Int Cardiovasc Res J.2020;**14**(4):148-152.icrj.108858

International Cardiovascular Research Journal

www.ircrj.com

Regional Distribution of Congenital Heart Disease in Iran; A Study on 1000 Iranian Hospitalized Patients in Three Years

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ARTICLE INFO

Article Type:
Research Article

Article History:
Received: 24 Aug 2020
Revised: 22 Oct 2020
Accepted: 27 Oct 2020

Keywords:
Congenital Heart Disease
Risk Factors
Epidemiology

ABSTRACT

Background: Congenital Heart Disease (CHD) is a major health problem around the world. Several maternal and fetal risk factors have been mentioned to be associated with development of CHD. However, the epidemiological pattern is different in various parts of the world. Thus, the present study aimed to demonstrate the descriptive characteristics of a group of Iranian children with CHD.

Objectives: The present study aimed to determine the regional distribution of CHD among 1000 Iranian hospitalized children during three years.

Methods: This cross-sectional study was conducted on 1000 Iranian children with CHD who were hospitalized in Rajaie Cardiovascular, Medical and Research Center, as a tertiary cardiovascular hospital (2017 - 2019). The participants were selected via convenience sampling. Clinical data were extracted from the patients' medical records and questionnaires and then, a comprehensive evaluation was performed.

Results: The median (IQR) age of the children was 18 (8 - 60) months. In addition, the mean ± SD of maternal age at pregnancy was 27.3 ± 5.92 years. Ventricular Septal Defect (VSD) was the most frequent CHD. Most of the patients were Fars (35.7%), Azeri (18.4%), and Kurd (10.7%). Besides, 58.7% of the patients lived in rural areas. The family history of CHD was present in 23.9% of the patients. Additionally, 41.4% of the patients' parents had consanguineous marriages. Spotting was the most common (48.7%) complication during pregnancy followed by infectious disease (24.2%), toothache (12.9%), and diabetes mellitus (7.8%).

Conclusions: The present study demonstrated the baseline neonatal and maternal characteristics of the patients with CHD, which revealed that some risk factors were common in these individuals. Hence, it is necessary to provide preventive strategies for modifiable risk factors, monitor high-risk pregnant women at shorter intervals, raise awareness in the general population, and perform genetic counselling, as appropriated. This was the first report of the CHD frequency in Iran.

1. Background

Congenital Heart Disease (CHD), the most common type of congenital anomalies, is a major health problem around the world (1). According to the literature review, the prevalence of CHD varied between 3.7 and 17.5/1000 live births in different geographical regions of the world; nine affected per 1000 live births have been reported in Asia (2, 3). With the prevalence of 1% mortality in the live births, CHD has been considered the leading cause of death in the first year of life (4-6). A considerable number of neonates who survive from CHD should undergo medical and/or surgical treatments and, consequently, a large proportion of healthcare costs and equipment are spent for these patients.

Heterogeneous etiologies have been revealed for CHD. In this context, various maternal and fetal factors have been mentioned to be associated with CHD among different cohorts. Maternal age, medical problems, and drug consumption during pregnancy, chemical exposures, consanguineous marriage, prematurity, and low birth weight were the probable factors (4, 7-9). Meanwhile,

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it has been stated that 15% of CHDs had a certain cause (10, 11).

Identifying the modifiable and non-modifiable risk factors plays an important role in primary and secondary prevention through early diagnosis and timely treatment. At present, although noninvasive techniques, including multi-slice spiral CT, Magnetic Resonance Imaging (MRI), and echocardiography, have resulted in great improvements in CHD diagnosis, development of cardiac defects leads to inevitable surgeries and interventions. This indicates the reasons why an early detection is important.

Given the high prevalence of consanguineous marriages, especially in rural areas in Iran, as well as some environmental factors, Iran has probably a remarked burden of this disease (12).

To the best of our knowledge, there are limited studies focusing on the contributing risk factors of CHD in Iran and the available works have evaluated a small number of patients.

2. Objectives

The present study aimed to determine the basic and clinical features of children with CHD, their maternal characteristics during pregnancy, and the prevalence of different types of CHD among Iranian children with documented CHD who referred to a cardiac tertiary care center.

3. Patients and Methods

This cross-sectional study was conducted on 1000 Iranian children with CHD who were hospitalized in Rajaie Cardiovascular, Medical and Research Center, the pediatric cardiology center of excellence affiliated to Iran University of Medical Sciences (2017 - 2019). The participants were selected via convenience sampling. Clinical data were extracted from the medical records and questionnaires. According to the recorded angiography, echocardiography, and MRI information, the CHD types were determined. The research protocol was approved by the local ethics committee of the hospital and the study was conducted in accordance with the Declaration of Helsinki. The primary objective of the current study was to present the general characteristics of a sample of Iranian children with CHD who were hospitalized in a cardiac tertiary hospital with respect to neonatal and maternal factors. The study also aimed to compare the findings to those of other similar works and to show any differences in the patterns of disease risk factors.

