

# **Birth outcomes of cases with conotruncal defects of heart - a population-based case-control study**

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## **Abstract**

*Objective.* In general the previous epidemiological studies evaluated cases with congenital heart defects (CHDs) together. However, different CHD-entities have different etiology, but in the vast majority of patients the underlying causes are unclear. The concept of our project is to evaluate the possible etiological factors in the origin of CHD-entities as homogeneous as possible. The aim of this study is to describe the birth outcomes of 4 different types of cases with conotruncal defects (CTDs), i.e. common truncus (truncus arteriosus), transposition of great vessels, tetralogy of Fallot, and double-outlet right ventricle.

*Methods.* Pregnancy/birth outcomes of 597 live-born cases with CTD, of 902 matched controls and 38,151 all controls without any defects were evaluated in the population-based large dataset of the Hungarian Case-Control Surveillance of Congenital Abnormalities completed by socio-demographic variables of their mothers.

*Results.* There was a male excess in cases with CTD with usual gestational age and preterm birth rate (except in cases with common truncus), but their mean birth weight was smaller and had a high rate of low birthweight. These data indicate intrauterine growth restriction of fetuses affected with CTD with some sex-difference and the birth outcomes also showed some difference among the 4 types of CTD cases.

*Conclusions.* Fetal CTD had no effect for gestational age at delivery but CTD associated with an obvious risk for fetal development inducing intrauterine growth restriction.

**Keywords:** congenital heart defects, conotruncal defect, common truncus (truncus arteriosus), transposition of great vessels, tetralogy of Fallot, double-outlet right ventricle, male excess, intrauterine growth restriction, population-based case-control study

## Introduction

Among structural birth defects, i.e. congenital abnormalities (CAs), CAs of heart and great vessels, the so-called *congenital heart defects (CHDs)* represent the most common group. The birth prevalence of cases with CHD was between 4 and 50 per 1000 live-births in different studies because their occurrence depends on the age at examination, the sensitivity of the examination technique, the case definition and the types of CHDs included [1-7]. A Hungarian population-based study of 2,259 children based on the pediatric cardiologic examination and/or the evaluation of autopsy report of each individual child, birth prevalence of CHDs was found as 10.2 per 1000 [8].

The care of infants/children with CHD has been revolutionized over the last decades, but their underlying causes have been obscured [9]. The strategies for prevention of CHDs cannot be developed without the knowledge of their risk or protective factors. Recent progress in human genetics has resulted in the identification of several genes causing CHDs [10], however, the role of possible environmental factors in the origin of CHDs in the vast majority of patients is unclear. Thus the aim of our project is to evaluate the possible etiological factors in the origin of CHDs in order to achieve the final goal: to prevent these CAs.

CHDs cannot be regarded as a single homogeneous CA-group because they have different manifestations, severity and etiology, in addition teratogenic factors do not uniformly increase the rates of all CHDs but rather tends to increase the occurrence of one or a limited number of specific CHDs [11]. Thus our study design was to differentiate CHD-types according to the recently proposed mechanistic classification of CHDs [12-15]. This recent classification split subtypes previously clinically same CHD- types such in ventricular septal defects [14]. However, the evaluation of embryonic development and maldevelopment of heart and great vessels helped to combine some previously clinically different CHD-entities into one pathogenetic group such as transposition of great arteries, common truncus

(truncus arteriosus), tetralogy of Fallot, and double-outlet right ventricle into one pathogenetic subgroup with the name of *conotruncal defects* (CTDs). CTDs represent the major anatomic phenotypes of outflow tract abnormalities, i.e. disturbances in the ventriculo-arterial portion of the ascending limb of the primitive S-shaped cardiac loop (the so-called conus or bulbus cordis) which will become septated by ridges derived from the endocardial cushions and by the aortico-pulmonary septum respectively, to form the divided arterial outflow from the right and left ventricles and of the pulmonary artery and aorta [12-15].

The main objective of our study is to evaluate the possible risk factors in the origin of 4 CTD-types in the population-based Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) [16]. However, first here we describe the birth outcomes of cases with different CTD-types and the socio-demographic features of their mothers.

## **MATERIALS AND METHODS**

The HCCSCA is based on the comparison of the exposures in the study pregnancy of mothers of cases and controls.

