



# Birth outcomes of cases with different congenital heart defects - a population-based study

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## Abstract

**Background:** In general, previous epidemiological studies evaluated congenital heart defects (CHDs) together. The aim of the present study was to identify possible etiological factors of different CHD-entities, because the underlying causes are unclear in the vast majority of patients.

**Objectives:** Different CHD-entities as homogeneously as possible with confirmed diagnoses were analyzed in the population-based large dataset of the Hungarian Case-Control Surveillance of Congenital Abnormalities.

**Methods:** 3,750 live-born singleton CHD-patients were analyzed according to birth outcomes, i.e. gestational age at delivery and birth weight, the rate of preterm birth, low birthweight and small for gestational age.

**Results:** The major findings of the study showed that cases with different CHD-entities had shorter gestational age at delivery and lower mean birth weight, and these variables associated with a higher rate of preterm birth and particularly with a much higher rate of low birthweight and small for gestational age. This study showed the importance of sex in the birth outcomes of some CHD-entities. The question is why several CHD-entities manifested more frequently in newborns with intrauterine growth restriction because fetal heart has a passive role before birth without pulmonary circulation.

**Conclusions:** The birth outcomes of cases indicate the effect of CHDs for fetal development. In addition maternal confounders have to consider. Finally, CHDs and intrauterine growth restriction as two developmental errors may have a common route, thus fetal growth and birthweight associated gene polymorphisms may have a role in the origin of CHDs.

**Keywords:** Congenital Heart Defects; Low Birthweight; Population-Based Study; Preterm Birth; Small for Gestational Age.

## 1. Introduction

The aim of our project is to reveal the possible environmental risk factors in the origin of CHDs in the population-based Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) (Czeizel et al. 2001). However, CHDs cannot be regarded as a single homogeneous CA (Botto et al. 2007) therefore; CHD-entities/groups were separated according to the classification of CHDs used in the Baltimore-Washington Infant Study (Ferencz et al. 1993, Ferencz et al. 1997). In addition syndromic/multiple CAs including CHD were excluded from the study material and only the serious cases with confirmed diagnosis due to lethal outcome or catheter diagnosis or surgical correction were included in the study and CHD-entities were evaluated as homogeneous CHD-entities as possible. This approach needs the previous analysis of birth outcomes of patients with CHD, and these data are presented here based on the HCCSCA (Czeizel et al. 2001).

## 2. Methods

### 2.1. The Hungarian Congenital Abnormality Registry (HCAR)

The HCAR was established as the first national-based registry of CAs in the world, 1962 (Czeizel 1997, Czeizel et al. 2014). Reporting of patients as cases with CA to the HCAR is mandatory for physicians from the birth until the end of first postnatal year. Most cases are reported by obstetricians (in Hungary practically all deliveries occur in inpatient obstetric clinics and birth attendants are obstetricians) and pediatricians (who are working in the neonatal units of inpatient obstetric clinics and various, general and specialized, e.g. cardiology inpatient and outpatient pediatric clinics). Autopsy is mandatory for all infant deaths and common (80%) in stillborn fetuses during the study period, and pathologists send a copy of the autopsy report to the HCAR if defects were identified. Since 1984, prenatal diagnostic centers were also asked to report malformed fetuses diagnosed prenatally with or without elective termination of pregnancy to the HCAR.

In the HCAR cases with CAs are differentiated into isolated (including single, sequence and complex groups) and multiple or syndromic (including CA-syndromes, CA-associations and



unclassified multiple CAs) categories (Czeizel et al. 1993). The multimalformed cases had 2 or more CAs in different organs with or without minor anomalies. Thus the unit of recording was the person and not the CA in the HCAR. The recorded total (birth + fetal) prevalence rate of cases with CA was 35 per 1000 informative offspring (live-born infants, stillborn fetuses and electively terminated malformed fetuses) between 1980 and 1996 (Czeizel 1997) and about 90% of major CAs were recorded in the HCAR (Czeizel et al. 1993).

## 2.2. The Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA)

Cases with CA including CHD in the HCCSCA were selected from the HCAR. Only those CA cases were selected from the HCAR for the HCCSCA that were reported to the HCAR during the first three months after birth or elective termination of pregnancy. In addition cases with CA-syndromes caused by gene mutations or chromosomal aberrations with preconception origin were excluded.