3.1. Statistical Analysis

This is a descriptive study aimed to determine the characterizations of 1000 children with CHD and their maternal conditions during pregnancy. The continuous variables were demonstrated as means with standard deviations or medians with 25th and 75th percentiles (Interquartile Range (IQR) boundaries), as appropriated. The categorical variables were reported as frequencies and percentages. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (Armonk, NY: IBM Corp).

4. Results

In the present study, 1000 children with CHD were investigated. The baseline characteristics of these patients have been presented in Table 1. Accordingly, the median age of the participants was 18 (8 - 60) months and their median age at diagnosis was 1 (0 - 3) month. In addition, males comprised 51.6% of the patients. Most of the patients were Fars (35.7%), Azeri (18.4%), and Kurd (10.7%). Besides, 58.7% of the patients lived in rural areas. The family history of CHD was present in 23.9% of the patients. In addition, 41.4% of the patients' parents had consanguineous marriages, 26% of whom were cousins.

The inheritance pattern of CHD was sporadic in 71.6%,

Table 1. Baseline Characteristics of the Children with Congenital Heart Disease

Variable	Number (Percentage)
Age (months)	18 (8 - 60)*
Gender (male)	516 (51.6)*
Age at diagnosis (months)	1 (0-3)*
Race	
Fars	357 (35.7)
Azeri	184 (18.4)
Kurd	107 (10.7)
Lur	94 (9.4)
Gilak	62 (6.2)
Mazandarani	63 (5.3)
Arab	88 (8.8)
Turkmen	27(2.7)
Baloch	28 (2.8)
Type of residence	
Urban	413 (41.3)
Rural	587 (58.7)
Family history	239 (23.9)
History of surgery	189 (18.9)
History of non-cardiac surgery	26 (2.6)
Type of marriage	
Consanguineous marriage	414 (41.4)
Non-consanguineous marriage	586 (58.6)
Type of parents' relationship	
Cousin	260 (26)
Distant relative	158 (15.8)
Inheritance pattern	
Sporadic	716 (71.6)
Autosomal dominant	22 (2.2)
Autosomal recessive	91 (9.1)
Familial	171 (17.1)
Method of diagnosis	
Echocardiography	975 (97.5)
CT angiography	10 (1)
Cardiac catheterization	12 (1.2)
Cardiac MRI	3 (0.3)
Patient's other diseases	182 (18.2)
Parents' disease	
No	906 (90.6)
Cardiac	20 (2)
Non-cardiac	74 (7.4)
Sibling's disease	
No	906 (90.6)
Cardiac	20 (2)
Non-cardiac	74 (7.4)

The data have been shown as mean ± SD, median (25th-75th percentiles), or number (percentages).

Figure 1. Distribution of the Children with Congenital Heart Disease According to Their Current City

autosomal dominant in 2.2%, autosomal recessive in 9.1%, and familial in 17.1% of the patients. Echocardiography was the most common (97.5%) modality of diagnosis in the study population. Moreover, 2% of the parents and 2% of the siblings had cardiac diseases.

The distribution of CHD patients in different cities of Iran has been depicted in Figure 1. Accordingly, 28.8% of the children with CHD were from Tehran, the capital of Iran. Other provinces with high percentages of patients with CHD consisted of Khuzestan (10%) and Northern provinces including Golestan (5.5%), Mazandaran (5.1%), and Gilan (5%).

The characteristics of the mothers during their pregnancy courses have been demonstrated in Table 2. As the table depicts, the mean ± SD of maternal age at pregnancy was 27.3 ± 5.92 years and 3.5% of the CHDs were diagnosed in pregnant women. Additionally, 20.6% of the mothers had a history of abortion and 21.9% had undergone In Vitro Fertilization (IVF). Spotting was the most common pregnancy complication, which occurred in 48.7% of the mothers. Infectious disease (24.2%), toothache (12.9%), and diabetes mellitus (7.8%) were the other most common problems. Furthermore, the history of any type of drug intake during pregnancy was positive in 29.2% of the patients.

The frequencies and percentages of different types of CHD in the study population have been shown in Table 3. Accordingly, Ventricular Septal Defect (VSD) was the most frequent CHD (31%) followed by Atrial Septal Defect (ASD) (13) in 19.8% and Tetralogy of Fallot (TOF) in 19.6% of the participants. The other frequent CHDs were pulmonary stenosis (7.6%), transposition of the great arteries (7.3%), Patent Ductus Arteriosus (PDA) (11.2%), and Bicuspid Aortic Valve (BAV) (1%). However, none of the patients had dextrocardia.

