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. cardiologic 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	1943	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

mean birth weight was lower nearly 200 g due to mainly CT and TF.

Mean gestational age and birth weight were evaluated in male and female singletons separately as well (Table 3). In the population control group, the mean gestational age was 0.1 wk shorter while the mean birth weight was 137 g smaller in males than in females. In general mean gestational age was shorter and mean birth weight was lower in both sexes of cases than in population controls. However, there were four exceptions (i) there was a longer gestational age in both male and female cases with TGA, (ii) mean gestational age was longer in female cases with DORV than in population controls, (iii) the mean birth weight was larger in male cases with DORV and (iv) mean birth weight was similar in males with A/SPV to the mean birth weight in the male population controls. The mean birth weight of female cases was smaller than in population controls in all CHD-entities/groups.

Table 4 summarized the figures of categorical birth outcomes, i.e. rate of PTB, LBW and SGA in cases with different CHD-entities/groups compared with the figures of population controls, and the differences are expressed in OR with 95% CI. Of 16 CHD-entities, 6 (PDA, ASD-II, CAVC. HLH, CAPA and VSD) had higher rate of PTB. Of 16 CHD-entities, 14 showed higher rate of LBW but the two exceptional (DORV and VAS) had also

higher rate of LBW, but the difference did not reach the level of significance though was near to it. The rate of SGA was also higher in most CHD-entities. Only four LSOD-entities were exceptional.

In the next step, categorical birth outcomes of cases were differentiated according to sex (Table 5 and 6). ASD-II and PDA showed a higher rate of PTB in both sexes, while it occurred only in females with CAVC. The higher rate of LBW was observed in most CHD-entities of both sexes, particularly in male cases. Only VAS was exceptional in both sexes, in addition TGA, DORV and A/SPV in males, SV. A/STV, COA and OCAA in females did not show a significantly higher rate of LBW. The rate of SGA was also higher in most CHD-entities, except in male cases with DORV, A/SPV and three entities of LSOD: VAS, HLH, COA and female cases with SV, CAVC, A/STV and four entities of LSOD.

The rate of PTB was higher in male cases while LWB and SGA were higher in females. In cases with VSD, ASD-II, RSOG and LSOD groups, the rate of PTB, LBW and SGA was higher in females than in males. The rate of LBW and SGA was higher in female cases with PDA and CTD group, but the rate of PTB was higher in males.

Table 3: Number of Singletons, in Addition Male and Female Singletons and Their Mean Gestational Age at Delivery and Mean Birth Weight in Different Study Groups and Population Controls (PC) As Reference (R)