Population controls were defined as newborn infants without CAs and were selected from the National Birth Registry of the Central Statistical Office for the HCCSCA based on case lists for each quarter of the years from the HCAR. In general, two controls were matched to every case according to sex, birth week, and district of parents' residence. If controls were twins, only one of them was randomly selected as controls for the HCCSCA.

A letter with informed consent was mailed continuously to the address of the mothers of cases and controls immediately after their selection for the HCCSCA and requested that they send us the prenatal maternity logbook, discharge summary of their delivery and every medical record concerning their pregnancy and their child's CA. These documents were sent back within four weeks.

The mean + S.D. time elapsed between the end of pregnancy and return of the "information package" (including logbook, discharge summary, signed informed consent, etc.) in our prepaid envelope was 3.5 + 2.1 and 5.2 + 2.9 months in cases and population controls, respectively.

In addition regional district nurses were asked to visit all non-respondent case mothers and to evaluate the available medical documents. Unfortunately, district nurses could visit only 200 non-respondent (Czeizel et al. 2003) and 600 respondent (Czeizel & Vargha 2004) control mothers in two validation studies because the ethics committee considered this follow-up to be disturbing for the parents of all healthy children.

The necessary information was available for 96.3% of cases (84.4% from replies and 11.9% from visits) and 83.0% of population controls (81.3% from replies and 1.7% from visits). The signed informed consent was sent back by 98% of mothers. The name and address were deleted in 2% of subjects without signed informed consent. The flow of cases and population controls in the HCCSCA was reported previously (Ács et al. 2005). The data of sex and birth outcomes in cases were based on the Notification Form of Cases with CA in the HCAR confirmed by the discharge summary of delivery in the HCCSCA. The sex and birth outcomes of population controls were evaluated by the help of the discharge summary of delivery in the HCCSCA. The gestational age at delivery was calculated in a week from the first day of the last menstrual period while the definition of preterm birth (PTB) was as the time of birth of live-born babies in less than 37 completed gestation weeks. The rate of low birthweight (LBW) newborns (less than 2500 gram) was calculated based on birth weight, while the definition of small for gestational age (SGA) was birth weight less than 2500 g in newborn infants born on 37th gestational week or later.

The method of data collection was changed in 1997 (since all case and control mothers are visited and questioned at home by regional nurses, but these data have not been validated at the time

of this analysis), and it explains that here only the 17 years' dataset of the HCCSCA, 1980-1996 are evaluated.

## 2.3. Study design of cases with CHD

The major evaluation problem of CHDs was that in general cases with CA were reported immediately after birth to the HCAR and about 50% of cases with CHD were reported as unspecified CHD, because the exact diagnosis of CHDs needed further time consuming examinations. The collection of medical data of cases with CA in the HCCSCA was 3.5 + 2.1 months later thus, we could get specified CHD diagnoses in further 20% of cases. The remaining 30% of CHD cases with unspecified diagnosis were expected to have been cared for or had surgical intervention in the pediatric cardiologic institutions in Hungary. Thus the staff of the HCCSCA visited the cardiologic in- and outpatient clinics in 2008 and reviewed the medical records of patients. In cases with unspecified CHD, wherever possible, the diagnoses were modified to specific CHD. In addition, the previous diagnosis of CHD was checked and sometimes modified. If previously reported cases were not identified in the records of pediatric cardiologic institutions, we corresponded with mothers to clarify the fate and/or diagnosis of these cases in 2009 and 2010. However, if these mothers were not found or cases had further unspecified CHD, or mothers refused to collaborate, the cases were excluded from the study.

There were three selection steps in the evaluation of cases with CHD:

- i) Cases with syndromic CHD due to major mutant genes (e.g. Holt-Oram) or chromosomal aberrations (e.g. Down) were excluded from the HCCSCA, and unclassified multiple CAs including CHD were also excluded from the study.
- ii) Cases with CHD were classified according to the system of The Baltimore-Washington Infant Study (Ferencz et al. 1993, Ferencz et al. 1997), including homogeneous structural entities/groups of CHD with a sufficient number of cases.
- iii) Some types of CHD have a wide spectrum of manifestations, including spontaneous closure of ventricular or atrial septal defects, ductus arteriosus, etc. Thus finally only cases with lethal outcomes verified by autopsy record or with documented catheter diagnoses or surgical corrections were included in the study.

