

**Holmes LB et al.** The AED (Antiepileptic Drug) Pregnancy Registry. A 6-year experience. *Arch Neurol* 61, 673-78, 2004

Type of study	Prospective cohort (The North American AED Pregnancy Registry)
Where	Massachusetts
When	1997-2002
Characteristics of the starting cohort	Pregnant women (United States and Canada) exposed to an anticonvulsant drug, who called a toll-free telephone number of the registry to enroll. Women are subdivided into 2 groups: "pure" prospective (do not know, at the time of enrollment, whether the fetus has a malformation) and "traditional" prospective (some knowledge of the status of the fetus, typically after having prenatal screening by ultrasound). Women are not enrolled after the pregnancy has ended
Characteristics of the disease	Not indicated
Ascertainment of drug exposure	Each woman was interviewed by telephone at enrollment, at 7 months' gestation and post partum, (up to 8 to 12 weeks after the expected date of delivery). The structured interviews include questions on dose, frequency, and medical indication of each medication; signs and symptoms of epilepsy (or mood disorders); the apparent cause and family history of epilepsy
Exposure definition	Intake as monotherapy during the first trimester of pregnancy. For this study, an anticonvulsant drug was defined as a drug prescribed to suppress seizure activity. The term monotherapy was used when only 1 anticonvulsant drug was taken at any time during pregnancy. The term polytherapy was used when more than 1 anticonvulsant was taken, either concurrently or consecutively
Size of the studied cohort	Exposed women: 3002 recruited, of these 2330 (77.6%) reported taking an anticonvulsant as monotherapy. For this study women exposed to phenobarbital as monotherapy: 165 recruited; 146 (77 in the pure and 69 in the traditional prospective group) in follow-up (7 withdrawals, 12 lost to follow up); 146 infants. Unexposed reference group women: Internal comparison: 796 recruited, infants External comparison: 69,277 infants
Exposed cohort	Newborns exposed to a specific drug
Control cohort	Internal comparison: newborns not exposed to the studied drug (exposed to 3 other frequently used AED monotherapies, mothers in the pure prospective group) External comparison: with the number of cases expected on the basis of the rate from the Active Malformations Surveillance Program at Brigham and Women's Hospital, Boston and other hypothetical rates ranging from 1% to 3%
Malformations ascertainment	The written descriptions in the pediatricians' examinations were reviewed separately by 2 registry dysmorphologists, blinded to exposure status, to determine inclusion or exclusion. Major malformations identified by 5 days of age
Malformations definition	Major malformation: structural abnormality with surgical, medical, or cosmetic importance. Exclusions were as follows: minor anomalies, deformations, physiological features due to prematurity, such as undescended testes, birthmarks, genetic disorders and chromosomal abnormalities, and any finding by

	<p>prenatal sonography, such as absence of one kidney, or at surgery (or autopsy) that was not identified by an examining pediatrician</p>
Prevalence of malformations among control offspring	<p>Internal comparison: 2.9%  External comparison: baseline rate: 2.24%, reduced to 1.62% after exclusion of infants with genetic disorders and chromosome abnormalities</p>
Analysis	<p>Initially, the rates of malformations, RR and 95%CI among infants exposed were determined for the infants of both pure and traditional prospective enrollees. Later, the Scientific Advisory Committee decided to use only the findings in the infants of pure prospective enrollees to reduce potential bias</p>
Strengths	<ul style="list-style-type: none"> <li>- The most extensive information available to date on this drug's risks to the exposed fetus</li> <li>- Thorough search of medical records of mothers and infants (initially from 4 sources: the mother's neurologist, her obstetrician, the birthing hospital and the infant's paediatrician; since 2000 from: woman's neurologist and the infant's physician. Medical records from pediatricians were received for 58% of the neonates in the pure prospective group and 71% of the neonates in the traditional prospective group)</li> <li>- Exposures and outcome were ascertained prospectively</li> <li>- Internal and external comparison</li> <li>- Good characterization and definition of birth defects: 2 registry dysmorphologists, blinded to exposure status</li> <li>- High agreement between the reports of the mother and the written reports of her infant's paediatrician on the presence of a major malformation</li> <li>- Loss to follow up: 7.2% (2.1% in the entire registry)</li> <li>- Evaluation of the study's power analyses</li> <li>- Information on folic acid supplement</li> </ul>
Weaknesses	<ul style="list-style-type: none"> <li>- Women self-selected by calling the Service for counselling</li> <li>- Malformations in anticonvulsant-exposed infants were restricted to those identified at birth: some birth defects may not be included because they appear later after birth</li> <li>- The identity of the 3 drugs used by internal controls not provided</li> <li>- Information reviewed on the external controls more extensive than information obtained by mail from the registry-enrolled infants' physicians</li> <li>- Pregnancy registries evaluated the frequency of all malformations, not specific malformations (small number of subjects)</li> <li>- No detailed information regarding different types of epilepsy and dosage of drugs</li> <li>- Not indicated if the interviewers were aware of anticonvulsant drugs used by women</li> </ul>
Main results	<p>Five (6.5%) of 77 pure pregnancies with exposure to phenobarbital monotherapy were associated with major malformations. When compared with the background rate (1.6%), there was a significantly increased risk (RR 4.2, 95%CI 1.5-9.4). There was no significant difference in the rate of malformations among phenobarbital-exposed infants in comparison with those exposed to the other AEDs (RR 2.0, 95%CI 0.9-4.5)</p>