### *The Hungarian Case-Control Surveillance System of Congenital Abnormalities*

*Cases* with CA including CTD in the HCCSCA were selected from the Hungarian Congenital Abnormality Registry (HCAR) [17]. The reporting of cases with CA is mandatory for physicians to the HCAR, and most 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 was mandatory for all infant deaths and common (80%) in stillborn fetuses during the study period. Pathologists sent a copy of the autopsy report to the HCAR if defects were identified in stillbirths and infant deaths. Since 1984 prenatal diagnostic centers were also asked to

report malformed fetuses diagnosed prenatally with or without elective termination of pregnancy to the HCAR. The recorded total (birth + fetal) prevalence of cases with CA was 35 per 1000 *informative offspring* (live-born infants, stillborn fetuses and electively terminated malformed fetuses) between 1980 and 1996 [17] and about 90% of major CAs were recorded in the HCAR [18].

Cases reported to the HCAR after the first 3 months of births or termination of pregnancies (23% of all cases, affected mainly with mild CA) and cases with CA-syndromes caused by gene mutations or chromosomal aberrations with preconception origin were excluded from the HCCSCA.

The so-called *controls* were defined as newborn infants without CA. 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 every case according to sex, birth week in the year when the case was born and district of parents' residence. If controls were twin, only one of these twin-pairs was selected randomly for the HCCSCA.

A structured questionnaire with an explanatory letter and printed informed consent was mailed continuously to the address of mothers immediately after the selection of cases and controls for the HCCSCA. Mothers were also requested to send us the prenatal maternity logbook, discharge summary of their deliveries and every medical record of their child's CA. The questionnaire requested information on maternal characteristics (demographic data, history of previous pregnancies, etc.) and pregnancy complications.

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

In addition regional district nurses were asked to visit all non-respondent case mothers and to help them to fill-in the same questionnaire used in the HCCSCA and to evaluate the available medical documents. Unfortunately district nurses could visit only 200 non-respondent and 600 respondent control mothers in two validation studies [19, 20] because the ethics committee considered this follow-up to be disturbing for the parents of all healthy children. Another validation study showed the low reliability of retrospective maternal self-reported information regarding smoking and alcohol drinking during the study pregnancy [21]. The number of smokers and alcohol drinkers during the study pregnancy therefore were evaluated only in those mothers, who were visited and questioned at home, but these data were completed on the basis of cross interview of family members living together, and finally the so-called family consensus was recorded. The smoking habit was evaluated on the number of cigarettes per day while three groups of drinking habit were differentiated: abstinent or occasional drinkers (less than one drink per week), regular drinkers (from one drink per week to daily one drink), and hard drinkers (more than one drink per day).

The necessary information was available for 96.3% of cases (84.4% from replies and 11.9% from visits) and 83.0% of 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 controls in the HCCSCA was reported previously [22].

The data of birth outcomes were based on the Notification Form of Cases with CA in the HCAR confirmed by the discharge summary of delivery and maternal information in the questionnaire. The birth outcomes of controls were evaluated by the help of the latter two data sources. The gestational age was calculated from the first day of the last menstrual period. The rate of low birthweight (less than 2500 gram) and large birth weight (4500 or more g) newborns, in addition the rate of preterm births (less than 37 completed gestation weeks or

less than 259 days) and postterm birth (42 or more weeks) were estimated on the basis of gestational age at delivery and birth weight on the basis of discharge summaries of deliveries in pregnant women. Measurements of birthweight as the indicators of fetal growth are expressed in relation to specified gestation weeks.

Among maternal characteristics, age and birth order (parity) were recorded in the HCAR but these variables were checked in the HCCSCA completed by pregnancy order, marital and employment status based on the prenatal maternity logbook and maternal questionnaire. The maternal employment is good indicator of socioeconomic status in Hungary [23].

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.

#### *Study design of CTD*

The major problem of cases with CHD was that about 50% of these cases were reported to the HCAR as unspecified CHD, because the exact diagnosis of CHD needed further time consuming examinations. The collection of medical, personal and exposure data of cases with CA in the HCCSCA was  $3.5 \pm 2.1$  months later thus we were able to get specified CHD diagnoses in further 20% of cases. However, the rest, i.e. nearly 30% of our CHD cases had no specified diagnoses in the HCCSCA. We supposed that most cases with CHD were cared or had surgical intervention in the pediatric cardiologic institutions in Hungary, therefore one of us (M. Cs-Sz.) visited these cardiologic in- and outpatients clinics in 2008. Medical records were reviewed and the previous diagnosis of specified CHDs was checked (and corrected it if necessary) and the previous unspecified CHDs were modified to specified CHD diagnoses.

At the evaluation of CTDs we had 3 selection steps.

