

**Canger R et al.** Malformations in offspring of women with epilepsy: a prospective study. *Epilepsia*, 40, 1231-1236, 1999

Type of study	Prospective cohort, with external control (the internal cohort of unexposed control is too small being based on 25 women)
Where	Italy
When	1977-1996
Characteristics of the starting cohort	Pregnant women with epilepsy at a single maternity clinic (all women were entered in the study before the 20 week of gestation)
Characteristics of the disease	First trimester of pregnancy: frequent convulsive seizures (2.2%), sporadic convulsions (11.7%), no convulsive seizures (86.0%)
Exposure definition	Intake (one or more antiepileptic drugs (AED)) during pregnancy
Ascertainment of drug exposure	AED blood levels tested monthly
Size of the studied cohort	628 pregnancies and 517 women: only the first pregnancies included in the analysis (65 pregnancies excluded: early spontaneous (38), early voluntary (20) abortions for psycho-social reasons, lack of data (7)): exposed: 427 women; 419 singleton newborns (8 ended with a therapeutic abortion due to malformation) unexposed to AED : 25 women; 25 singleton newborns
Exposed cohort	Newborns exposed in utero to a group of drugs
Control cohort	Newborns not exposed in utero to the studied drugs
Malformations definition	- Abnormalities of the essential embryonic structure or requiring special therapy (spreading device or surgery) during the first year of life - Classified as: (a) genetic/chromosomal, (b) severe/mild structural malformations, (c) deformities. Minor anomalies not considered
Malformations ascertainment	At the time of delivery the infants underwent a standardized examination by a pediatrician, and a more detailed clinical examination on day 5
Prevalence of malformations among control offspring	Not exposed = 0.0% General population = 2.3% (EUROCAT study)
Analysis	Regression analysis, the $\chi^2$ , the Kruskal-Wallis, the Mann-Whitney tests
Strengths	- Exposure and outcome ascertained prospectively - Maternal AED levels concentrations tested monthly - Information on drug exposure levels , any other drugs, seizure frequency, intercurrent illnesses, reproductive end points
Weaknesses	- Control subjects without epilepsy not included - Wide gestational age range of inclusion - Not indicated if information on maternal exposure status was available at the time of paediatrician's examination (probably yes) - Possibility of confounding by indication - Some birth defects may not be included because they appear later after birth - No information about different types of epilepsy, folic acid use - Strengths and weaknesses not indicated in the discussion
Main results	- The overall rate of malformations was 9.7% (5.3% structurally severe, 2.2% mild, 0.4% chromosomal/genetic, 1.8% deformities). No malformation detected in the 25 untreated patients - 69.2% of patients had monotherapy, 23.0% two AED, 2.2%

three AED. No significant difference in the outcomes was found by comparing all monotherapies with all polytherapies, the plasma levels or doses (with the exception of the valproate group), the group of maternal idiopathic generalized epilepsies and partial epilepsies. No correlation was found between malformations and seizure frequency in the first trimester