Our cases, therefore, represent homogeneous groups of severe manifestations of different entities of CHD.

## 2.4. Statistical analysis

The software GNU R 2.14, RStudio 0.97 version was used for the statistical analysis of data. At the evaluation of quantitative birth outcomes such as gestational age at delivery and birth weight of newborn infants, Student t-test was used. At the evaluation of categorical variables: PTB, LBW and SGA were analyzed by odds ratios (OR) with 95% confidence intervals (CI) in a multivariable unconditional regression model at the comparison of cases and population controls. At the calculation of adjusted OR, maternal age and birth order were considered.

## 3. Results

The number of cases with different CHD-entities/groups and their abbreviations are shown in Table 1. Of 22 CHDs, 17 were CHD-entities, however, 4-4 entities were combined as CTD, RSOD and LSOD groups, respectively, and other rare CHDs were evaluated together in the group of OCHDs while other unspecified complex CHDs (e.g. VSD + ASD) in the group of CCHD. The birth outcomes of the latter two CHD-groups including heterogeneous CHDs will not be evaluated here in detail.

Finally, 3,849 cases with confirmed diagnosis were evaluated, but 15 occurred in stillborn fetuses. The sex (percentage proportion of boys) and twin rate (%) of different CHD-entities/groups were

analyzed in 3,834 live-born cases compared to the Hungarian newborns as reference (51.3%) in Table 1. The proportion of boys was 50.7%, while the rate of twin deliveries was 2.2% in the Hungarian newborns. The sex of cases with total CHD was near to the population reference figure, but their rate of twins was 2 fold higher.

The evaluation of birth outcomes of cases with CHD was based on singletons because 84 twin cases had drastically shorter gestational age and smaller birth weight. Thus finally 3,750 singleton live-born cases with different CHD-entities and groups

were evaluated. Our population-based data set included 37,741 singleton live-born population controls without CA, 1.8% of all live-births in Hungary and their birth outcomes corresponded well to the data of the Hungarian newborn population. Beyond sex of newborns, maternal age and birth order also have effect for birth outcomes. At the calculation of adjusted p value and OR, sex of cases and population controls, maternal age and birth order were considered (Table 2).

**Table 1:** Number of Live-Births, Boys and Twins in Different Study Groups

Study groups	Abbreviation	Total N	Boys		Twins	
			No.	%	No.	%
Hungarian newborns		2,134,150	1,094,017	51.3	1,088	1.1
Ventricular septal defect*	VSD	1,659	801	48.3	28	1.7
Single ventricle	SV	76	40	52.6	4	5.3
Atrial septal defect secundum	ASD-II	471	221	46.9	17	3.6
Common atrioventricular canal	CAVC	79	32	40.5	2	2.5
Patent ductus arteriosus	PDA	181	77	42.5	6	3.3
Common truncus	CT	44	31	70.5	1	2.3
Transposition of great arteries	TGA	307	169	55.0	5	1.6
Tetralogy of Fallot	TF	222	127	57.2	6	2.7
Double outlet of right ventricle	DORV	24	12	50.0	0	0.0
Conotruncal defects	CTD	597	339	56.8	12	2.0
Atresia/stenosis of pulmonary valve	A/SPV	72	37	51.4	0	0.0
Atresia/stenosis of tricuspid valve	A/STV	13	5	38.5	0	0.0
Ebstein's anomaly	EA	7	6	85.7	0	0.0
CAs of pulmonary artery	CAPA	108	60	55.6	1	0.9
Right sided obstructive defects	RSOD	200	108	54.0	1	0.5
Valvular aortic stenosis	VAS	56	37	66.1	0	0.0
Hypoplastic left heart	HLH	76	49	64.6	3	3.9
Coarctation of aorta	COA	113	71	62.8	1	0.9
Other CAs of aorta	OCAA	57	38	66.7	3	5.3
Left sided obstructive defects	LSOD	302	195	64.6	7	2.3
Other isolated CHD	OCHD	186	86	46.2	5	2.7
Other complex CHD	CCHD	83	44	53.0	2	0.2
Total	CHD	3,834	1,943	50.7	84	2.2

\*perimembranous and muscular ventricular septal defects

**Table 2:** Mean Maternal Age and Birth Order in Groups of Singleton Live-Born Cases with Different CHD Groups/Entities and Population Controls (PC) in the HCCSCA.