I. Cases with syndromic CTD due to major mutant genes such as CA-syndromes (e.g. Holt-Oram) or chromosomal aberrations (e.g. Down syndrome) were excluded from the HCCSCA. Unidentified multiple CAs including CTD were also excluded in the study. The group of CTD belongs to the complex CAs (more than one CA in the same organ, e.g. heart) in the group of isolated CAs, these cases were planned to include the study.

II. Only cases with well-defined diagnosis of four well-known types of CTDs were included to the study:

(i) *Truncus arteriosus communis* (i.e. common arterial trunk) (TAC) is a CHD in which truncus arteriosus is not properly differentiated into the two great arteries. One large single artery receiving blood from both right and left ventricles, has one semilunar valve and distributes blood to both systematic and pulmonary circulations. The pulmonary artery may arise either as a single vessel or as two separate vessels from the trunk. A ventricular septal defect is present in all cases. Survival is limited because of a large shunt and eventual pulmonary hypertension or left ventricular failure.

(ii) *Transposition of great arteries* (with or without ventricular defects and pulmonary or tricuspid atresia) (TGA), the aorta arises from the right ventricle in the anterior position and the pulmonary artery from the left ventricle in a posterior position. This complete transposition creates two parallel circulations, this situation obviously is incompatible with life, thus only surgical intervention can protect the life. Complete transposition of great vessels may exist with intact ventricular septum, with ventricular septal defect, with double-outlet right ventricle and with pulmonary/tricuspid atresia.

(iii) *Tetralogy of Fallot* (TOF), classically this CHD comprises of 4 components: large ventricular septal defect, an aorta overriding the ventricular septal defect, severe infundibular pulmonic stenosis (small pulmonary valve and pulmonary artery) or atresia and

right ventricular hypertrophy. Thus TOF is characterized by biventricular origin of the aorta above large ventricular septal defect. TOF causes cyanosis and these patients need surgical shunts.

(iv) *Double-outlet right ventricles (DORV)*. In this rare CHD (about 1 % of cases with CHD), more than 50% of the semilunar valve orifices of both great arteries arise from the morphologic right ventricle. In most cases, the ventricles display a D loop, and the pulmonary arterial origin is normally positioned, arising from a conus above the right ventricle. The aorta also arises from the right ventricle above conal tissue. In most cases, the aortic origin is to the right (d-malposition) of the pulmonary arterial origin, with the two vessels in a side-by-side relationship. Rarely, the aortic origin is distinctly anterior to the pulmonary origin or the aorta arises to the left (l-malposition) of the pulmonary artery. Cases with DORV were reported only in the 1990s in the HCAR due to the recent recognition of this CHD-entity.

III. Only cases with confirmed diagnosis based of surgical records or autopsy reports were included to the study, e.g. without surgical intervention DORV is lethal CA. Some cases with CTD were not found in the records of cardiologic institutions, in these cases we had a correspondence with mothers to clarify the status of their children in 2009 and 2010. Thus finally only lethal cases with autopsy report of survival cases with surgical correction were included to the study. If parents refused the collaboration or the diagnosis was not unequivocal, these cases were excluded from the study. Thus the diagnosis of our CTD cases had a high validity.

*Controls* were differentiated into two groups: matched controls of cases with different CTD-types evaluated in the study and all controls of the HCCSCA.

*Statistical analysis*

The software GNU R version 2.14, RStudio version 0.97 was used for the analysis of variables. First, frequency tables were made for the main birth outcomes of cases with CTD, and controls. Second, at the evaluation of quantitative data of birth outcomes of newborn infants and mothers such as age and pregnancy/birth order, Student t test was used while categorical variables of mothers regarding as marital and employment status were analyzed by chi square test. At the evaluation of categorical birth outcomes odds ratios (OR) with 95% confidence intervals (CI) were calculated in multivariable conditional regression model at the comparison of cases and their matched controls, and multivariable unconditional regression model at the comparison of cases and all controls.

## **RESULTS**

Our population-based data set included 598 cases with CTD (Table 1), including 44 cases with TAC, 307 cases with TGA, 223 cases with TOF and 24 cases with DORV. In addition, we evaluated 902 matched controls and 38,151 all controls without CA and 20,896 malformed controls with non-cardiac isolated CA. Of 598 cases, one with TOF was diagnosed in stillborn male fetus. Matched and all controls were live-born babies due to their selection criteria, thus only 297 live-born cases were also evaluated in the study.

