

Czeizel AE et al. A case-control study of congenital abnormality and dimenhydrinate usage during pregnancy. *Arch Gynecol Obstet* 2005, 271:113-118

Type of study	Population-based case-control (Hungarian Case-Control Surveillance of Congenital Abnormalities-HCCSCA)
Where	Hungary
When	1980-1996
Cases	22,843 newborns or fetuses with congenital abnormalities (CAs). Cases with isolated CAs and multiple CAs of the HCCSCA were identified from the data set of the Hungarian Congenital Abnormality Registry (HCAR) reported in the first 3 months after births or termination of pregnancies. These cases comprised 77% of the HCAR. Three mild CAs (such as congenital dislocation of the hip based on the Ortolani click, congenital inguinal hernia, and hemangiomas), minor variants (eg umbilical hernia), and CA syndromes of Mendelian and chromosomal origin were excluded
Case prevalence among the population	The total recorded prevalence of cases with CA diagnosed from the 2 nd trimester of pregnancy through to the age of one year was 35 per 1,000 informative offspring (liveborn infants, stillborn fetuses and malformed fetuses after elective termination of pregnancy). Approximately 90% of major CAs were reported to the HCAR during the study period
Controls	38,151 newborns without any defects. Controls without CA were selected from the National Birth Registry of the Central Statistical Office, followed by 1-2 months of case notification. Two newborns were matched to every case according to sex, week of birth and district of parents' residence
Exposure definition	<ul style="list-style-type: none"> - Oral and suppository dimenhydrinate treatment in the first trimester and entire pregnancy - Recommended protocol: 50-100mg tablets/suppositories four times per day (usual dose 200-400mg) - Mean duration of treatment: 1.9 months (cases), 2.1 months (controls)
Ascertainment of drug exposure	<p>Exposure data were obtained from three different sources:</p> <ul style="list-style-type: none"> - a structured questionnaire and a list of drugs and diseases mailed to the mothers immediately after the selection of cases and controls (information on pregnancy complications, maternal diseases and drugs and supplements during pregnancy according to gestational months and family history of CAs) - mothers were asked to send the antenatal care logbook and other medical records - regional nurses were asked to visit and question all non-respondents
Prevalence of exposure among controls	4.5%
Analysis	<ul style="list-style-type: none"> - Crude and adjusted prevalence OR and 95%CI were estimated (McNemar test and logistic regression to control for potential confounders: maternal age, birth order, marital/employment status, acute/chronic maternal diseases, other drugs) - Two groups, dimenhydrinate alone and dimenhydrinate plus other drugs were differentiated in the analysis; oral and suppository (used rarely, <2%) treatments were combined
Strengths	<ul style="list-style-type: none"> - Large, racially homogenous, population-based data set - Standardized answers (structured questionnaire, list of drugs and diseases) - Thorough search of exposure data

	- Good characterization of cases
Weaknesses	<ul style="list-style-type: none"> - Control infants with no birth defects (risk of recall bias) - Drug intake based on maternal report: 58.0% cases, 43.6% controls (risk of recall bias) - Information available for a total of 96.3% cases, 83.1% controls: the response rate was somewhat lower in the controls than in the cases (risk of selection bias) - Active follow up for all non respondents in the case group, but only 200 families in the control group (risk of selection bias) - Despite the size of the population-based data set there were no cases or only a limited number of cases in some CA groups - Multiple comparisons can produce occasional associations by chance - Possibility of confounding by indication - Most women given studied drug used other drugs
Main results	There was no indication of teratogenicity with dimenhydrinate. A lower rate of obstructive uropathy was found in infants born to mothers treated with dimenhydrinate during the first trimester of pregnancy, confirmed by the medically recorded drug use