug exposure and, in particular, with uncontrolled seizure activity.<sup>3,5,17,19</sup> In the present study, however, no significant difference in preterm birth rates was observed between women who were exposed to antiepileptic medication throughout pregnancy and those who were not. This finding may be explained by the inclusion of a highly selected population consisting only of patients who remained seizure-free during pregnancy and received monotherapy.

Levetiracetam is a widely used antiepileptic drug that is well tolerated during pregnancy and is primarily eliminated via the renal route.<sup>20</sup> Owing to its low teratogenic potential, its ability to provide effective seizure control throughout pregnancy, and the lack of evidence indicating significant adverse effects on long-term cognitive performance in children, levetiracetam has been increasingly preferred in pregnancies complicated by epilepsy.<sup>10,21,22</sup> It is well established that antiepileptic drugs cross the placenta and may pose potential risks to fetal development.<sup>23</sup> Compared with healthy pregnancies, women with epilepsy have been reported to have an approximately threefold increased risk of congenital malformations, largely attributable to antiepileptic drug exposure.<sup>21</sup> However, this increased risk has been shown to be mainly associated with exposure to carbamazepine, phenobarbital, phenytoin, and valproate.<sup>19,21</sup> In contrast, the lowest risk of major congenital malformations has been reported in pregnancies exposed to lamotrigine and levetiracetam.<sup>21</sup> In a study evaluating levetiracetam monotherapy, the rate of congenital malformations was higher than that in the control group, although the difference did not reach statistical significance, and the observed anomalies were pre-

dominantly isolated cardiac defects.<sup>24</sup> In the present study, no congenital malformations were observed; however, this finding may be attributable to the relatively small sample size and the limited ability of the study to detect rare outcomes.

Previous studies have demonstrated that exposure to antiepileptic drugs is associated with an increased risk of low birth weight, admission to the NICU, and a fifth-minute APGAR score below 7.<sup>3,19,25</sup> In particular, adverse outcomes related to low birth weight have been reported in pregnancies complicated by epilepsy with levetiracetam exposure.<sup>24,26</sup> Consistent with these findings, this study demonstrated that neonates exposed to levetiracetam had lower birth weights and higher rates of NICU admission. Although the neonatal birth weight in the levetiracetam group was lower than that of the non-medicated group, the median value remained above 2500 g, which is the accepted threshold for low birth weight. Furthermore, no statistically significant difference was observed between the two groups in terms of the proportion of neonates with low birth weight. These findings may suggest that levetiracetam has a relatively favorable safety profile regarding neonatal birth weight. However, definitive conclusions cannot be drawn based on the present study alone, and further studies are required to substantiate these results. No statistically significant differences were observed between the groups with respect to common indications for NICU admission, including preterm delivery, low birth weight, low first- or fifth-minute APGAR scores, and the overall rate of preterm birth. Although congenital anomalies were not defined as exclusion criteria, no major structural or chromosomal congenital anomalies were detected in either group. A substantial proportion of neonates in the medication-treated group were admitted to the NICU primarily for clinical observation and precautionary monitoring. The higher NICU admission rate in the medication-treated group may therefore reflect a more cautious neonatal management approach and a lower threshold for observation in pregnancies exposed to antiepileptic drugs, rather than an increase in overt perinatal morbidity. In the present study, no significant associations were found between antiepileptic drug use and maternal age, parity, duration of epilepsy, or gestational age at delivery. This finding suggests that baseline maternal and gestational characteristics were comparable between the groups and are unlikely to account for the observed neonatal differences.

One of the main strengths of this study is the evaluation of a homogeneous patient population consisting exclusively of women who received levetiracetam monotherapy and remained seizure-free throughout pregnancy. This approach allowed for a clearer assessment of the effects of levetiracetam exposure on perinatal outcomes by minimizing the potential confounding effects of seizure activity and polytherapy. In addition, the fact that all antenatal follow-up and deliveries were conducted at a single center ensured data integrity and standardized obstetric assessments. The findings should be interpreted in light of several constraints, most notably the retrospective design, which limits causal interpretation. The limited sample size may have made it difficult to evaluate outcomes such as rare congenital anomalies. In addition, classification according to epilepsy types could not be performed. Furthermore, the association between maternal serum levetiracetam levels and perinatal outcomes could not be evaluated due to the limited sample size. Therefore, the findings of this study should be supported by larger, prospective studies.

### Conclusion

The present study demonstrated that neonatal birth weight was lower and the rate of NICU admission was higher in pregnant women with epilepsy who used levetiracetam monotherapy. No congenital malformations were observed in either group, and no significant differences were found between the groups with respect to preterm birth, low birth weight, or APGAR scores. Levetiracetam is widely used during pregnancy and is generally considered safe; however, further investigation may be warranted regarding the decrease in neonatal birth weight and the increased rates of NICU admission observed in the present study, as well as in some previous reports. Confirmation of these findings will require well-designed prospective studies with larger sample sizes.

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### Conflict of Interest Statement

The authors have no conflict of interest.

### Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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