Cases with TAC had a robust (70.5%), while cases with TGA (55.0%) and TOF (57.7%) slight male predominance. The sex ratio of cases with DORV (12; 50.0%) did not differ from the expected data of the Hungarian newborn population (51.3 % of males).

At the evaluation of total group of cases with CTD (Table 2), the mean gestational age at delivery was similar in cases and in matched and all of controls. However, the mean birth weight was smaller with 163 grams and 199 grams compared to matched controls and all controls, respectively. These findings were in agreement with the rate of preterm births and low birthweight newborns. The rate of preterm births was somewhat but not significantly

lower in the group of cases with CTD than in the groups of matched and all controls while the rate of low birthweight was significantly: 2.4-fold and 2.6-fold higher in cases than in the matched and all controls. Thus, the major finding of this analysis is an obvious intrauterine fetal growth retardation of cases with CTD. There was a somewhat higher rate of postterm birth and large birthweight in cases with CTD though the number of these births was limited.

We attempted to evaluate the birth outcomes of the 4 types of CT-CVA separately as well (Table 3).

The mean gestational age was much shorter and the mean birth weight was significantly smaller in cases with TAC than in their controls and these variables associated with a high rate of preterm birth and extremely high rate of low birthweight. These data indicate beyond shorter gestational age an obvious intrauterine growth restriction.

The birth outcomes of cases with TGA showed a controversial pattern. The mean gestational age was somewhat longer with lower rate of preterm birth, but the mean birth weight was smaller and it associated with a higher rate of low birthweight. Thus intrauterine growth restriction was also observed in this type of TGA.

The pattern of birth outcomes in cases with TOF was also different. The mean gestational age was somewhat shorter and the rate of preterm birth was lower in these cases than in controls but these differences did not reach the level of significance. However, the mean birth was 224 and 279 g smaller with the 2.7 and 2.5 fold higher rate of low birthweight newborns in cases with TOF than in their matched and all controls. Thus intrauterine growth restriction was also obvious.

The birth outcomes of cases with DORV were similar to cases with TGA though the rate of low birthweight was higher.

In conclusion, birth outcomes of TGA, TOF and DORV showed some similarities with the main characteristic of intrauterine growth restriction. However, TAC had a more obvious

male predominance with much worse birth outcomes both in the rate of preterm birth and low birthweight.

Table 4 summarized the birth outcomes of cases with CTD according to sex. The mean gestational age of cases did not show obvious difference from the figures of different controls either in females or males. Thus the significantly lower rate of preterm birth in females cases was an expected finding, similar trend was not seen in male cases. The mean birth weight was lower in females than in males both in the groups of cases and in their controls as in general. However, female cases had smaller birth weight (194 and 224 g) than in their matched and all controls compared to the smaller birth weight (142 and 159 g) in male cases than in their controls. Thus there was no significant difference in mean gestational age of female and male cases than in their controls but the rate of preterm birth was lower in female cases and both sexes had a higher rate of low birthweight due to their intrauterine growth restriction.

Among maternal variables (Table 5), first the total group of cases with CTD is analyzed. The mean maternal age was somewhat higher in case mothers than in all controls and particularly in matched control mothers. The mean birth order of case mothers was higher due to larger proportion of multiparous women than of matched and all control mothers. There was no difference in mean pregnancy order (live- and stillbirths + miscarriages) between case and control mothers and this finding is against the higher rate of miscarriages in the previous pregnancies of case mothers.

The rate of unmarried mothers was similar among the study groups. There was no obvious difference in the distribution of maternal employment status among the study groups, though the proportion of housewives was higher in the group of case mothers than in control mothers. In Hungary most of these women belonged to the lower socioeconomic status.

Table 6 summarizes the maternal variables in cases with different CTD types. Mean maternal age was different among different groups of cases with CTD from the lowest (25.1 yr) in the group of TAV to the highest in the group of DORV (26.6 yr). The mean birth order did not follow the mean maternal age, because it was the highest (2.0) both in the mothers of cases with TAC (with the youngest mean maternal age) and in the mothers of cases with DORV (i.e. with the eldest mean maternal age). The highest mean pregnancy order was also observed in the group of cases with TAC indicating a higher rate of miscarriages in the previous pregnancies of these mothers. The previously mentioned lower socio-economic status (semi- and unskilled workers, housewives) was found in the mothers of cases with different CTD, but it was most obvious in the group of TAC (40.9%) compared to TGA (33.2%), TOF (33.8%), DORV (32.4%) and particularly in all controls (28.0%) .

