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Folic acid sensitive birth defects in association with intrauterine exposure to folic acid antagonists

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Abstract

Since the protective effect of folic acid (FA) on birth defects is well known, it is reasonable to assume intrauterine exposure to FA antagonists increases the risk on these defects. We have therefore performed case–control analyses to investigate the risk of intrauterine exposure to FA antagonists, using data on births from the EUROCAT Northern Netherlands registry from 1997 to 2002. Of the 815 cases, 11 were exposed to a FA antagonist compared to 16 of the 1402 controls. For FA sensitive defects as a group, the study showed no effect after exposure to a FA antagonist (odds ratio (OR) = 1.18, 95% CI: 0.55–2.57). We found no effect after exposure to a dihydrofolate reductase inhibitor (DHFRI) (OR 0.44, 95% CI: 0.12–1.54), but we did find a statistically significant effect after exposure to an antiepileptic drug (OR = 3.45, 95% CI: 1.04–11.48). This study supports the findings of various other studies on the teratogenicity of antiepileptics. An association between DHFRIs and FA sensitive defects was not found.

Keywords: Neural tube defects; Congenital heart defects; Orofacial clefts; Limb reduction defects; Urinary tract anomalies; Folic acid antagonists; Human; Antiepileptics

1. Introduction

Experimental as well as observational studies have shown a protective effect of folic acid (FA), alone or in a multivitamin, on neural tube defects (NTDs) [1,2] and other defects like heart anomalies [3,4], orofacial clefts [5,6], limb reduction defects [3,5], urinary tract anomalies [5,7], omphalocele [8], and anal atresia [9]. If FA decreases the risk of having a child with one or more of these congenital anomalies, it is reasonable to assume that intrauterine exposure to a FA antagonist increases this risk. Two studies have been published on this association by Hernandez-Diaz et al. [10,11]. They found an increased risk of NTDs, heart anomalies and orofacial clefts after exposure to FA antagonists. A study by Werler et al. describes the possible teratogenicity of folic acid antagonists among other drug exposures, in an Australian population [12]. Unfortunately, their numbers were too small to distinguish between different groups of folic acid antagonists.

It is very important to reproduce epidemiological studies in databases with different characteristics and compare the findings, especially in this case since trimethoprim, one of the folic acid antagonists, is regarded safe during pregnancy. Therefore, the aim of this study was to investigate whether

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intrauterine exposure to a FA antagonist in the first weeks of pregnancy is associated with an increased risk of FA sensitive birth defects within the EUROCAT Northern Netherlands database.

2. Materials and methods

2.1. Study population

In January 2004, we selected live births, stillbirths and abortions from 1997 to 2002 from the EUROCAT Northern Netherlands registry. In this registry live births, stillbirths and abortion data with congenital anomalies are registered since 1981. Until 1996, information about the pregnancy outcome and the mother's condition, diseases and drug use was collected through the physician or midwife who reported the birth. Since 1997, parents have been sent a questionnaire in order to collect information about their characteristics like age, education, and family history. A request for access to their pharmacy data was included as well. After receiving the pharmacy data, mothers were asked by phone if drugs reported by the pharmacy were actually used and in which time period the drugs were used. Data about over-the-counter (OTC) drugs, illness during pregnancy, and life style aspects like smoking and alcohol consumption were provided by the parents as well. Information about the anomaly was provided by physicians, midwives, clinical geneticists and pathologists.

No age limits for discovering an anomaly were applied, which means that besides anomalies leading to abortions and anomalies discovered at birth, anomalies discovered even years after birth are recorded as well.

Of the in total 2658 births from the selected years, 441 (16.4%) were excluded, since data on drug exposure were missing. The mothers of these subjects did not fill out the questionnaire and therefore data of the pharmacy were not collected. The remaining 2217 births were either case or control. In total 120,214 children were born in the northern Netherlands from 1997 to 2002 [13].

2.2. Cases and controls

Cases were defined as having a FA sensitive defect, including NTDs, congenital heart anomalies, orofacial clefts, limb reduction defects, urinary tract anomalies, omphaloceles and anal atresias ($n = 815$). Births with chromosomal or monogenic defect with a FA sensitive defect as well were not defined as cases, unless the FA sensitive anomaly is not part of the chromosomal defect. For example, a Down syndrome with a neural tube defect is a case, since a neural tube defect is not part of the syndrome. A Down syndrome with a heart anomaly is not a case. Controls were all births not defined as cases ($n = 1402$) including 401 chromosomal or monogenic defects.

2.3. Exposure assessment

We considered a fetus to have been exposed, if the mother reported using a FA antagonist any time during the first 10 weeks after her last menstrual period. FA antagonists can be divided into two groups: the dihydrofolate reductase inhibitors (DHFRIs) and compounds that interact with other enzymes in folate metabolism, mainly antiepileptics. Dihydrofolate reductase is the enzyme that converts the inactive form of FA into active metabolites. Examples of DHFRIs are methotrexate, sulfasalazine, triamterene, pyrimethamine and trimethoprim. The antiepileptics that influence folate metabolism are carbamazepine, phenobarbital, phenytoin, primidone, valproic acid and lamotrigine.

If the numbers allowed it, the use of FA was included in the analyses. Exposed to FA was then defined as having used FA during all 10 weeks after the last menstrual period. Other use of FA was defined as not exposed.

2.4. Data analysis

p-Values were calculated, with chi-square tests or *t*-tests where applicable, to compare the cases and controls. Trend analyses were performed for ordinal data. Logistic regression was used to determine odds ratios (ORs) and 95% confidence intervals (95% CIs). If the numbers allowed, subanalyses were made per group of anomalies and per drug group.

3. Results

In Table 1, the characteristics of 815 cases and 1402 controls are shown. These groups differ in type of birth, gravidity and education of the mother. Among the controls, more live births, miscarriages, and induced abortions occurred. For the mothers of the controls, this pregnancy was more often the first one. A low level of educational attainment was slightly more frequent among case mothers and a middle education level more frequent among control mothers although the *p*-value of the trend analysis was not statistically significant ($p = 0.067$). In the case group, more males were born compared to the control group, but this difference was not statistically significant.

Of the 815 cases, 11 (1.3%) were exposed to a FA antagonist in the first 10 weeks after the last menstrual period; 3 of these (0.4%) were exposed to a DHFRI (all 3 to trimethoprim) and 8 (1.0%) to an antiepileptic drug (2 to carbamazepine, 4 to valproate, 1 to carbamazepine + valproate and 1 to carbamazepine + valproate + primidone). Of the 1402 controls, 16 (1.1%) were exposed to a FA antagonist of which 12 (0.8%) to a DHFRI (seven to trimethoprim, two to trimethoprim + sulfoxamide and 3 to sulfasalazine) and 4 (0.3%) to an antiepileptic drug (1 to carbamazepine, 2 to valproate and 1 to carbamazepine + valproate). None of the cases or controls were exposed to a DHFRI as well as to an antiepileptic drug.