Study Groups	Total N	Gestational age Mean S.D. p=	Birth weight Mean S.D. p=	Male gestational age N Mean S.D. p=	Male birth weight Mean S.D. p=	Female gestational age N Mean S.D. p=	Female birth weight Mean S.D. p=
PC	37,741	39.4 2.0 R	3,282 506 R	24,536 39.4 2.0 R	3,330 508 R	13,205 39.3 2.1 R	3,193 489 R
VSD	1,631	39.1 2.3 0.000	3,059 590 0.000	784 39.2 2.3 0.001	3,141 608 0.000	847 39.1 2.3 0.187	2,983 564 0.000
SV	72	39.3 2.4 0.918	3,090 549 0.003	38 39.0 2.4 0.246	3,136 590 0.027	34 39.6 2.4 0.252	3,038 504 0.117
ASD-II	454	38.2 3.1 0.000	2,870 737 0.000	218 38.3 2.9 0.000	2,986 699 0.000	236 38.1 3.3 0.000	2,762 757 0.000
CAVC	77	38.7 2.5 0.006	3,024 635 0.000	31 39.1 2.2 0.530	3,176 666 0.102	46 38.4 2.6 0.006	2,922 599 0.000
PDA	175	38.3 3.2 0.000	2,701 764 0.000	74 37.9 3.4 0.000	2,724 789 0.000	101 38.6 3.0 0.004	2,685 749 0.000
CT	43	38.5 3.3 0.012	2,876 738 0.000	30 38.9 3.2 0.299	2,962 772 0.000	13 37.5 3.5 0.003	2,678 634 0.000
TGA	302	39.5 1.9 0.115	3,160 584 0.000	166 39.6 2.0 0.303	3,264 588 0.097	136 39.5 1.8 0.160	3,033 556 0.000
TF	216	39.3 1.9 0.882	3,009 532 0.000	123 39.3 1.9 0.836	3,067 570 0.000	93 39.3 1.8 0.915	2,931 470 0.000
DORV	24	39.4 2.0 0.913	3,171 563 0.301	12 39.3 1.6 0.825	3,409 426 0.587	12 39.5 2.4 0.665	2,933 597 0.073
CTD	585	39.4 2.0 0.699	3,083 583 0.000	331 39.4 2.1 0.802	3,169 605 0.000	254 39.3 2.0 0.609	2,973 536 0.000
A/SPV	72	39.3 2.4 0.987	3,094 706 0.007	37 39.6 2.2 0.398	3,334 578 0.596	35 38.9 2.6 0.477	2,841 746 0.000
A/STV	13	37.3 3.7 0.000	2,616 899 0.000	5 36.0 5.2 0.000	2,450 1,416 0.000	8 38.1 2.5 0.166	2,720 455 0.011
EA	7	38.3 3.1 0.139	2,700 609 0.002	6 38.2 3.4 0.111	2,725 663 0.004	1 39.0 0.0 0.801	2,550 0 0.154
CAPA	107	38.9 2.7 0.039	3,009 716 0.000	60 38.9 2.4 0.075	3,039 660 0.000	47 38.9 3.1 0.308	2,972 787 0.003
RSOD	199	38.9 2.7 0.006	3,003 727 0.000	108 39.0 2.6 0.038	3,095 705 0.000	91 38.8 2.9 0.107	2,895 743 0.000
VAS	56	39.1 2.4 0.545	3,038 529 0.001	37 39.0 2.1 0.284	3,051 516 0.002	19 39.4 3.0 0.635	3,013 566 0.184
HLH	73	38.7 2.9 0.004	2,960 644 0.000	47 38.7 3.0 0.018	3,000 659 0.000	26 38.6 2.6 0.108	2,888 622 0.002
COA	112	38.9 2.6 0.035	3,083 615 0.000	71 38.8 2.6 0.018	3,120 651 0.001	41 39.1 2.6 0.715	3,018 548 0.034
OCAA	54	38.3 2.7 0.001	2,997 692 0.000	37 38.4 2.3 0.004	3,008 646 0.000	17 38.2 3.5 0.066	2,973 805 0.153
LSOD	295	38.8 2.6 0.000	3,028 621 0.000	192 38.7 2.6 0.000	3,056 626 0.000	103 38.9 2.8 0.118	2,977 611 0.000
OCHD	181	38.2 3.0 0.000	2,828 731 0.000	83 38.4 2.9 0.000	2,963 703 0.000	98 38.0 3.0 0.000	2,714 739 0.000
CCHD	81	39.1 2.4 0.305	3,053 603 0.000	42 38.5 2.6 0.003	3,045 662 0.000	39 39.6 2.0 0.095	3,062 540 0.114
Total	3,750	38.9 2.5 0.000	3,007 643 0.000	1,901 38.9 2.5 0.000	3.092 646 0.000	1,849 38.6 2.6 0.000	2,920 629 0.000

Table 4: Number of Singletons, and Rates of Their Preterm Birth (PTB), Low Birthweight (LBW) and Small for Gestational Age (SGA) in Different Study Groups and Population Controls (PC) As Reference