Only 58 case mothers were visited at home, 12 (20.7%) smoked cigarettes during the study pregnancy. The proportion of smokers was 19.8% in all control mothers. The number of regular and hard drinkers was 5 and 2, together was 7 (12.1) during the study pregnancy of case mothers. The rate of regular and hard drinkers together was 1.2% in all control mothers. This shows a 10.8-fold increased odds for drinkers (with CI: (3.3 , 32.9)).

## **DISCUSSION**

The major findings of our study indicated male excess and an intrauterine fetal growth restriction in cases with CTD.

The cardiac outflow tract, i.e. the group of CTD had tremendous changes in their clinical treatment and understanding in their etiopathogenesis. The first patient with tetralogy of Fallot was operated in 1945 by Blalock-Taussig shunt (24) and now most infants affected with CTD have surgical intervention in the first year of life with a remarkable survival rate of

80%. (The highest mortality is among infants with TAC and DORV.) A major breakthrough in the understanding of etiopathogenesis of CTD was the discovery that migrating neural crest cells form part of the aorticopulmonary septum and the cardiac outflow tract (25-27). Thus CTD are the CA of mesenchymal cell migration with an obvious sensitivity of specific environmental agents, e.g. retinoid acid exposure (28) due to specific patterns of retinoic acid binding proteins which could lead to a rational interpretation of the timing and action of specific teratogens.

The male excess among cases with CTD found in our and other studies (14, 29-32) is worth mentioning because it is against the usual X-linked inheritance and support the hypothesis of sex-modified threshold level in CTD polygenic system.

An important finding of the study is that fetal CTD had no effect for gestational age and rate of preterm birth. . However, CTD associate with and obvious risk for fetal development and it was recognized on the basis of intrauterine growth retardation. Thus intrauterine life hemodynamic alterations due to CTD may affect size and growth patterns (33). However, our study showed first the sex difference in the birth outcomes of cases with different CDT-types. Female cases had a lower rate of preterm birth. In addition our data indicated differences in the birth out comes of CTD-types, e.g., cases with TAC had a higher rate of both preterm birth and low birthweight, the other 3 type of CTDs associated with a somewhat lower rate of preterm birth but higher of low birthweight newborns. The mothers of TAC had a lower maternal socioeconomic status.

The somewhat elder mothers found in our and other studies (14, 34) are arguments for some genetic predisposition of CTDs.

Previously many studies showed an association between drinking habit of pregnant women and characteristic pattern (fetal alcohol syndrome/effect) of CAs including CHD as well in their children (35, 36). Tikkanen and Heinonen (32) found a much higher risk of conal

malformations in the children of pregnant women with alcohol drinking during the first trimester of pregnancy. Our study confirmed it though it was based only a subsample of our material, however, these data were collected through a cross interview of mothers and their close family members, excluding the very unreliable maternal self-reported information, and the association was strong.

Our study did not find association of smoking during pregnancy with the higher risk of CTD as in other studies (32, 14).

The strengths of our study are connected with the large population-based data set of the HCCSCA including 597 live-born cases with CTD, 902 matched and 38,151 all controls without CAs in the ethnically homogeneous Hungarian (Caucasian) population. The ascertainment of cases with CTD was high due to nearly complete surgical intervention (with precise diagnosis) and/or infant death (due to obligatory autopsy) in this group of CHDs. Prenatal diagnosis of severe CHD fetuses was not introduced in Hungary during the study period. Cases with CAs were reported by medical doctors and reported diagnoses were critically checked in the HCAR (17). In addition the validity of CHD-diagnoses has been improved due to the recent medical records in the HCCSCA (16) and due to the follow-up of our cases in cardiologic institutions and correspondence with mothers. We did our best to work with cases as homogeneous CHD as possible, therefore syndromic/unidentified multiple cases including CTD were excluded from the study. Birth outcomes of cases and controls were medically recorded.

However, there were some weaknesses of our study: (i) The rarity of some CTD-types creates difficulties in the evaluation of different anatomic subtypes, e.g. we were not able to differentiate the two subtypes of transposition of great vessels on the basis of great artery relationship such as transposed (parallel) and normal (spiral) (12) (ii) Data regarding lifestyle

factors, such smoking habit and alcohol drinking were available in a subsample of mothers visited at home.

