

Kaaja E et al. Major malformations in offspring of women with epilepsy. *Neurology* 60, 575-579, 2003

Type of study	Prospective cohort
Where	Finland
When	1980-1998
Characteristics of the starting cohort	Pregnant women with epilepsy at a single maternity clinic
Characteristics of the disease	<ul style="list-style-type: none"> - Of all parturients at the institution, 1.0% were women with epilepsy - Grand mal (58.5%), grand mal and others (11.5%), partial (psychomotor, temporal lobe) (19.8%), unclassified/unknown (10.1%) - 6.1% grand mal seizures and 11.5% other types of seizures during the first trimester
Exposure definition	<ul style="list-style-type: none"> - Intake (one or more antiepileptic drugs (AED)) during the first trimester of pregnancy (the same drugs were usually continued throughout pregnancy) - Fetal drug exposure defined as one that prevailed at 7 weeks of gestation
Ascertainment of drug exposure	Assessment of serum concentrations of folate and AED at the end of the first trimester (data on serum folate available in 70.8%, on AED in 90.1% users)
Size of the studied cohort	<p>988 pregnancies followed up (18 pregnancies excluded: miscarriages (6), termination for maternal indication (1), lost to follow up (11)):</p> <p>970 pregnancies in 641 women with epilepsy: exposed: 733 included (7 sets of twins); 740 singleton newborns unexposed reference group: 237 included (2 sets of twins); 239 singleton newborns</p>
Exposed cohort	Newborns exposed in utero to a group of drugs
Control cohort	Newborns not exposed in utero to the studied drugs
Malformations definition	Major: if it was fatal, was likely to cause a serious handicap, or required surgery
Malformations ascertainment	<ul style="list-style-type: none"> - Infants of women with epilepsy examined by a neonatologist for possible malformations at birth and at discharge from the hospital (age: 2-6 days). Charts of the infants admitted to the pediatric clinic reviewed for possible diagnosis of malformations - Autopsy performed in all cases of stillbirth, results reviewed for any malformation-related findings - The charts in the cases of terminations of pregnancy reviewed as regards to major malformations
Prevalence of malformations among control offspring	0.8% (major malformations)
Analysis	<ul style="list-style-type: none"> - Crude and adjusted OR and 95% CI were estimated (logistic regression to control for potential confounders: maternal intake of alcohol, low level of education, parity, smoking, grand mal seizures during the first trimester, use of AED, low serum folate) - Differences between proportions tested by using the χ^2 test and Fisher's exact probability test
Strengths	<ul style="list-style-type: none"> - Women enrolled during early pregnancy: exposures, data on seizures, folate levels and outcome ascertained prospectively - Maternal AED levels and serum folate concentrations measured at the end of the first trimester - Thorough information about drug exposure - Information about characteristics of the disease, reproductive

	<p>end points (miscarriages, termination of pregnancies, stillbirths), lost to follow up</p> <ul style="list-style-type: none"> - The first study on human teratogenicity of oxcarbazepine
Weaknesses	<ul style="list-style-type: none"> - Control subjects without epilepsy not included - Not indicated if information on maternal exposure status was available at the time of paediatrician's examination - Possibility of confounding by indication - Some birth defects may not be included because they appear later after birth - The study is too small to estimate a greater risk of teratogenesis at high drug levels
Main results	<ul style="list-style-type: none"> - The occurrence of major malformations was independently associated with use of carbamazepine (OR 2.5, 95% CI 1.0-6.0), valproate (OR 4.1, 95% CI 1.6-11.0), oxcarbazepine (OR 10.8, 95% CI 1.1-106.0), low serum folate concentration (OR 5.8, 95% CI 1.3-27.0), and low maternal level of education (OR 3.0, 95% CI 1.3-6.8). Major malformations were not associated with seizures during the first trimester - Major malformations were detected in the 3.8% fetuses exposed to maternal AED (p=0.02). The risk of major malformation increased with the number of AED used (one drug-3.1%, two drugs-5.8%, three/four drugs 8.3% (p=0.02 per trend)). 80% of patients had monotherapy, mostly carbamazepine, phenytoin, valproate

