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Association of certain chronic maternal diseases with the risk of specific congenital heart defects: a population-based study

A. Vereczkey [a,*], B. Gerencsér [b], A.E. Czeizel [c], I. Szabó [d]

[a] Versys Clinics, Human Reproduction Institute, Budapest, Hungary
[b] Alfréd Rényi Institute of Mathematics, Hungarian Academy of Sciences, Budapest, Hungary
[c] Foundation for the Community Control of Hereditary Diseases, Budapest, Hungary
[d] Department of Obstetrics and Gynaecology, University of Pécs, Pécs, Hungary

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ABSTRACT

Objective: Previous epidemiological studies have evaluated cases with all congenital heart defects (CHDs), rather than analysing different types of CHD. The objective of this study was to evaluate the possible association of certain chronic maternal diseases with the risk of different types of CHD, because the role of possible environmental factors in the origin of CHDs is unclear in the vast majority of patients.
Study design: Different types of CHD, diagnosed after lethal outcome (autopsy report) or after surgical intervention (catheter or correction), were evaluated in order to estimate the possible role of chronic maternal diseases in their origin. This analysis was based on the rates of medically recorded chronic maternal diseases in 3562 live-born cases with CHDs, 38,151 population controls without any birth defects, and 16,602 malformed controls with other isolated congenital abnormalities, using the data set of the population-based Hungarian Case–Control Surveillance of Congenital Abnormalities (1980–1996).
Results: Maternal epilepsy treated with carbamazepine and migraine were found to be associated with higher risk of ventricular septal defect; panic disorders were associated with higher risk of hypoplastic left heart; type I diabetes mellitus was associated with higher risk of coarctation of the aorta; chronic hypertension was associated with higher risk of ventricular septal defect, common atrioventricular canal and common truncus; and paroxysmal supraventricular tachycardia was associated with higher risk of atrial septal defect secundum, common atrioventricular canal and ventricular septal defect.
Conclusion: In conclusion, certain chronic maternal diseases were found to be associated with higher risk of specific CHDs. Appropriate treatment of these diseases may help to prevent these CHDs.

Introduction

Congenital heart defects (CHDs) are the most common (4–50 per 1000 live-births) [1,2] and serious [3] structural birth defects (i.e. congenital abnormalities). The care of infants/children with CHDs has been revolutionised over recent decades [4], and progress in human genetics has resulted in better understanding of the genes associated with CHDs [5]. However, the role of possible environmental factors in the origin of CHDs is unclear in the vast majority of patients [6,7]. As such, this study aimed to investigate possible associations between chronic maternal diseases and the risk of CHDs.

CHDs have heterogeneous manifestations and origins [8]. The classification of CHDs used in the Baltimore-Washington Infant Study [9,10] was adopted in this study. Newborn infants affected with a single type of CHD, diagnosed by lethal outcome (autopsy report) and/or surgical intervention (catheter or correction), in the data set of the population-based Hungarian Case–Control Surveillance of Congenital Abnormalities (HCCSCA) [11] were included in this study.

Materials and methods

Study subjects

Patients (i.e. cases with congenital abnormalities including CHDs in the HCCSCA) were selected from the Hungarian Congenital Abnormality Registry (HCAR) [12,13]. Reporting of cases with congenital abnormalities to the HCAR is mandatory for physicians, and autopsy is mandatory for all infant deaths; pathologists send a

* Corresponding author at: 1138 Budapest, Madarász Viktor utca 47-49, Hungary. Tel.: +36 1 3944 412; fax: +36 1 3944 412.
E-mail addresses: attila.vereczkey@versysclinics.com, eva.margittai@eok.sote.hu (A. Vereczkey).

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copy of the autopsy report to the HCAR if defects are identified. Approximately 90% of major congenital abnormalities were recorded on the HCAR [14].

Only those cases with congenital abnormalities who were reported to the HCAR during the first 3 months after birth were selected for the HCCSCA. In addition, cases with congenital abnormality syndromes caused by gene mutations or chromosomal aberrations with preconceptional origin were excluded.

In the HCCSCA, controls were defined as newborn infants without congenital abnormalities, matched to cases by sex, birth week and district of parents' residence. The source of these controls was the National Birth Registry of the Central Statistical Office for the HCCSCA. In general, two controls were matched to each case.

Collection of exposure data and confounding factors

An explanatory letter and an informed consent form were posted to the mothers of cases and controls immediately after their selection for the HCCSCA, and they were asked to supply their prenatal maternity logbook and all medical records concerning their diseases during the study pregnancy and their child's congenital abnormality. These documents were returned within 4 weeks. Prenatal care is mandatory for pregnant women in Hungary, and women who do not attend for prenatal care do not receive a maternity grant or maternity leave. As such, nearly 100% of pregnant women attended for prenatal care, on average, seven times between 6 weeks of gestation and the end of pregnancy. Obstetricians in prenatal care are obliged to record pregnancy complications, maternal diseases and related medicinal products for women during pregnancy in the logbook.

The mean ± standard deviation time between the end of pregnancy and return of the 'information package' (i.e. logbook, discharge summary and informed consent form) in the prepaid envelope was 3.5 ± 2.1 and 5.2 ± 2.9 months for cases and controls, respectively.