In conclusion, our findings showed male excess and intrauterine growth restriction of cases with CTD, some difference in the birth outcomes of male and females cases and of different types of CTDs and confirmed the role of regular/hard drinking in the origin of CTDs

### **Acknowledgement**

This project was supported by the Hungarian Egészségügyi Tudományos Tanács Pályázati Irodája (Grant Office of Scientific Committee of Health Ministry) and Versys Clinics, Human Reproduction Institute, Budapest, Hungary

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Table 1. Pregnancy outcomes of cases with the different types of CT-CVA

Data set	Total		Sex ratio (No. of boys)		Stillbirth		Postnatal death (based on 597 live-born cases)	
Types of CTG	No.	%	No.	No.	%	%	No.	%
TAC	44	7.4	31	0	0.0	70.5	18	40.9
TGV	307	51.3	169	0	0.0	55.0	52	16.9
TOF	223	37.3	128	1	0.5	57.7	43	19.4
DORV	24	4.0	12	0	0.0	50.0	8	33.3
Total	598	100.0	340	1	0.2	57.0	121	20.3

Table 2. Live-birth outcomes of cases with conotruncal defect (CTD), in addition of matched and all controls

Variables	Cases (N=597)		Matched controls (N=902)				All controls (N=38,151)			
	No.	%	No.	%	OR	95% CI	No.	%	OR	95% CI
Livebirth outcomes										
Quantitative	Mean	S.D.	Mean	S.D.	t=	p=	Mean	S.D.	t=	p=
Gestational age (wk)*	39.4	2.0	39.3	2.1	0.93	0.353	39.4	2.1	0.00	1.000
Birth weight (g)**	<b>3,077</b>	588	3,240	490	5.61	<0.001	3,276	511	8.22	<0.001
Categorical	No.	%	No.	%	OR	95% CI	No.	%	OR	95% CI
Twins	13	2.2	11	1.2	1.80	0.80-4.05	410	1.1	2.05	1.17-3.58
Preterm birth*	49	8.2	84	9.3	0.87	0.60-1.26	3,496	9.2	0.89	0.66-1.19
Postterm birth*	6	1.0	4	0.4	2.28	0.64-8.11	151	0.4	2.55	1.13-5.80
Low birthweight**	87	<b>14.6</b>	56	6.2	2.58	1.81-3.67	2,167	5.7	2.83	2.25-3.57
Large birthweight**	9	1.5	3	0.3	4.59	1.24-17.0	315	0.8	1.84	0.94-3.58

\*Adjusted for sex of cases/controls, in addition to the age, parity (birth order) and employment status of mothers

\*\* Adjusted for sex of cases/controls, in addition to the age, parity (birth order), employment status of mothers and gestational age of newborns

Bold numbers show significant associations

Table 3. Live-birth outcomes of cases with different types of CTD, in addition of matched and all controls

Study groups/ Birth outcomes	Cases		Matched controls				All controls			
TAC	(N=44)		(N=58)				(N=38,151)			
Quantitative	<i>Mean</i>	<i>S.D.</i>	<i>Mean</i>	<i>S.D.</i>	<i>t=</i>	<i>p=</i>	<i>Mean</i>	<i>S.D.</i>	<i>t=</i>	<i>p=</i>
Gestational age (wk)	<b>38.6</b>	3.3	39.6	1.6	1.85	0.069	39.4	2.1	1.61	0.115
Birth weight (g)	<b>2,919</b>	782	3,305	491	2.87	0.005	3,276	511	3.03	0.004
Categorical	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>OR</i>	<i>95% CI</i>	<i>No.</i>	<i>%</i>	<i>OR</i>	<i>95% CI</i>
Preterm birth*	8	<b>18.2</b>	1	1.7	12.7	1.5-105.6	3,496	9.2	2.2	1.0-4.7
Low birthweight**	15	<b>34.1</b>	3	5.2	9.5	2.5-35.5	2,167	5.7	8.6	4.6-16.0
TGA	(N=307)		(N=489)				(N=38,151)			
Quantitative	<i>Mean</i>	<i>S.D.</i>	<i>Mean</i>	<i>S.D.</i>	<i>t=</i>	<i>p=</i>	<i>Mean</i>	<i>S.D.</i>	<i>t=</i>	<i>p=</i>
Gestational age (wk)*	<b>39.5</b>	1.9	39.2	2.1	2.08	0.038	39.4	2.1	0.92	0.359
Birth weight (g)**	<b>3,150</b>	586	3,235	496	2.11	0.035	3,276	511	3.76	0.001
Categorical	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>OR</i>	<i>95% CI</i>	<i>No.</i>	<i>%</i>	<i>OR</i>	<i>95% CI</i>
Preterm birth*	25	8.1	48	9.8	0.8	0.5-1.4	3,496	9.2	0.9	0.6-1.3
Low birthweight**	36	<b>11.7</b>	35	7.2	1.7	1.1-2.8	2,167	5.7	2.2	1.6-3.1
TOF	(N=222)		(N=323)				(N=38,151)			
Quantitative	<i>Mean</i>	<i>S.D.</i>	<i>Mean</i>	<i>S.D.</i>	<i>t=</i>	<i>p=</i>	<i>Mean</i>	<i>S.D.</i>	<i>t=</i>	<i>p=</i>
Gestational age (wk)	39.3	1.9	39.4	2.1	0.58	0.563	39.4	2.1	0.78	0.434
Birth weight (g)	<b>2,997</b>	535	3,221	471	5.05	<0.001	3,276	511	7.77	<0.001
Categorical	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>OR</i>	<i>95% CI</i>	<i>No.</i>	<i>%</i>	<i>OR</i>	<i>95% CI</i>