Study groups	Total N	Maternal age		Birth order	
		Mean	S.D.	Mean	S.D.
PC	37,741	25.4	4.9	1.7	0.9
VSD	1,631	25.6	5.2	1.9	1.2
SV	72	25.9	5.7	1.9	1.0
ASD-II	454	26.0	5.8	2.1	1.3
CAVC	77	26.4	5.4	2.1	1.3
PDA	175	25.7	5.2	2.0	1.4
CT	43	25.1	4.2	2.0	1.2
TGA	302	26.0	5.0	1.9	1.2
TF	216	25.2	5.3	1.8	1.0
DORV	24	26.6	4.3	2.0	0.8
CTD	585	25.7	5.1	1.9	1.1
A/SPV	72	25.8	5.2	1.9	1.2
A/STV	13	25.0	4.1	1.7	1.0
EA	7	24.3	7.6	1.6	1.1
CAPA	107	26.3	5.9	2.1	1.3
RSOD	199	26.0	5.6	2.0	1.2
VAS	56	24.8	4.5	1.9	1.1
HLH	73	25.9	5.4	1.8	1.0
COA	112	25.9	5.6	2.0	1.0
OCAA	54	26.4	6.1	1.9	0.9
LSOD	295	25.8	5.4	1.9	1.0
OCHD	181	26.1	5.7	2.0	1.3
CCHD	81	25.9	5.3	1.8	1.0

Mean gestational age and birth weight of cases with different CHD entities/groups were compared to population controls, and differences were expressed in p values (Table 3). Cases with EA are not evaluated due to their limited number, thus the birth outcomes of 16 CHD-entities are analyzed.

The first impression is that the severity of CHD-entities did not correlate with the shorter mean gestational age: there is no difference in mean gestational age between severe TGA, DORV, SV, TF and population controls, while the shortest gestational age was observed in cases with A/STV, ASD-II, OCAA, and PDA.

All 16 CHD-entities had lower mean birth weight than population controls; the difference did not reach the level of significance only in cases with DORV. The shortest gestational age associated with a lower mean birth weight in cases with A/STV, PDA, ASD-II, and OCAA. The largest mean birth weight was recorded in the groups of TGA and DORV. Another impression is that the well-known relation between gestational age and birth weight is not obvious in some CHD-entities. For example, the combined mean gestational age was 39.4 wk in the group of cases with CTD, similar to the figure of population controls, nevertheless their





country region, when each individual child was examined personally by a pediatric cardiologist in 1971-1972 or the autopsy report was evaluated in dead children (Mészáros et al. 1975). Thus the Hungarian rate of CHDs corresponded to the internationally reported figures (Hoffman et al. 2004, Reller et al. 2008, Dolk et al. 2011). In general, the sex of cases with different CHD-entities was also similar in our material than in other studies (Ferencz et al. 1993, Reller et al. 2008). However, our study showed the importance of sex in the birth outcomes of some CHD-entities.

The birth outcomes of cases with different CHD-entities/groups were presented in The Baltimore-Washington Infant Study 1981-1989 (Ferencz et al. 1997). For example, mean gestational age and mean birth weight was  $38.1 \pm 0.3$  wk and  $2,939 \pm 60$  g in cases with ASD-II while these figures were  $38.2 \pm 3.1$  wk and  $2,870 \pm 737$  g in our material, but the mean gestational age and birth weight of controls was  $39.6 \pm 0.1$  wk and  $3,351 \pm 10$  in The Baltimore-Washington Infant Study. The OR (95% CI) for SGA was 2.7 (1.7-4.1) in The Baltimore-Washington Infant Study [13] and 3.5 (2.4-4.9) in our material, respectively.

TGA was also not associated with a higher rate of PTB in The Baltimore-Washington Infant Study (Ferencz et al. 1997) as in our study, and the birth outcomes of cases with LSOG group were also similar in the two study material.

Only mean gestational age and birth weight were published in Metropolitan Atlanta Congenital Defects Program (Reller et al. 2008). The mean gestational age was 38.0 wk in cases with PDA similar to 38.3 wk in our material. However, there was some difference in the mean gestational age (38.5 vs. 39.5 wk) of cases with TGA in there and our material though the difference in mean birth weight was small (3,173 vs. 3,160 g).

