Risk factors of congenital heart diseases: A hospital-based case-control study in Isfahan, Iran

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Original Article

Abstract

BACKGROUND: Improving knowledge towards risk factors for congenital heart disease (CHD) is important because of its high mortality and morbidity and trying for prevention of occurrence of CHD.

METHODS: This case-control study was conducted on a total of 898 children with their mothers, who referred to the Clinic of Pediatric Cardiology of School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, during the years of 2014 to 2016. Cases comprised of 464 children with CHD diagnosed by echocardiography and controls were 434 sex- and age-matched children without any evidence of CHD, who were admitted for a heart check-up at the same study period and in similar conditions. The children's parents completed check lists for collecting demographic characteristics, family history of CHD, history of obesity in mother, history of abortion and diseases in mother, use of medicine during pregnancy, exposure to teratogens during pregnancy, and children characteristics such as birth height and birth weight, etc.

RESULTS: Based on the results of data analyses with multiple logistic regression model [odds ratio (OR) with 95% confidence interval (CI)], history of obesity in mother before pregnancy, history of abortion, parental consanguinity, exposure to cigarette smoke during pregnancy, exposures to teratogens in the first trimester of the pregnancy, and use of medicine during pregnancy were associated with an increased odds of CHDs.

CONCLUSION: Results of this study emphasizes the use of policies that enhance pre-marital counseling, regular counseling during pregnancy, treatment of mothers' disease, and enhancing knowledge of women of childbearing age about exposure to certain teratogens for controlling risk factors of CHD.

Keywords: Congenital Heart Defects; Risk Factors; Pediatrics

Introduction

Congenital malformations in the heart and great vessels mainly appear during intrauterine development. The global incidence of congenital cardiovascular defects varies in the range of 0.47% to 1.17% of live births.[1] Various etiological factors have been identified; however, the exact reasons for these abnormalities have remained unclear. A multifactorial etiology is now accepted as a combination of both genetic and environmental factors for these defects.[2,3] It seems that the genetically predisposed fetus when exposes to environmental triggers may suffer cardiac morphogenetic abnormalities within intrauterine growth period.[4] In fact, an interaction between genetic susceptibility and exposing to environmental stimulators may lead to congenital heart disease (CHD). A variety of both neonatal and maternal risk factors have been introduced to be related to certain heart defects. Results of studies showed that the incidence rate of CHD increased after exposure of pregnant mother to rubella virus.[5,6]

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Consuming some drugs during pregnancy such as thalidomide, some anticonvulsant drugs, alcohol, lithium, sex hormones, folic acid antagonists, diazepam, corticosteroids, and methamphetamines, phenothiazine, and cocaine is associated with different severities of CHDs.[5,7] Diabetic mothers are also more predisposed to CHD.[8] Moreover, higher incidence of these abnormalities is also identified in some chromosomal anomalies such as Down syndrome (DS), Turner's syndrome (TS), and deletion of chromosome 22.[9-11] Based on the genetic science, the association between some single nucleotide polymorphisms and occurrence of CHDs has been also indicated.[12,13] Thus, the cause of CHDs is largely on the basis of multifactorial inheritance hypothesis. Some types of CHDs are minor without significant effects on physical function of the affected patients. However, emergency surgery may be required in about one-fourth of patients within first year of birth.[14] Also, some complex surgical procedures may be needed to repair these anomalies which may lead to potential complications and prolonged hospitalization.[15] In this regard, discovering risk factors is very important for managing and treatment of CHD. Consequently, in order to make suitable planning for control of causative factors in these anomalies, it is necessary to conduct careful studies for identifying main risk factors in CHD. Therefore, the aim of this study was to investigate risk factors of CHDs in children in Isfahan, Iran.

Materials and Methods

This case-control study was conducted on a total of 898 children with their mothers, who referred to Clinic of Pediatric Cardiology, School of Medicine, Isfahan University of Medical Sciences, during the years of 2014 to 2016. All children were referred to this clinic for heart check-up, and they were visited by pediatric cardiologist with complete physical examination and complementary diagnostic tests such as echocardiography. Then, 464 children with documented CHD were selected as the case group and 434 children without CHD who were sex-and age-matched were selected as the control group.

The inclusion criteria were children with CHD confirmed on clinical manifestations as well as complementary diagnostic tests such as echocardiography, cardiac catheterization and angiography, computed tomography (CT) scan, or magnetic resonance imaging (MRI). The exclusion criteria were children with acquired heart disease such as ischemic or rheumatologic defects, and refusing to participate in the study. This study was approved by the Ethics Committee of Isfahan Cardiovascular Research Institute. Participation in this study was voluntary. All information collected from participants was kept confidential.