Preterm birth*	14	6.3	33	10.2	0.6	0.3-1.1	3,496	9.2	0.7	0.4-1.1
Low birthweight**	32	<b>14.4</b>	17	5.3	3.0	1.6-5.6	2,167	5.7	2.8	1.9-4.1
DORV	(N=24)		(N=32)				(N=38,151)			
Quantitative	<i>Mean</i>	<i>S.D.</i>	<i>Mean</i>	<i>S.D.</i>	<i>t=</i>	<i>p=</i>	<i>Mean</i>	<i>S.D.</i>	<i>t=</i>	<i>p=</i>
Gestational age (wk)*	39.4	2.0	39.5	2.1	0.18	0.086	39.4	2.1	0.00	1.000
Birth weight (g)**	<b>3,171</b>	563	3,382	584	1.37	0.178	3,276	511	0.91	0.370
Categorical	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>OR</i>	<i>95% CI</i>	<i>No.</i>	<i>%</i>	<i>OR</i>	<i>95% CI</i>
Preterm birth*	2	8.3	2	6.3	1.4	0.2-10.4	3,496	9.2	0.9	0.2-3.8
Low birthweight**	4	<b>16.7</b>	1	3.1	6.2	0.7-59.6	2,167	5.7	3.3	1.1-9.7

\*Adjusted for the age, parity (birth order) and employment status of mothers

\*\* Adjusted for the age, parity (birth order), employment status of mothers and gestational age of newborns

Bold numbers show significant associations

Table 4. Live-birth outcomes of cases with CTD, and their matched and all controls according to the sex of newborns

Variables/ Females	Cases (N=258)		Matched controls (N=401)				All controls (N=13,352)			
	Mean	S.D.	Mean	S.D.	t=	p=	Mean	S.D.	t=	p=
Quantitative										
Gestational age (wk)*	39.3	2.0	39.2	2.2	0.60	0.547	39.3	2.1	0.00	1.000
Birth weight (g)**	<b>2,963</b>	538	3,157	478	4.72	<0.001	3,187	494	6.63	<0.001
Categorical	No.	%	No.	%	OR	95% CI	No.	%	OR	95% CI
Preterm birth*	17	<b>6.6</b>	47	11.7	0.53	0.30-0.95	1,427	10.7	0.59	0.36-0.97
Low birthweight**	42	<b>16.3</b>	30	7.5	2.40	1.46-3.96	929	7.0	2.60	1.86-3.64
Variables/males	(N=	339)	(N=	501)			(N=	24,799)		
Quantitative	Mean	S.D.	Mean	S.D.	t=	p=	Mean	S.D.	t=	p=
Gestational age (wk)*	39.4	2.1	39.4	2.0	0.00	1.000	39.4	2.0	0.00	1.000
Birth weight (g)**	<b>3,164</b>	611	3,306	491	3.57	0.001	3,323	514	4.72	<0.001
Categorical	No.	%	No.	%	OR	95% CI	No.	%	OR	95% CI
Preterm birth*	32	9.4	37	7.4	1.31	0.80-2.14	2,069	8.3	1.15	0.79-1.65
Low birthweight**	45	<b>13.3</b>	26	5.2	2.80	1.69-4.63	1,238	5.0	2.91	2.12-4.01

Adjusted for the age, parity (birth order), employment status and folic acid use of mothers

\*\* Adjusted for the age, parity (birth order), employment status, folic acid use of mothers and gestation age of newborns

Bold numbers show significant associations

Table 5. Main variables of mothers of cases with CTD,in addition of their matched and all controls

