Risk Factors of Congenital Heart Diseases: A Case-Control Study in Northwest Iran

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ARTICLE INFO

ABSTRACT

Introduction: Congenital heart diseases are of immense importance and also a high prevalence. Contributing factors to developing these defects have not been abundantly studied. Therefore, the current study was conducted aiming at determining the effective factors on Congenital Heart Disease (CHD) in newborn infants of Northwest Iran. **Methods**: A case-control study was carried out in North-West of Iran from 2002 to 2012 and a total of 473 infants entered the study. Required data were obtained through check lists completed by the information of hospital records and interview with mothers of 267 newborn infants with CHD together with medical records of mothers as the case group, and 206 medical records of healthy infants at the same period all together with those of their mothers as the control group. The obtained data were statistically analyzed using descriptive statistical methods, T-test, Spearman's correlation coefficient, and Multi-variable Logistic Regression Model (OR with 95% CI), using SPSS.19. In the present study, P value less than 0.05 was considered statistically significant. **Results**: Based on the results of univariable analyses, the number of previous cesarean sections, past medical history of diseases, gestational age (GA), fetal weight at birth, diastolic blood pressure, fetal heart rate, pulse rate, fetal hemoglobin and hematocrit levels, and fetal head circumference at birth have significant relationship with incidence of congenital abnormalities (P<0.05). Family history, past cesarean sections history, past medical history and GA had significant relationship with CHD incidence. **Conclusion**: Based on the results of present study, in order to control and reduce the cases of CHD, it is crucial to make proper decisions and implement policies for reducing cesarean cases, lowering consanguineous marriages, providing proper pre-marriage counseling, prompt treatment of mothers' illnesses, improving pregnancy health care and mothers' health status for the purpose of better well-being of newborn infants.

Introduction

Congenital Heart Diseases (CHD), affecting infants since birth onward[1], are one of the most common health dilemmas and mortality causes of newborn infants.[2-4] This malady is usually due to abnormal development or lack of growth of fetal organs. The problems of these diseases are usually tolerable during intrauterine life but their complications emerge with the birth of infant, closure of the arterial ducts and foramen oval and termination of fetal blood circulation.[5] Various statistics estimate the global prevalence of 4 up to 10 cases per 1000 live births for these diseases.[6,7] However, in general, the prevalence of this disease is approximated as eight in 1000.[2] A clinical study in Iran showed a mean prevalence of 12.30 per 1000 live births between 1998 and 2007.[8] Recent studies conducted for identifying the contributing factors in incidence of this disease have figured out various factors which could be generally divided into two groups of environmental and genetic factors. Recently, it has been declared that the effect of the environmental factors is much more than that of the genetic factors, but still there is very limited and incomplete data about main reasons for incidence of this disease.[9,10] Among the most important factors the following have been studied in most of surveys: the individual social variables such as occupation, educational background, health status, smoking and alcohol consumption habits of

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mother, mothers' past medical history and emotional status, family history of disease, consanguineous marriages, sex, age, delivery method and many other factors.[11-16] There are very limited studies on determining effective factors of these diseases in Iran and available data identifying effective factors have mainly been obtained from studies of other countries.[17] As well as other diseases, lack of accurate data on effective factors of its incidence may lead to undesirable outcomes in treatment and prevention of this disease. Therefore, in order to make proper planning and decision in controlling and managing these diseases, it is necessary to conduct accurate studies to identify effective factors in developing these diseases. The present study aimed to investigate causative factors in frequency of CHD in newborn infants in Northwest Iran.

Materials and methods

The participants of this case-control study were newborn infants as well as their mothers whose information had been collected from Tabriz Alzahra and Madani Educational and Medical Centers, Tabriz, Iran. In this study, a total of 473 newborn infants with their mothers were enrolled into study between 2002 and 2012. All hospital records of newborn infants with CHD, consisting of a total of 267 cases with hospital records of their mothers were selected and used as the case group in the study. Meanwhile, 206 hospital records of healthy infants who were born in this center at the same period and in similar conditions with that of the case group were selected randomly and used as the control group. Required information was collected using checklists of hospital records of infants and their mothers as well.

The variables included: mother's age, family history, number of gravidities, infant's sex, weight at birth, smoking and alcohol consumption habits of mother, consanguineous marriages, cesarean section history, fetal head circumference at birth, postnatal care (PNC) of mother, body mass index (BMI) of mother during pregnancy, mother's diseases and received therapies, diastolic and systolic blood pressure, gestational age (GA), fetal heart rate (FHR), pulse rate (PR), hemoglobin (Hb), hematocrit (Hct) and other variables. Inclusion criteria for the case group were having CHD and exclusion criteria were having other congenital defects and developing respiratory distress syndrome. Inclusion criteria for the control group included well-being from all aspects and birth in the same period (during 2002-2012). Studied mothers in both groups were same in terms of Iron and folic acid supplementation during pregnancy and none had scarcity of receiving of these supplements. For the purpose of obtaining data from hospital records, permission was acquired from regional ethics committee of Tabriz University of Medical Sciences, and also consent of hospital authorities was achieved. Also researches were committed to respect all privacy policies of information and keep the personal information confidential.

Obtained data were statistically analyzed using descriptive statistical methods (frequency, percentage, mean, and Standard Deviation), T-test, Chi square, Spearman's correlation coefficient and logistic regression model and using SPSS version 19. P value less than 0.05 was considered statistically significant. About multi-variable analysis of regression model, all variables with P values of less than 0.2 in univariable analysis, were considered for logistic regression model and were analyzed simultaneously to compute confounding factors.