After receiving written informed consent from parents in both groups, the study data were collected through checklists. The checklist variables consisted of the following details:

Characteristics of checklist variables included age, sex, parents' level of education, parents' occupation, number of children per family, and birth weight.

Maternal variables characteristics that were collected with checklists included history of obesity in mother before pregnancy, history of abortion, parental consanguinity, radiation and X-rays exposure during pregnancy, history of smoking and exposure to cigarette smoke during pregnancy, the maternal exposure to teratogens in the first trimester of the pregnancy (including hair color, canned food, detergents, insecticides, alcohol, and opioids), use of mobile phone, family history of CHD, history of diseases in mother [including diabetes, heart diseases, hypertension (HTN), hypothyroidism, etc.], and use of medicine during pregnancy. The checklist variables were completed by an expert person through the interview with mothers of children with CHD (self-report) as the case group, and mothers of healthy children as the control group and also the information of hospital records for CHD such as echocardiographic report was used for the case group.

Data were reported as mean and standard deviation (SD) for quantitative variables and frequencies and percentages for qualitative variables. Continuous variables were compared using independent samples t-test. For checking normality assumption of the data, Kolmogorov-Smirnov test (K-S test) was used. Categorical variables were compared using chi-square test or Fisher's exact test if needed.

The multiple logistic regression model [odds ratio (OR) with %95 confidence interval (CI)] was used for estimating the association between risk factors of CHD and CHD. For the statistical analysis, the SPSS statistical software (version 25, IBM Corporation, Armonk, NY, USA) was used. P < 0.050 was considered significant.

Results

A total of 474 children with CHD and 436 sex- and age-matched children without any evidence of CHD

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and their parents were recruited. The characteristics for case and control groups were presented in table 1. 253 (53.4%) of cases and 231 (53.0%) of controls were male (P = 0.900). The mean age for the case group was 3.22 ± 3.35 years and for the control group was 3.57 ± 3.49 years (P = 0.120). The mean weight for cases and controls were 2.96 ± 0.56 kg and 2.98 ± 0.53 kg, respectively (P = 0.640). The mean height for cases was 48.54 ± 30.30 cm, and for controls was 48.93 ± 2.92 cm (P = 0.060). Results in table 1 showed that parents' occupation, parents' level of education, and the number of children per family were different in case and control groups.

As shown in table 2, compared with mothers in the control group, a number of mothers in CHD group had obesity before pregnancy (27.0% vs. 17.7%, P < 0.001), history of abortion (14.6% vs. 47.0%, P < 0.001), and consanguineous marriage (32.5% vs. 18.6%, P < 0.001). More mothers in case group had exposure to cigarette smoke during pregnancy (23.2% vs. 11.9%, P < 0.001) and teratogens including hair color (9.7% vs. 4.1%, P = 0.001), canned food (17.3% vs. 5.3%, P = 0.001), detergents (21.7% vs. 10.8%, P < 0.001), and using tobacco, alcohol, and opium (3.6% vs. 0.7%, P = 0.003) in the first trimester of pregnancy in both group.

Moreover, results in this study showed that family history of CHD (P = 0.006), mother's diseases such as diabetes and hypothyroidism (P < 0.001), as well as the use of medications such as metformin and levothyroxine (P < 0.001) during pregnancy may have an effect on the occurrence of CHDs.

Variables for determining and identifying the most important risk factors of CHDs were included in a multiple logistic regression model. The risk factors were coded as Yes/No indicator variables. They were obesity in mother before pregnancy, history of abortion, parental consanguinity, radiation and X-rays exposure, history of smoking, and exposure to cigarette smoke during pregnancy.