Study groups	Total N	Preterm birth (PTB) No. % OR, 95% CI	Low birthweight (LBW) No. % OR, 95% CI	Small for gestational age (SGA) No. % OR, 95% CI
PC	37,754	3,385 9.0 Reference	2,023 5.4 Reference	816 2.2 Reference
VSD	1,631	192 **11.8** **1.24, 1.06-1.44**	257 15.8 **2.98, 2.58-3.43**	146 **9.0** **4.06, 3.36-4.87**
SV	72	8 11.1 1.13, 0.56-2.24	12 16.7 **3.10, 1.57-5.63**	5 **6.9** **3.01, 1.05-6.81**
ASD-II	454	100 **22.0** **2.60, 2.05-3.25**	120 26.4 **5.50, 4.40-6.84**	37 8.1 **3.49, 2.42-4.88**
CAVC	75	15 **19.5** **2.20, 1.04-3.79**	16 20.8 **4.00, 2.20-6.87**	9 12.0 **5.44, 2.51-10.44**
PDA	175	42 **24.0** **2.85, 1.98-4.02**	66 37.7 **9.55, 6.92-13.08**	34 19.4 **9.73, 6.51-14.15**
CT	43	8 18.6 2.02, 0.86-4.18	15 34.9 **8.62, 4.41-16.18**	10 23.3 **12.92, 5.97-25.63**
TGA	302	23 7.6 0.79, 0.50-1.19	33 10.9 **2.02, 1.37-2.87**	26 8.6 **4.04, 2.62-5.97**
TF	216	14 6.5 0.66, 0.36-1.09	30 13.9 **2.68, 1.77-3.91**	24 11.1 **5.33, 3.37-8.06**
DORV	24	2 8.3 0.86, 0.14-2.96	4 16.7 3.26, 0.93-8.79	4 16.7 **8.76, 2.52-23.55**
CTD	585	47 8.0 0.83, 0.60-1.11	82 14.0 **2.69, 2.10-3.40**	64 **10.9** **5.27, 3.98-6.86**
A/SPV	72	11 15.3 1.60, 0.79-2.94	13 18.1 **3.21, 1.66-5.74**	8 11.1 **4.72, 2.07-9.39**
A/STV	13	2 15.4 1.80, 0.28-6.84	5 38.5 **11.77, 3.43-36.5**	4 30.8 **20.71, 5.47-65.50**
EA	7	1 14.3 1.72, 0.09-10.39	2 28.6 **7.84, 1.09-37.77**	1 14.3 8.05, 0.42-48.22
CAPA	107	18 **16.8** **1.93, 1.12-3.15**	26 24.3 **4.86, 3.03-7.56**	13 12.1 **5.17, 2.72-9.03**
RSOD	199	32 **16.1** **1.80, 1.20-2.60**	46 23.1 **4.61, 3.24-6.43**	26 **13.1** **5.79, 3.70-8.69**
VAS	56	5 8.9 0.88, 0.30-2.02	7 12.5 2.17, 0.89-4.56	3 5.4 2.22, 0.54-6.10
HLH	73	13 **17.8** **2.13, 1.11-3.78**	11 15.1 **3.02, 1.49-5.57**	2 2.7 1.21, 0.20-3.89
COA	112	13 11.6 1.27, 0.67-2.19	14 12.5 **2.32, 1.26-3.95**	5 4.5 1.89, 0.67-4.22
OCAA	54	8 14.8 1.49, 0.65-3.01	12 22.2 **4.04, 2.01-7.55**	4 7.4 2.91, 0.87-7.20
LSOD	295	39 *13.2* *1.42, 1.00-1.98*	44 14.9 **2.77, 1.97-3.80**	14 **4.7** **1.99, 1.10-3.31**
OCHD	181	44 **24.3** **3.02, 2.12-4.25**	52 28.7 **6.25, 4.43-8.68**	19 10.5 **4.51, 2.68-7.17**
CCHD	81	9 11.1 1.25, 0.58-2.37	11 13.6 **2.66, 1.32-4.86**	6 7.4 **3.40, 1.31-7.26**
Total	3,750	528 14.1 **1.51, 1.36-1.67**	706 18.8 **3.68, 3.34-4.04**	360 **9.6** **4.39, 3.85-5.00**

Bold numbers show significant associations

Table 5: Number of Male Singletons, and Rates of Their Preterm Birth (PTB), Low Birthweight (LBW) and Small for Gestational Age (SGA) in Different Study Groups and Population Controls (PC) As Reference