Table 2. Maternal Characteristics During Pregnancy in the Study Population

Variable	
Maternal age at pregnancy	27.3 (5.92)
Parity leading to the current live birth	2 (1 - 3)
Diagnosis in pregnancy	35 (3.5)
History of abortion	206 (20.6)
IVF	219 (21.9)
Pregnancy problems	
Thyroid disease	55 (5.5)
Diabetes mellitus	78 (7.8)
Kidney disease	13 (1.3)
Infectious disease	242 (24.2)
Spotting	487 (48.7)
Toothache	129 (12.9)
Referral to dentist	48 (4.8)
Hypertension	46 (4.6)
Drug intake during pregnancy	292 (29.2)

Abbreviations: IVF, in vitro fertilization
The data have been shown as mean ± SD, median (25th-75th percentile), or number (percentages).

Table 3. The Frequencies and Percentages of Different Types of Congenital Heart Disease in the Study Population

Variable	
Tricuspid atresia	7 (0.7)
Mitral atresia	1 (0.1)
TGA	73 (7.3)
DORV	29 (2.9)
TOF	196 (19.6)
TAPVR	17 (1.7)
TAPVC	17 (1.7)
PAPVC	18 (1.8)
ASD	198 (19.8)
AVSD	12 (1.2)
VSD	310 (31)
Ebstein's anomaly	3 (0.3)
HLH	2 (0.2)
PS	76 (7.6)
PAS	2 (0.2)
AS	28 (2.8)
SVAS	1 (0.1)
COA	22 (2.2)
PDA	112 (11.2)
Dextrocardia	0
BAV	10 (1)

The data have been shown as number (percentages). Abbreviations: TGA, transposition of the great arteries; DORV, double outlet right ventricle; TOF, tetralogy of Fallot; TAPVR, total anomalous pulmonary venous return; TAPVC, total anomalous pulmonary venous connection; PAPVC, partial anomalous pulmonary venous connection; ASD, atrial septal defect; AVSD, atrioventricular septal defect; VSD, ventricular septal defect; HLH, hypoplastic left heart; PS, pulmonary stenosis; PAS, pulmonary artery stenosis; AS, aortic stenosis; SVAS, supravalvar aortic stenosis; COA, coarctation of the aorta; PDA, patent ductus arteriosus; BAV, bicuspid aortic valve.

5. Discussion

To determine the distributions and frequencies of CHDs, the present study was conducted on 1000 children with documented CHD who referred to the pediatric ward of a cardiac tertiary care center between 2017 and 2019. The patients were assessed on the basis of baseline neonatal and maternal characteristics to find out the most common risk factors of CHD in this population. The study population could be considered a good representative of the Iranian pediatric patients with CHD since Rajaie Cardiovascular, Medical and Research Center is the pediatric cardiology center of excellence in Iran. The patients under investigation

were assessed by expert cardiologists, which was the strength of the research. The relatively large number of patients investigated in the current work compared to the similar works performed in Iran might be deemed as another strong point of the study.

Up to now, many studies have been performed to discover the epidemiological pattern of and effective factors in developing CHD. However, it seems that the pathogenesis includes a combination of several genetic and environmental factors (14, 15). On the other hand, racial and ethnic factors have played an important role in the epidemiology of CHD in various parts of the world (4, 16). Hence, local studies would be a good guide for health policymakers. In this regard, elimination of the modifiable risk factors of CHD, determination of high-risk pregnancies, early diagnosis, and on-time treatment would save large health expenses.

According to the present study findings, more than half of the patients were male and the similar proportion were from rural areas. Regarding the individuals' race, Fars, Azeri, and Kurd were the three most common races. Furthermore, approximately one quarter of the study population had a positive family history of CHD. Given the maternal factors in the study population, history of abortion, IVF, presence of medical and gynecological complications during pregnancy (such as infectious diseases, diabetes mellitus, hypertension, and spotting), and drug intake during pregnancy could be highlighted. In a study on vaginal bleeding on 151 healthy pregnant women, spotting was recorded in 14 pregnancies (9%), but they were found to have successful pregnancies. The results implied that early bleeding (one day to one week) lead to healthy live births (17). However, the reported spotting in the current study population was nearly continued in the first trimester of pregnancy.