Table 1. Characteristics variables of cases with congenital heart disease (CHD) and controls

Variables	Case group (n = 474)	Control group (n = 436)	P
Age (year) (mean ± SD)	3.22 ± 3.35	3.57 ± 3.49	0.120
Birth weight (kg) (mean ± SD)	2.96 ± 0.56	2.98 ± 0.53	0.640
Birth height (cm) (mean ± SD)	48.54 ± 3.30	48.93 ± 2.92	0.060
Sex [n (%)]			0.900
Male	253 (53.4)	231 (53.0)	
Female	221 (46.6)	205 (47.0)	
Fathers' occupation [n (%)]			< 0.001
Worker	224 (47.3)	148 (33.9)	
Employed	78 (16.5)	82 (18.8)	
Self-employed	151 (31.9)	191 (43.8)	
Other jobs	21 (4.4)	15 (3.4)	
Father's education level [n (%)]			0.001
Primary school	201 (42.4)	133 (30.5)	
High school	157 (33.1)	178 (40.8)	
College	116 (24.5)	125 (28.7)	
Mothers' occupation [n (%)]			< 0.001
Employed	27 (5.7)	43 (9.9)	
Housewife	386 (81.4)	369 (84.6)	
Other jobs	61 (12.9)	24 (5.5)	
Mother's education level [n (%)]			< 0.001
Primary school	174 (36.7)	100 (22.9)	
High school	175 (36.9)	189 (43.3)	
College	125 (26.4)	147 (33.7)	
Number of children per family [n (%)]			0.010
1	222 (46.8)	223 (51.1)	
2	189 (39.9)	176 (40.4)	
3	43 (9.1)	34 (7.8)	
4	15 (3.2)	2 (0.5)	
More	5 (1.1)	1 (0.2)	

SD: Standard deviation

Table 2. Mother's risk factors in cases with congenital heart disease (CHD) and controls

Variables	Group		P
	Case group (n = 474)	Control group (n = 436)	
History of obesity in mother before pregnancy[*]	128 (27.0)	77 (17.7)	< 0.001
History of abortion	69 (14.6)	25 (47.0)	< 0.001
Consanguineous marriage	154 (32.5)	81 (18.6)	< 0.001
Exposure to cigarette smoke during pregnancy	110 (23.2)	52 (11.9)	< 0.001
Exposure to radiation during pregnancy	9 (1.9)	11 (2.5)	0.520
Family history of CHD	36 (7.6)	15 (3.4)	0.006
Mother's diseases[**]	70 (14.8)	31 (7.1)	< 0.001
Use of medicine during pregnancy[***]	94 (19.8)	47 (10.8)	< 0.001
Exposure to teratogens in the first trimester of pregnancy			
Hair color	46 (9.7)	18 (4.1)	0.001
Canned foods	82 (17.3)	23 (5.3)	< 0.001
Detergents (bleaches)	103 (21.7)	47 (10.8)	< 0.001
Insecticides	18 (3.8)	11 (2.5)	0.270
Tobacco, opium, alcohol	17 (3.6)	3 (0.7)	0.003
Use of mobile phone during pregnancy	421 (88.8)	396 (90.8)	0.310

Data are reported as number (%)
[*] History of obesity was assessed by mother's self-report (weight and height of mother before pregnancy); [**] Mother's diseases included diabetes and hypothyroidism; [***] Many drugs were used during pregnancy including metformin and levothyroxine
CHD: Congenital heart disease
For comparison of effective factors between case and control groups, chi-square test or Fisher's exact test was used.

Moreover, variables such as exposure to teratogens in the first trimester of the pregnancy (exposure to at least one of teratogens including hair color, canned foods, detergents, insecticide, alcohol, tobacco, and opium), use of mobile phone in pregnancy, family history of CHD, history of diseases in mother, and use of medicine during pregnancy were studied.

According to the results of table 3, variables that entered into the multiple logistic regression model, variables of history of obesity in mother before pregnancy (OR: 1.54, %95 CI: 1.10-2.17), history of abortion (OR: 2.16, %95 CI: 1.29-3.60), parental consanguinity (OR: 2.02, %95 CI: 1.46-2.81), exposure to cigarette smoke during pregnancy (OR: 2.00, %95 CI: 1.36-2.92), exposure to teratogens in the first trimester of the pregnancy (OR: 2.32, %95 CI: 1.68-3.20), and use of medicine during pregnancy (OR: 1.78, %95 CI: 1.16-2.71) were associated with an increased odds of CHDs.

Discussion

CHD is one of the most common causes of mortality in children. The studies about etiology of CHD has showed that there are multifactorial causes as a combination of both genetic and environmental factors for these defects.