Study groups	Total N	Preterm birth (PTB)			Low birthweight (LBW)			Small for gestational age (SGA)		
		No.	%	OR, 95% CI	No.	%	OR, 95% CI	No.	%	OR, 95% CI
PC	25,540	1,996	8.1	Reference	1,155	4.7	Reference	432	1.8	Reference
VSD	784	83	10.6	1.25, 0.98-1.57	117	14.9	3.29, 2.66-4.03	73	9.3	5.39, 4.12-6.95
SV	38	5	13.2	1.52, 0.52-3.60	7	18.4	4.05, 1.61-8.87	3	7.9	4.38, 1.05-12.35
ASD-II	218	39	17.9	2.23, 1.54-3.14	45	20.6	4.50, 3.16-6.29	15	6.9	3.61, 2.02-6.00
CAVC	31	4	12.9	1.53, 0.45-3.95	6	19.4	4.30, 1.57-9.99	5	16.1	9.84, 3.29-23.98
PDA	74	20	27.0	3.85, 2.23-6.39	27	36.5	10.86, 6.59-17.57	11	14.9	9.18, 4.53-16.95
CT	30	4	13.3	1.41, 0.41-3.67	11	36.7	10.19, 4.58-21.60	8	26.7	18.80, 7.74-41.29
TGA	166	16	9.6	1.15, 0.65-1.87	14	8.4	1.74, 0.95-2.92	9	5.4	3.09, 1.45-5.76
TF	123	9	7.3	0.81, 0.38-1.52	18	14.6	3.22, 1.87-5.24	14	11.4	6.61, 3.58-11.31
DORV	12	1	8.3	0.84, 0.05-4.93	0	00.0	0.00, 0.00-1.21	0	0.0	0.00, 0.00-1638.50
CTD	331	30	9.1	1.04, 0.69-1.49	43	13.0	2.78, 1.97-3.82	31	9.4	5.43, 3.63-7.86
A/SPV	37	5	13.5	1.56, 0.53-3.71	3	8.1	1.50, 0.36-4.24	1	2.7	1.29, 0.07-6.05
A/STV	5	1	20.0	3.56, 0.18-24.27	3	60.0	44.91, 7.34-344.8	2	40.0	47.13, 6.14-288.44
EA	6	1	16.7	2.18, 0.11-14.02	2	33.3	11.52, 1.54-61.26	1	16.7	12.86, 0.66-81.52
CAPA	60	9	15.0	1.91, 0.87-3.72	13	21.7	4.87, 2.49-8.89	7	11.7	5.80, 2.35-12.24
RSOD	108	16	14.8	1.86, 1.04-3.09	21	19.4	4.39, 2.62-7.02	11	10.2	5.30, 2.63-9.64
VAS	37	3	8.1	0.87, 0.21-2.45	4	10.8	2.11, 0.62-5.40	2	5.4	2.80, 0.45-9.35
HLH	47	7	14.9	1.93, 0.78-4.08	6	12.8	2.91, 1.10-6.42	1	2.1	1.16, 0.07-5.36
COA	71	9	12.7	1.60, 0.74-3.08	9	12.7	2.70, 1.24-5.22	2	2.8	1.39, 0.23-4.47
OCAA	37	5	13.5	1.54, 0.52-3.65	8	21.6	4.82, 2.03-10.21	2	5.4	4.26, 1.02-11.99
LSOD	192	24	12.5	1.51, 0.95-2.28	27	14.1	3.02, 1.95-4.51	8	4.2	2.16, 0.97-4.16
OCHD	83	19	22.9	3.1, 1.79-5.12	18	21.7	4.88, 2.76-8.20	5	6.0	3.04, 1.06-6.89
CCHD	42	7	16.7	2.3, 0.93-4.91	7	16.7	3.90, 1.57-8.39	4	9.5	5.36, 1.59-13.56
Total	1,901	247	13.0	1.55, 1.34-1.79	318	16.7	3.69, 3.22-4.23	166	8.7	4.93, 4.07-5.94

Bold numbers show significant associations

Table 6: Number of Female Singletons, and Rates of Their Preterm Birth (PTB), Low Birthweight (LBW) and Small for Gestational Age (SGA) in Different Study Groups and Population Controls (PC) As Reference

