

25 Matalon S et al. The teratogenic effect of carbamazepine: a meta-analysis of 1255 exposures. *Reprod Toxicol* 16, 9-17, 2002

Type of study	<p>Meta-analysis: Studies: 16 included (criteria for inclusion: English language, prospective design):</p> <ul style="list-style-type: none"> - Hiilesmaa VK, Teramo K, Granstrom ML. <i>Lancet</i> ii, 165-7, 1981 - Kaneko S, Otani K, Fukushima Y et al. <i>Epilepsia</i> 29, 459-67, 1988 - Jones KL, Lacro RV, Johnson KA et al. <i>NEJM</i> 320, 1661-6, 1989 - Rosa FW. <i>NEJM</i> 321, 674-7, 1991 - van der Pol ML, Hadders-Algra M, Huisjes H et al. <i>Am J Obstet Gynecol</i> 164, 121-8, 1991 - Kaneko S, Otani K, Kondo T et al. <i>Neurology</i> 42, 68-74, 1992 - Lindhout D, Meinardi H, Meijer JWA et al. <i>Neurology</i> 42, 94-110, 1992 - Scolnik D, Nulman I, Rovet J et al. <i>JAMA</i> 271, 767-70, 1994 - Water CH, Belai Y, Gott PS et al. <i>Arch Neurol</i> 51, 250-3, 1994 - Ornoy A, Cohen E. <i>Arch Dis Child</i> 75, 517-20, 1996 - Lindhout D et al. <i>Epilepsia</i> 38, 981-90, 1997 - Canger R, Battino D, Canevini MP et al. <i>Epilepsia</i> 40, 1231-6, 1999 - Samren EB, Van Duijn CM, Lieve Christians GCM et al. <i>Ann Neurol</i> 46, 739-46, 1999 - Wide K, Winblad B, Tomson T et al. <i>Epilepsia</i> 41, 854-61, 2000 - Diav-Citrin O, Shechtman S, Arnon J et al. <i>Neurology</i> 57, 321-4, 2001 - Holmes LB, Harvey EA, Coull BA et al. <i>NEJM</i> 15, 1132-8, 2001 <p>excluded (criteria for exclusion: retrospective studies, no specific information about carbamazepine (CBZ), studies with no sufficient information on outcomes): not indicated</p>
When	Not indicated
Characteristics of the recruited patients	<ul style="list-style-type: none"> - Women treated during pregnancy with CBZ alone or with CBZ and other antiepileptic drugs, for epileptic seizures or any other indication - Newborns exposed to the studied drug with and without major malformations; newborns non exposed to the studied drug with and without major malformations
Characteristics of the treated diseases	Women with epilepsy or any other indication to treatment
Exposure definition	Intake during the first trimester or during pregnancy
Ascertainment of drug exposure	Not indicated
Size of the studies included for meta-analysis	<p>1,255 exposed liveborn infants 3,938 non exposed liveborn infants (3,756 normal control, 182 epileptic women with no treatment)</p>
Malformations definition	<ul style="list-style-type: none"> - Indicated for each study - Criteria of Holmes: only those structural anomalies that have serious medical, surgical, or cosmetic consequences (major congenital anomalies evaluated both according to the determinations of individual authors and using the criteria of Holmes)
Malformations ascertainment	Not indicated
Prevalence of malformations among offspring	<p>2.3% in normal control group 2.7% in untreated epileptic women</p>
Analysis	<ul style="list-style-type: none"> - All included studies pooled and weighted - Summary OR and 95% CI calculated using the Mantel-Haenszel method - Continuous data summarized by calculation of the effect size for each and combination by the inverse variance method - Test for heterogeneity: not indicated
Strengths	<ul style="list-style-type: none"> - Ability of the meta-analysis to increase the sample size and the statistical power - Two reviewers independently reviewed the retrieved articles - Evaluation of the study's power analyses - Information on malformations definition for each study - The effect on OR of having different malformations definition indicated
Weaknesses	<ul style="list-style-type: none"> - Combination of well-designed studies with poorly designed ones - Negative studies more likely not published and not identified - Wide ranging definitions for identification of malformations - Absence of control groups in some of the studies - Stillborn infants not included (in most studies data referred to all antiepileptic drugs) - Not indicated the excluded studies and test for heterogeneity - No information about ascertainment of drugs exposure and malformations - No description of the type of anomalies in the control offspring in most studies

Main outcomes

CBZ therapy increased the rate of congenital anomalies, mainly neural tube defects, cardiovascular and urinary tract anomalies, and cleft palate ($P < 0.05$, OR 3.0, 95% CI 2.6-4.1 for aggregate data; $P < 0.05$, OR 2.6, 95% CI 1.8-3.6 for controlled studies). A combination of CBZ with other antiepileptic drugs is more teratogenic than CBZ monotherapy. Children born to untreated epileptic women do not appear to have an increased rate of major birth defects. CBZ also appears to reduce gestational age at delivery