Table 3. Odds ratio (OR) and 95% confidence interval (CI) for congenital heart disease (CHD) according to risk factor in the multiple logistic regression model

Variables	OR	%95 CI	P
History of obesity in mother before pregnancy	1.54	1.10-2.17	0.012
History of abortion	2.16	1.29-3.60	0.003
Smoking mother during pregnancy	5.20	0.56-48.37	0.147
Consanguineous marriage	2.02	1.46-2.81	< 0.001
History of diseases in mother	1.41	0.83-2.33	0.168
Use of medicine during pregnancy	1.78	1.16-2.71	0.007
Radiation and X-rays exposure during pregnancy	0.53	0.20-1.41	0.207
Exposure to cigarette smoke during pregnancy	2.00	1.36-2.92	< 0.001
Exposure to teratogens during pregnancy[*]	2.32	1.68-3.20	< 0.001
Use of mobile phone in pregnancy	0.89	0.55-1.44	0.650
Family history of CHD	1.68	0.86-3.27	0.124

Risk factors were considered as a binary variable (Yes/No) in the multiple logistic regression model
[*] Exposure to teratogens during pregnancy: Exposure to at least one of teratogens including hair color, canned food, detergents, insecticides, tobacco, opium, and alcohol
OR: Odds ratio; CI: Confidence interval; CHD: Congenital heart disease

In our survey, we attempted to determine risk factors of CHD to help early prediction of these abnormalities. Results of this study showed that among studied main factors for CHD, maternal weight in pregnancy, history of abortion, consanguineous marriage, drug use during pregnancy, and exposure to cigarette smoke and teratogens had significant relationship with incidence of CHD. According to the results, prevention of risk factors of CHD before pregnancy may lower the incidence of CHD.

As previously pointed, both genetic and environmental factors can be major causes of congenital heart anomalies. Similar findings to our observations can be found in previous studies.

Results of this study revealed the maternal weight in CHD group more than that of the control group. The results of studies of Brite et al.,[16] Persson et al.,[17] and Kmietowicz[18] showed that increased maternal weight had a significant statistical relationship with increased risk for CHD.

Also, in the present study among investigated diseases, hypothyroidism and diabetes in case group were more than that of the control group. The results of this study are consistent with the results of Grattan et al.[19] and Naghavi-Behzad et al.,[20] based on the results, more attention to the treatment of a mother's illnesses before pregnancy is necessary.

In this study, there was a significant relationship between the history of abortion and increased risk for CHD. Regarding association between history of abortion and increased risk for CHD, epidemiological studies have reported conflicting results on the association of CHD risk in offspring with a maternal history of prior pregnancies and abortions. A recent meta-analysis showed a positive effect of maternal gravidity on increased CHD risk. Also, a history of abortion was associated with a 24% higher risk of these defects. When stratified by abortion category, risk for heart defects increased by 18% and 58% with a history of spontaneous abortion and induced abortion, respectively.[21] In another study by Taksande et al., 10.61% of those with heart defects had a history of previous abortions, while only 2.79% had a history of CHD in previous child or malformed babies.[22]

The result of a data analysis showed that consanguineous marriage had a significant relationship with CHD. In Ul Haq et al.[23] study, consanguineous marriage and family history of CHD were known as independent risk factors for CHD. Because of the major role of consanguineous marriage in developing CHD and also due to the high prevalence of consanguineous marriage in Iran population especially in rural areas, higher prevalence of these defects can be predicted in such population.

Results of multiple regression in this study showed that history of treatment with drug by mother and exposure to cigarettes smoke and teratogens during pregnancy had a significant relationship with CHD. Results of study by Nicoll showed that in addition to smoking mother during pregnancy and some of the many components of cigarette smoke, exposure to teratogens such as pesticides, metals, and detergents had a significant relationship with CHD.[24] This data was consistent with the results of the present study. Therefore, mothers must be aware of risk factors of CHD and their effects on their infant's health during pregnancy.

The strong point of this study is that at first, the diagnosis of each CHD in case group was confirmed by a pediatric cardiologist and documented by echocardiography. Second, the children's age and sex between cases and controls were matched.

There are also a number of limitations in this study. Most data in this study were based on the parents' self-report, which could be a source of recall bias. As in any case-control study, we cannot rule out differential recall in cases and controls.

Conclusion

We could show that among all neonatal and maternal factors as well as demographic and socioeconomic factors, maternal obesity, history of abortion, consanguineous marriage, also exposure to teratogens could affect the incidence of CHD. Based on the results of this study, it seems necessary to make programs for preventing maternal obesity before pregnancy, improving pregnancy health care, lowing consanguineous marriage, prompt treatment of mothers' disease, and decreasing exposure to cigarette smoke and teratogens during pregnancy.

Conflict of Interests

Authors have no conflict of interests.

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