Some difference in the birth outcomes of cases with different CHD-entities may be connected with the different ascertainment and selection of cases in different studies. We evaluated the severe cases with lethal outcome or after catheter diagnoses or surgical correction, thus or cases represented the tip of an iceberg. Thus the difference in birth outcomes of cases with different severe CHD-entities suggests the different pathogenesis of CHD-entities.

The question is why several CHD-entities are manifesting more frequently in newborns with PTB and mainly with LBW/SGA, because intrauterine growth restriction was observed in most CHD-entities. Three options are worth discussing.

- i) It is difficult to believe that a localized CA in the heart such as ASD-II can induce intrauterine fetal growth restriction because the fetal heart has a passive role before birth without pulmonary circulation. Nevertheless, our data indicate the effect of a fetal heart defects for fetal development. First Rosenthal (Rosenthal 1996) suggested that intrauterine life hemodynamic alterations due to the CHD may affect size and growth pattern of fetuses.
- ii) Possible confounding factors such as maternal age, birth order and socioeconomic status have to evaluate as well. Maternal age and birth order were considered for the calculation of adjusted p and OR values in this study. The poor socioeconomic status is associated with lower birth weight in general and e.g. in cases with VSD (Vereczkey et al. 2012). However, this effect cannot explain the differences among CHD-entities/groups. Drinking and mainly smoking habits are also important. However, our studies showed a similar rate of these lifestyle factors in the mothers of cases with CHD, thus these adverse lifestyle factors cannot explain totally the difference in fetal growth restriction of fetuses (Czeizel et al. 2003). Maternal diseases and related drug treatments were also analyzed without any association with higher risk of intrauterine growth restriction of cases with CHD (Ács et al. 2010).
- iii) CHDs and intrauterine growth restriction as two developmental errors may have a common route. Recently, the association of some gene polymorphisms with fetal growth and birth weight was shown (Freathy et al. 2010), thus it

would be interesting to test the effect of these gene variants in the origin of CHDs.

The strengths of our study are connected with the large population-based data set of the HCCSCA, including 3,750 singleton live-born cases with CHD and 37,741 singleton live-born population controls without CAs in the ethnically homogeneous Hungarian (Caucasian) population. Cases with CHD were reported by medical doctors and reported diagnoses were critically checked in the HCAR (Czeizel 1997, Czeizel et al. 2014). In addition, the validity of CHD-diagnoses has been improved due to the available medical records on 3.5 + 2.1 months after the birth in the data set of the HCCSCA (Czeizel et al. 2001) and finally due to the follow-up of our cases in cardiologic institutes. We did our best to work with cases with CHD-entities as homogeneous as possible; therefore, cases with syndromic/multiple CA including CHD were excluded and finally only cases after catheter diagnosis or surgical correction or lethal outcome based on medical documents were planned to evaluate in the study. The data of birth outcomes were medically recorded.

However, there were some weaknesses of our study. (i) The diagnosis of CHDs was accomplished during the study period (1980-1996), i.e. mainly before the spectacular improvement of medical technology, particularly echocardiography. However, our cases with CHD were selected until the end of third postnatal month and mainly surgically corrected or lethal cases were included in the study, thus mainly more severe CHDs cases were evaluated. (ii) Another weakness of our study is the lack of data regarding smoking and drinking habit in the total material of mothers of cases and controls. Our previous validation study showed the low reliability of retrospective self-reported information on these habits in control mothers and mainly in case mothers (Czeizel et al. 2003). Thus only the family consensus data after the home visit in a subsample of cases and controls were evaluated; therefore, we cannot consider the smoking and drinking habit as confounder in the mothers of all cases and controls.

In conclusion, our findings showed significant difference in the birth outcomes of cases with CHD compared to their population controls. The higher rate of LBW and SGA indicates intrauterine fetal growth restriction in several CHD-entities and the sex of cases has some effect for their fetal development. The intrauterine growth restriction as a general developmental process may have some role in the origin of some CHD-entities. Nevertheless, birth outcomes of different CHD-entities were different and these findings confirmed the different pathogenesis of CHD-entities.

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## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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