

**Wide K et al.** Major malformations in infants exposed to antiepileptic drugs in utero, with emphasis on carbamazepine and valproic acid : a nation-wide, population-based register study. *Acta Paediatr* 93, 174-76, 2004

Type of study	Population-based retrospective cohort
Where	Sweden
When	1995-2001
Characteristics of the cohort	Newborns whose mothers reported the use of antiepileptic drugs (AEDs) in pregnancy, identified in the Swedish Medical Birth Registry
Characteristics of the disease	Incidence of epilepsy during pregnancy: estimated 3-4 per 1,000 (approximately 70% of all cases were identified)
Ascertainment of drug exposure	Prospective : information on drug use reported by the pregnant women During early pregnancy
Exposure definition	Intake in early pregnancy
Size of the studied cohort	Exposed infants: 1,398 (1256: monotherapy; 130: 2 AEDs; 11: 3 AEDs; 1: 4 AEDs) Reference group infants: all born during the study period 582,656, used to estimate the expected numbers
Exposed cohort	Newborns exposed to AEDs in early pregnancy
Control cohort	All infants, not exposed to the studied drugs, reported to the Swedish Medical Birth Registry during the study period
Malformations ascertainment	Information based on International Classification of Diseases codes recorded in the Medical Birth Registry, on record linkage with the Swedish Register of Congenital Malformations, on the Hospital Discharge Registry. The recording of congenital malformations was done by the paediatrician at the routine examination
Malformations definition	Severe malformations: were excluded preauricular tag, patent ductus arteriosus in preterm infant, congenital laryngeal stridor, undescended testicle, hip dislocation, pes calcaneovalgus, unspecified foot deformity, facial asymmetry and naevus. To compare the malformation rate of infants exposed to AED with that of all infants in the population, only malformations identified in the Medical Birth Registry were used. For comparisons within the group of AED exposed infants, all malformation diagnoses irrespective of source were used
Prevalence of malformations among control offspring	Not indicated
Analysis	Adjusted OR and 95%CI (to control for potential confounders: year of birth, maternal age, parity and smoking in early pregnancy)
Strengths	- Drug use reported by the pregnant women early in pregnancy -Nation-wide population based study - Multiple sources for malformation identification reduced the risk of ascertainment bias
Weaknesses	- No information on the number of therapeutic abortions, the different types of epilepsy or drug dosage - Available information on maternal drug use at the time of paediatrician's examination (possible bias of malformation recording in some cases) - Possibility of confounding by indication
Main results	The OR for AED-exposed infants (n=1,398) to have a congenital

malformation was 1.86, 95%CI 1.4-2.4. Exposure to valproic acid in monotherapy compared with carbamazepine gave OR 2.5, 95%CI 1.4-4.7). 90% (1,256) of the exposed infants: AEDs in monotherapy (56% carbamazepine, 21% valproic acid). If exposed to AEDs in monotherapy (n=1,256) OR: 1.61, 95%CI 1.2-2.2 and if exposed to AEDs in polytherapy (n=142) OR: 4.20, 95%CI 2.4-7.5. The two ORs differ significantly ( $z=3.0$ ,  $p<0.01$ )