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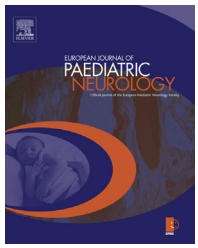

Original article

# Pregnancy and neurodevelopmental outcomes with in-utero antiepileptic agent exposure. A pilot study

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ABSTRACT

*Objective:* To assess pregnancy outcomes on women exposed to monotherapy with antiepileptic agents.

*Methods:* Questionnaires were sent to women with epilepsy in our practice who were pregnant between 2006 and 2011. 62/86 patients (72%) who responded were on monotherapy. 24 fetuses (63%) were exposed to lamotrigine, 11 (28%) to levetiracetam, 2 (5.2%) to topiramate, 1 (2.6%) to gabapentin, 17 (27%) to carbamazepine, 5 to phenytoin and 2 to valproate.

*Results:* There were 55 (88%) live births and 7 unsuccessful pregnancies (miscarriages/stillbirths). Unsuccessful pregnancies were reported in 2/24 gestations exposed to lamotrigine, 2/11 to levetiracetam and 3/17 to carbamazepine. Delayed motor development or speech delay requiring therapy and special programming was noted in 2/24 children prenatally exposed to lamotrigine, 3/17 exposed to carbamazepine and 1/2 children exposed to valproate.

*Conclusion:* Our pilot study of children exposed to antiepileptic drug monotherapy in-utero demonstrated a favorable trend for successful pregnancy outcomes and developmental trajectory.



## 1. Introduction

There are multiple reports available correlating the use of traditional antiepileptic drugs during gestation with a higher incidence of unsuccessful pregnancies and their effect of prenatal exposure on the neurodevelopmental outcome of the child.[1–5] The individual impact of each drug on cognitive outcome is different, with recent reports showing that intelligence quotient is affected in children exposed to valproate compared to other antiepileptic drugs.[6] Data on the relative

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safety of newer antiepileptic medication in pregnancy are limited due to the relatively short time of commercial availability of the agents and the need for longer clinical and functional follow up required for children exposed to them.[7]

Our objectives of this pilot study were to assess the pregnancy outcomes and the effect on the development of children of women exposed to antiepileptic drug monotherapy during their gestation.

## 2. Material and methods

Questionnaires were sent to women with epilepsy in our practice who were pregnant between 2006 and 2011. Participants signed institutional review board approved informed consents and returned the information in pre-stamped return packets. Eligibility to participate in the survey required antiepileptic medication use for epilepsy at any point during the pregnancy. We investigated expectant mothers on monotherapy.

The questionnaire is comprised of twenty five questions including the timing of the onset of the obstetric care, the number of antiepileptic drugs used during the gestation, folate use, pregnancy complications, number of seizures during pregnancy, occurrence of status epilepticus during pregnancy, gestational age at delivery, type of delivery, complications at delivery, neonatal APGAR scores, and neonatal intensive care unit admission.

Abnormal developmental outcomes were defined as speech and/or delay requiring special services, including speech, occupational and/or physical therapy. The developmental outcomes were assessed at 2 years of age by developmental specialists assigned by the school districts. Unsuccessful pregnancies were defined as spontaneous miscarriages and stillbirth. Women who were lost to follow up were excluded from the survey.

## 3. Results

There were 91 questionnaires sent. 62 of the 86 patients who responded were on monotherapy. All 62 pregnancies reported were singleton. 38 fetuses (69%) were exposed to medication approved after 1990 and 24 fetuses (31%) to older antiepileptic drugs. 24 fetuses were exposed to lamotrigine, 11 to levetiracetam, 2 to topiramate and 1 to gabapentin. Also 17 fetuses were exposed to carbamazepine, 5 to phenytoin and 2 to valproate. There were no major malformations noted. The average age of the expectant mothers were 22 years for valproate, 28 for levetiracetam, 31 for lamotrigine, 27 for gabapentin, 27 for carbamazepine, 25 for phenytoin and 25 years for topiramate.

All women were on folic acid prior to the onset of the pregnancy and received standard prenatal care throughout the gestation starting at the first trimester. Seizures during the pregnancy were reported in 8 expectant mothers on lamotrigine, 3 on levetiracetam, 2 on carbamazepine and 1 on gabapentin of who only 3 children had abnormal development (3/14, 21%). Antiepileptic levels were tested on all the women with breakthrough seizures and notably for lamotrigine were sub therapeutic for 4 of the 8 expectant mothers.

Premature delivery (less than 36 weeks gestation) was reported in 3 women on lamotrigine, 2 on levetiracetam and 5 on carbamazepine.

There were 55 (88%, 55/62) live births and 7 unsuccessful pregnancies (miscarriages/stillbirths). Unsuccessful pregnancies were reported in 2 gestations exposed to lamotrigine (3% of total, 2/24 exposed to lamotrigine), 2 to levetiracetam (3% of total, 2/11 exposed to levetiracetam) and 3 to carbamazepine (5% of total, 3/17 exposed to carbamazepine).

Of the 17 pregnancies exposed to carbamazepine 2 resulted in stillbirths and 1 resulted in spontaneous miscarriage. Maternal ages at the onset of the pregnancy were twenty-three and thirty-six years. Neither of these women had seizures during their pregnancies.

Of the 24 pregnancies exposed to lamotrigine 2 resulted in spontaneous miscarriages. Maternal ages at conception were twenty-eight and thirty-six years. Neither of these women had seizures during their pregnancies.

Of the 11 pregnancies exposed to levetiracetam 2 gestations resulted in stillbirth. Maternal ages at conception were twenty-eight and forty years. The forty year old mother did not have any prior pregnancies. Neither of these women had seizures during their pregnancies (Table 1a).

Abnormal development was noted in 6 children: 2/24 prenatally exposed to lamotrigine monotherapy (3.5% of total children), 3/17 exposed to carbamazepine monotherapy (5% of total children) and 1/2 children exposed to valproate monotherapy (2% of total children).

Of the children exposed to carbamazepine in-utero, 1 child was diagnosed with autistic spectrum disorder requiring occupational therapy. Maternal age at this conception was twenty-seven years. The pregnancy was complicated by gestational diabetes and two focal onset seizures with

**Table 1a – Demographics and pregnancy outcomes.**

| AED | Number of fetuses exposed | Average age of expectant mothers | # of seizures during pregnancy | Premature delivery | Pregnancy outcomes | |
|---|---|---|---|---|---|---|
| | | | | | Infant births | Miscarriages/ stillbirths |
| Lamotrigine | 24 | 31 | 8 | 3 | 22 | 2 |
| Levetiracetam | 11 | 28 | 3 | 2 | 9 | 2 |
| Topiramate | 2 | 25 | – | – | 2 | – |
| Gabapentin | 1 | 27 | 1 | – | 1 | – |
| Carbamazepine | 17 | 27 | 2 | 5 | 14 | 3 |
| Phenytoin | 5 | 25 | – | – | 5 | – |
| Valproate | 2 | 22 | – | – | 2 | – |