Study groups	Total N	Preterm birth (PTB)			Low birthweight (LBW)			Small for gestational age (SGA)		
		No.	%.	OR, 95% CI	No.	%	OR, 95% CI	No.	%	OR, 95% CI
PC	13,214	1,389	10.5	Reference	864	6.5	Reference	384	2.9	Reference
VSD	847	109	12.9	1.13, 0.91-1.38	140	16.5	2.46, 2.01-2.99	73	8.6	2.80, 2.14-3.63
SV	34	3	8.8	0.74, 0.18-2.10	5	14.7	2.11, 0.71-5.11	2	5.9	1.81, 0.29-6.06
ASD-II	236	61	25.8	2.37, 1.96-3.59	75	31.8	5.71, 4.24-7.63	22	9.3	2.92, 1.80-4.52
CAVC	46	11	23.9	2.40, 1.15-4.63	10	21.7	3.42, 1.58-6.80	4	8.7	2.86, 0.85-7.21
PDA	101	22	21.8	2.06, 1.24-3.28	39	38.6	7.60, 4.95-11.52	23	22.8	8.29, 4.99-13.27
CT	13	4	30.8	3.77, 1.01-11.70	4	30.8	7.34, 1.94-23.32	2	15.4	7.04, 1.06-27.55
TGA	136	7	5.1	0.43, 0.18-0.86	19	14.0	2.13, 1.26-3.44	17	12.5	4.47, 2.55-7.36
TF	93	5	5.4	0.47, 0.17-1.05	12	12.9	2.09, 1.07-3.73	10	10.8	4.01, 1.92-7.49
DORV	12	1	8.3	0.73, 0.04-3.81	4	33.3	7.66, 1.97-25.58	4	33.3	18.67, 4.78-63.42
CTD	254	17	6.7	0.58, 0.34-0.92	39	15.4	2.50, 1.73-3.52	33	13.0	4.88, 3.27-7.08
A/SPV	35	6	17.1	1.51, 0.56-3.45	10	28.6	4.69, 2.09-9.74	7	20.0	7.15, 2.82-15.84
A/STV	8	1	12.5	1.02, 0.05-5.94	2	25.0	3.81, 0.53-17.63	2	25.0	9.52, 1.34-43.88
EA	1	0	0.0	0.00, 0.00- inf	0	0.0	0.00, 0.00-inf	0	0.0	0.00, 0.00-Inf
CAPA	47	9	19.1	1.88, 0.85-3.76	13	27.7	4.76, 2.37-9.03	6	12.8	4.41, 1.65-9.88
RSOD	91	16	17.6	1.64, 0.91-2.76	25	27.5	4.60, 2.80-7.35	15	16.5	5.84, 3.17-10.09
VAS	19	2	10.5	0.89, 0.14-3.14	3	15.8	2.38, 0.54-7.47	1	5.3	1.68, 0.09-8.44
HLH	26	6	23.1	2.45, 0.89-5.84	5	19.2	3.12, 1.02-7.89	1	3.8	1.22, 0.07-5.87
COA	41	4	9.8	0.83, 0.25-2.09	5	12.2	1.83, 0.62-4.32	3	7.3	2.46, 0.59-6.93
OCAA	17	3	17.6	1.44, 0.33-4.50	4	23.5	3.07, 0.84-9.03	1	5.9	1.47, 0.08-7.43
LSOD	103	15	14.6	1.30, 0.72-2.19	17	16.5	2.45, 1.39-4.08	6	5.8	1.81, 0.70-3.86
OCHD	98	25	25.5	2.74, 1.69-4.31	34	34.7	6.62, 4.23-10.19	14	14.3	4.61, 2.45-8.06
CCHD	39	2	5.1	0.43, 0.07-1.43	4	10.3	1.54, 0.46-3.92	2	5.1	1.71, 0.28-5.67
Total	1,849	281	15.2	1.37, 1.19-1.58	388	21.0	3.34, 2.92-3.83	194	10.5	3.53, 2.94-4.24

Bold numbers show significant associations

4. Discussion

The major findings of the study suggested that in general cases with different CHD-entities had a shorter gestational age at delivery and lower mean birth weight, and these variables associated with a higher rate of PTB and particularly with a much higher rate of LBW and SGA.

Three CHD-entities and/or groups are worth more discussion.

i) Cases with ASD-II had localized small defect of an atrial septum (Fyler 1992, Vereczkey et al. 2013), nevertheless, their mean gestational age was 1.2 wk shorter and their mean birth weight was 412 g smaller than population controls. The rate of PTB, LBW and SGA was 2.4. 4.9 and 3.7 fold higher in cases with ASD-II than in population controls, respectively. Thus intrauterine growth restriction was characteristic for ASD-II, mainly in female cases. There was no robust difference in the mean gestational age of males and females (1.1 vs. 1.2 wk), but the mean birth weight (431 g) was smaller in females than in males (314 g). The rate of PTB (2.5 vs. 2.2 fold) and LBW (4.9 vs. 4.4 fold) was higher in female cases that in male cases compared to their appropriate sex controls. However, this difference was reverse in the rate of SGA (3.2 vs. 3.8 fold).

ii) TGA is severe CHD-entity, nevertheless, newborns with TGA had somewhat longer gestational age (0.1 wk), but mean birth weight was 66 and 160 g smaller in male and female cases than in male and female controls, respectively. There was no higher rate of PTB in male and female cases, LBW rate was higher only in female cases. However, SGA showed a higher rate in both sexes. Thus TGA had no effect for the gestational age and PTB, but TGA was associated with intrauterine growth restriction, mainly in female cases.

iii) In general, the four types of LSOD had no higher rate of PTB in male and female cases, and only HLH had a higher rate of LBW in both sexes. In addition, the rate of LBW was higher in males with COA and OCAA, while higher rate of SGA occurred only in male cases with OCAA. Thus intrauterine growth restriction occurred mainly in males.

The birth prevalence of CHDs was 7.06 + 0.91 per 1000 in Budapest, 1963-1965 based on the HCAR completed with active search of records in all pediatric and pathologic institutions (Czeizel et al. 1972). However, the birth prevalence of CHDs was 10.2 + 2.1 per 1000 in a Hungarian population-based study of a

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 ± 0.3 wk and $2,939 \pm 60$ g in cases with ASD-II while these figures were 38.2 ± 3.1 wk and 2.870 ± 737 g in our material, but the mean gestational age and birth weight of controls was 39.6 ± 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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