Variables	Case mothers (N=597)		Matched control mothers (N=902)		All control mothers (N=38,151)				
	No.	%	No.	%	No.	%			
<b>Quantitative</b>									
Maternal age					$X^2_3$		$X^2_3$		$p=$
- 19	48	8.0	71	7.9			3,277	8.6	
20 – 29	426	71.4	674	74.4			27,602	72.3	
30 -	123	20.6	157	17.4			7,272	19.1	
Mean, S.D.	25.7	5.0	25.2	4.8	$t=$	$p=$	25.5	4.9	$t=$ $p=$
Birth order					$X^2_2$	$p=$			$X^2_2$ $p=$
1	261	43.7	443	49.1			18,209	47.7	
2 or more	336	56.3	459	50.9			19,942	52.3	
Mean, S.D.	1.9	1.1	1.7	1.0	$t=$	$p$	1.7	0.9	$t=$ $p$
Pregnancy order					$X^2_2$	$p=$			$X^2_2$ $p=$
1	234	39.2	396	43.9			16,320	42.8	
2 or more	363	60.8	506	56.1			21,831	57.2	
Mean, S.D.	2.0	1.3	1.9	1.2	$t=$	$p$	1.9	1.2	$t=$ $p$
<b>Categorical</b>	No.	%	No.	%	$X^2_1$	$p=$	No.	%	$X^2_1$ $p=$
Unmarried	22	3.7	42	4.7			1,472	3.9	
Employment status					$X^2_6$	$p=$			$X^2_6$ $p=$
Professional	56	9.4	88	9.8			4,423	11.6	
Managerial	145	24.3	250	27.7			10,265	26.9	
Skilled worker	174	29.1	280	31.0			11,908	31.2	
Semiskilled worker	100	16.7	161	17.8			6,161	16.1	
Unskilled worker	41	6.9	46	5.1			2,187	5.7	
Housewife	62	10.4	58	6.4			2,354	6.2	
Others	19	3.2	19	2.1			853	2.2	

Table 6. Main variables of mothers of live-born cases with different types of CTD and all controls

Variables	Cases with TAC (N=44)		Cases with TGA (N=307)		Cases with TOF (N= 222)		Cases with DORV (N=24)		Cases with CTD (N=597)		All controls (N=38,151)	
	No.	%	No.	%.	%	No.	No.	%	No.	%	No.	%
Quantitative												
Maternal age												
- 19	4	9.1	23	7.5	21	9.5	0	0.0	48	8.0	3,277	8.6
20 - 29	33	75.0	215	70.0	160	72.1	18	75.0	426	71.4	27,602	72.3
30 –	7	15.9	69	22.5	41	18.4	6	25.0	123	20.6	7,272	19.1
Mean, S.D.	25.1	4.1	25.9	5.0	25.3	5.3	26.6	4.3	25.7	5.0	25.5	4.9
Birth order												
1	16	36.4	137	44.6	101	45.5	6	25.0	261	43.7	18,209	47.7
2 or more	28	63.6	170	55.4	121	54.5	18	75.0	336	56.3	19,942	52.3
Mean, S.D.	2.0	1.2	1.9	1.2	1.8	1.1	2.0	0.8	1.9	1.1	1.7	0.9
Pregnancy order												
1	14	31.8	123	40.1	91	41.0	6	25.0	234	39.2	16,320	42.8
2 or more	30	68.2	184	59.9	131	59.0	18	75.0	336	60.8	21,831	57.2
Mean, S.D.	2.3	1.4	2.0	1.2	2.0	1.3	2.2	1.0	2.0	1.3	1.9	1.2
Categorical	No.	%	No.	%.	No.	%	No.	%	No.	%	No.	%
Unmarried	3	6.8	9	2.9	10	4.5	0	0.0	22	3.7	1,472	3.9
Employment status												
Professional	2	4.5	33	10.7	19	8.6	2	8.3	56	9.4	4,423	11.6
Managerial	7	15.9	77	25.1	52	23.4	9	37.1	145	24.3	10,265	26.9
Skilled worker	15	34.1	87	28.3	68	30.6	4	16.7	174	29.1	11,908	31.2
Semiskilled worker	7	15.9	51	16.6	38	17.1	4	16.7	100	16.7	6,161	16.1
Unskilled worker	6	13.6	19	6.2	15	6.8	1	4.2	41	6.9	2,187	5.7
Housewife	5	11.4	32	10.4	22	9.9	3	12.5	62	10.4	2,354	6.2
Others	2	4.5	8	2.6	8	3.6	1	4.2	19	3.2	853	2.2