The frequency of different types of CHD in the present study was similar to that reported in other works (7, 18-20). VSD, ASD, and TOF were the three most common CHDs in the current work. In a prospective cohort study by Fung el al. (4), 2339 patients with CHD who were below 18 years old were compared to 199 controls with respect to prenatal risk factors. The results revealed the increasing impact of prenatal factors on CHD development, including family history of CHD, medication intake and smoking during pregnancy, increased parental age at the time of conception, and maternal infectious diseases and type I diabetes during pregnancy. Another large prevalence study (1) on 29098 live infants reported a prevalence of 76/10000 live births. The results also revealed that twin pregnancies, positive family history, parity ≥ 3, and increased maternal age could be considered the risk factors of CHD. In the same vein, Abqari et al. (7) evaluated 400 cases and 400 controls through multivariate logistic regression in a case-control study and indicated that increased maternal and paternal age, poor obstetric history, and infectious diseases were the risk factors. It is noteworthy that a significant number of patients' parents had consanguineous marriages in the current work (41.4%). This could be considered a cultural risk factor in Iran, which was similar to Southern and Western Asian and North African countries, while the rate of consanguinity was less than 0.5% in European countries (21, 22). Jalili et al. (19) evaluated 774 patients with CHD to identify the frequency of different types of the disease and the possible risk factors. Based on the results, ASD, VSD, and TOF were the most common CHDs in this group. In addition, consanguineous marriage was present in 63.8% of the patients' parents and 37.4% of the mothers had the history of taking at least one drug during pregnancy. In another research (23) performed on 234 CHD cases in southwestern Iran, consanguinity (48.7%), other anomalies (21.2%), maternal hypertension (27%), diabetes mellitus during pregnancy (24.5%), and positive family history (11.1%) were common in patients with CHD. Roodpeym et al. (24) compared 346 patients with CHD to the same number of controls who were admitted at the same time concerning any differences in the risk factors. Presence of CHD in the siblings, genetic abnormalities, and malformations in other parts of the body were noted to be the significant risk factors for CHD. However, drug intake and maternal problems in the first trimester of pregnancy, history of abortion, and consanguineous marriage were not among the significant risk factors in that study. In another case-control study (8) evaluating a total of 250 individuals in each group, parental consanguinity was present in 48.8% of the patients in the CHD group (versus 28.9% in the control group). In addition to consanguineous marriages, maternal illnesses during pregnancy, family history of CHD, and low birth weight were the other risk factors of CHD. However, maternal age, neonate's gender, and drug intake during pregnancy were not significant risk factors for CHD. A case-control study in northwest of Iran (25) also investigated 267 patients with CHD and 206 controls via multivariate logistic regression. The results revealed that consanguineous marriage, gestational age ≥ 32 weeks, history of cesarean section, and maternal disease had significant relationships with the development of CHD.

Knowing about the presence of CHD in other children or in parents themselves would be helpful to identify the high-risk neonates. Accordingly, if the first child suffers from CHD, the probability of developing CHD has been estimated to be 2 - 6% in the second child and 2-3% in the third child. Meanwhile, parents' CHD and positive family history have been considered risk factors for development of CHD among children. Therefore, genetic counseling for the next pregnancy is recommended for parents with a child suffering from CHD.

5.1. Study Limitations

One of the study limitations was the lack of a control healthy group, which could have led to bias. Although this study with 1000 participants was the first investigation of a large CHD population in Iran, a larger sample size could have resulted in more accurate reporting of the frequencies. Moreover, only hospitalized patients were entered into this study, which might have led to the loss of mild or late onset CHD types, such as BAV, resulting in bias. Additionally, this study could not be the representative of the CHD incidence in the Iranian community as information about the total pregnancy registry in Iran was not available. Furthermore, collection of data through genetic counseling rather than documented evidence might have resulted in recall bias.

Finally, this study was done in just one cardiac tertiary care center in Iran. Hence, future studies are recommended to be carried out in multiple cardiac centers.

The present study demonstrated the baseline neonatal and maternal characteristics of the patients with CHD, which revealed that some risk factors were common in these individuals. Therefore, it is necessary to provide preventive strategies for modifiable risk factors, monitor high-risk pregnancies at shorter intervals, raise awareness in the general population, and perform genetic counselling.

5.2. Clinical Trial Registration Code

This study was done in accordance with the patients' medical records and was not a clinical trial.

5.3. Ethical Approval

RHC.AC.IR.REC.1395.46; 24 December 2016

5.4. Informed Consent

Written informed consent was obtained from each study participant.

Acknowledgements

This project was conducted in Rajaie Cardiovascular, Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran and was approved by Rajaie Heart Center's Ethics Committee (RHC.AC.IR.REC.1395.46; 24 December 2016).

Authors' Contribution

SK collected the data. SK and NM wrote the manuscript. MM and MM evaluated the patients. SMZ analyzed the epidemiological aspect. SK, BR, and NM performed project management and provided the final approval.

Funding/Support

This project was conducted in Rajaie Cardiovascular, Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran (95012).

Financial Disclosure

The authors have no financial interests related to the material in the manuscript.

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