Regional district nurses were asked to visit all case mothers who did not respond, and to evaluate the available medical documents. Unfortunately, the district nurses could only visit 200 non-respondent control mothers [15] and 600 respondent control mothers [16] in two validation studies because the ethics committee considered that this follow-up might be disturbing for the parents of healthy children.

Data on chronic maternal diseases were available for 96.3% of cases (84.4% from postal replies and 11.9% from visits) and 83.0% of controls (81.3% from postal replies and 1.7% from visits). Signed informed consent forms were returned by 98% of mothers; names and addresses were deleted for the 2% of subjects who did not provide signed informed consent.

The method of data collection was changed in 1997, but these data had not been validated at the time of this analysis. As such, this study is based on the 17-year dataset of the HCCSCA from 1980 to 1996.

Study design of cases with CHDs

In general, cases with congenital abnormalities were reported immediately after birth to the HCAR. Approximately 50% of cases with CHDs were reported as unspecified CHDs, because the exact diagnosis required further time-consuming examinations. The HCCSCA researchers were able to specify the type of CHD in a further 20% of cases by evaluation of the medical data of cases with congenital abnormalities 3.5 ± 2.1 months after birth. For the remaining 30% of live-born cases without a specific CHD diagnosis, it was anticipated that they would have received care or surgical intervention at a paediatric cardiology institution; therefore, the HCCSCA researchers visited these cardiology in- and outpatient clinics in 2008. Medical records were reviewed, and unspecified CHDs were changed to specific CHD diagnoses where possible. For cases with a diagnosis of CHD who were not found in the records of paediatric cardiology institutions, their mothers were contacted to clarify the fate and/or diagnosis in 2009 and 2010. Cases that could not be traced, cases without a specific CHD diagnosis, and cases whose mothers did not wish to participate were excluded from the study.

Cases with multiple congenital abnormalities including CHDs were also excluded from the study. In addition, because some types of CHD have a wide spectrum of manifestations including spontaneous closure of ventricular or atrial septal defects, ductus arteriosus, etc., only cases with lethal outcomes (verified by autopsy record) or who had undergone surgical intervention (cardiac catheter diagnosis or correction) were included in the study.

There were two control groups in this study: (i) the live-born population controls without any congenital abnormalities; and (ii) the live-born malformed controls with other isolated congenital abnormalities from the HCCSCA dataset.

Statistical analysis of data

GNU R 2.14, RStudio 0.97 version was used for statistical analysis. Associations between certain chronic maternal diseases

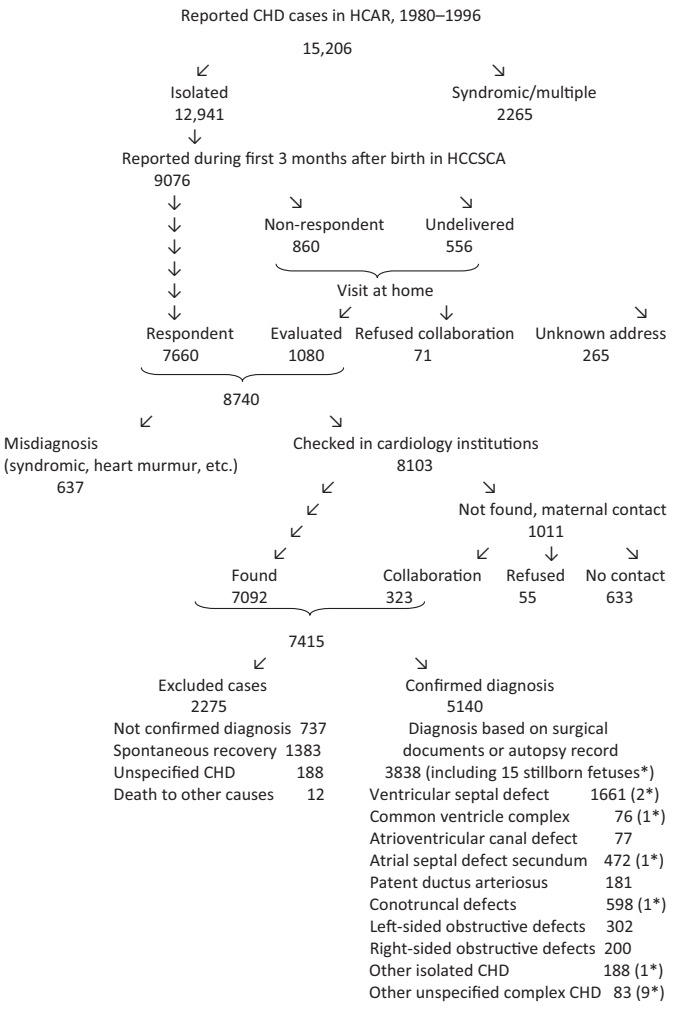

Fig. 1. Flow of cases with congenital heart defects (CHDs) from the Hungarian Congenital Abnormality Registry (HCAR) to the Hungarian Case–Control Surveillance of Congenital Abnormalities (HCCSC).