



## ABSTRACT

L. UNGAR<sup>1</sup>, L.B. HOLMES<sup>1</sup>, D.F. WYSZYNSKI<sup>2</sup>. <sup>1</sup>Massachusetts General Hospital, Genetics and Teratology Unit, Pediatric Service, Boston, MA, <sup>2</sup>Boston University School of Medicine, Department of Medicine, Boston, MA. Exclusion And Inclusion Criteria For Major Malformations: Impact On Studies Of Potential Teratogens

Many studies of potential teratogens initially focus on how maternal exposure affects the percentage of infants born with major malformations. For example, the North American AED (Anti-Epileptic Drug) Pregnancy Registry found that monotherapy Phenobarbital (PB) or sodium valproate (VPA) exposure raised the rate of major malformation from a baseline of 1.62% to 6.5% (Arch Neurol 61:673-8, 2004) and 10.7% (Neurol 64:956-961, 2005), respectively. For both the exposed group and the unexposed comparison group, a set of inclusion/exclusion criteria were used to specify which features counted as major malformations. Major malformations were defined as structural abnormalities with surgical, medical, or cosmetic importance.

We tabulated the excluded physical features identified among infants whose mothers had enrolled in the North American AED Pregnancy Registry and had taken either PB or VPA as monotherapy during the first trimester of pregnancy. Of the 149 PB-exposed and 77 VPA-exposed children (total n=226), 38 (16.7%) had physical features (reported by the infant's mother and/or doctor) that were excluded. This total subdivided into minor anomalies (n=14; 6.2%), physiological features (n=9; 4.0%), deformations (n=3; 1.3%), anomalies diagnosed prenatally only (n=2; 0.9%), genetic etiologies (n=2; 0.9%), anomalies related to prematurity (n=2; 0.9%), anomalies diagnosed after the time window (birth to 5 days) (n=2; 0.9%), or others (n=4; 1.8%). Even excluding these physical features, exposure to each drug resulted in a significant increase in the frequency of major malformations in infants, as cited above: 1.62% baseline, 6.5% PB-exposed, 10.7% VPA-exposed. Including the excluded physical features, those already-increased malformation rates jumped dramatically to 27.3% for PB-exposed infants, and 25.5% for the VPA-exposed infants. Thus, including minor features as "major" abnormalities can unfairly and inappropriately exaggerate the apparent fetal effects of an exposure. It is essential that studies of potential teratogens set inclusion/exclusion criteria to evaluate their test group, and use the same criteria to evaluate their unexposed comparison group.

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