Results

A number of demographic characteristics for both groups are presented in Table 1. As shown in Table 1, there is a significant relation between age, weight, and fetal head circumference with presence of CHD. Although there was no significant relationship between GA and CHD, it was observed that the probability of CHD risk raised by increasing mother's GA.

Analyzing the results showed that mother and infant consanguinity exists in most cases ($P<0.001$) in which the most consanguinity occurs in blood groups O (65.5%), A (61%), B (54.3%), and AB (18.2%).

In terms of weight, the weight of 27.7% of infants in case group was less than 1500 g and about 11.7% were above 3500 g; while these figures in the control group were about 2% and 27.85% respectively. Results of Chi-square test showed that frequency distribution of weight in two study groups was statistically significant ($P<0.001$).

Other variables investigated in the present study were summarized in Table 2. The results of some studied variables such as illness, alcohol and smoking habits and blood/Rh group were not reportable in terms of significance and statistical comparison which was due to incomplete recording system in medical centers and cultural concerns. Generally, diabetes mellitus and hypertension were more prevalent in the case group. Alcohol consumption habits were reported only in 1 case. Smoking habit was observed only in one case in the control group and none of the mothers in case group had history of either smoking or alcohol consumption habits.

As shown in Table 2, except for systolic hypertension, PNC and delivery method, other variables had significant relationship with frequency of CHD. By increasing the number of cesarean deliveries, the risk of developing CHD increased in infants Among all cases, variables reported as significant in simultaneous logistic model were presented in Table 3.

Discussion

Congenital Heart Diseases (CHD) are one of the most prevalent causes of mortality in children. In recent years researchers declared various culprits for developing this disease. Generally, they divide these factors into two categories of environmental and genetic ones. Considering the fact that these factors could be different in various

Table 1. Demographic Characteristics of Case and Control Groups

Variables		Group		
		Case Group (N=267)	Control Group (N=206)	P
Sex	Male	147 (55.1)	117 (56.8)	0.7
	Female	120 (44.9)	89 (43.2)	
Gestational Age(w)		34.73±5.46	38.85±2.76	<0.001
Mother's Age (y)		28.31±6.80	27.18±6.29	0.09
Infant's Weight (gr)		2359.77±1003.92	3185.37±649.31	<0.001
Mother's Weight (kg)		74.62±12.63	77.00±13.5	0.12
Familial Marriage History		61 (22.8)	37 (18)	0.19
Infant's Blood Group	A	73 (40.1)	4 (36.4)	-
	B	36 (19.8)	2 (18.2)	
	O	61 (33.5)	4 (36.4)	
	AB	12 (6.6)	1 (9.1)	
Maternal Blood Group	A	100 (39.5)	72 (37.9)	0.58
	B	54 (21.3)	38 (20)	
	O	86 (34)	64 (33.7)	
	AB	13 (5.1)	16 (8.4)	
Infant Head Circumference (cm)		32.26±3.81	34.53±2.38	<0.001
* Data were reported in Number (%) and Mean±SD pattern				

Table 2. Comparison of Effective Factors Between Case and Control Groups

Variables		Group		P
		Case Group (N=267)	Control Group (N=206)	
Delivery Type	NVD	104 (39)	94 (45.6)	0.14
	C/S	163 (61)	112 (54.4)	
C/S History	None	187 (71.1)	163 (79.9)	0.01
	1	41 (15.6)	32 (15.7)	
	2	28 (10.6)	6 (2.9)	
	3	7 (2.7)	3 (1.5)	
PNC		81 (30.3)	67 (32.5)	0.61
Blood Pressure	Systolic (mm Hg)	117.65±18.29	114.88±14.20	0.35
	Diastolic (mm Hg)	75.13±12.03	71.81±9.35	0.008
FHR		140.43±11.18	140.86±4.86	0.03
Mother PR		82.91±8.19	80.71±4.47	0.007
Hemoglobin (HB)		12.17±1.76	11.78±1.33	0.007
Hematocrit (HCT)		37.14±5.42	35.94±3.85	0.005
Mother's Diseases		69 (25.8)	23 (11.2)	<0.001

C/S: Caesarean, NVD: Normal Vaginal Delivery
PNC: Postnatal Care, FHR: Fetal Heart Rate, PR: Pulse Rate
* Data were reported in Number (%) and Mean±SD pattern.

Table 3. Simultaneous Results of Variables in Logistic Regression Model

Variable	B	SE	Crude OR	95% CI	P
Consanguinity History	-0.77	0.28	0.45	0.26 - 0.79	0.005
Caesarean section History	-0.63	0.18	0.53	0.37 – 0.75	0.001
Mother's Diseases	0.85	0.31	2.34	0.26 – 1.08	0.007
Gestational Age					
Gestational Age ≥ 32 (w)	-9.23	1.24	1.01	0.26 – 1.08	<0.001

regions, it is necessary to conduct national and even local surveys to identify contributing factors to developing this disease. Results of current study showed that among studied factors, previous cesareans history, cardiac disease history, GA, infant's weight at birth, diastolic blood pressure, FHR, mother's PR, hemoglobin, hematocrit, and fetal head circumference at birth had significant relationship with incidence of CHD. Also based on the results of logistic regression analysis, family history, cesarean section history, past medical history, and GA had significant relationship with the incidence of congenital heart diseases.

The results of the present study showed that the great number of past cesarean cases significantly raised the possibility of developing CHD in newborn infant. In most of other studies conducted in this field, it was found that by increasing the pregnancy numbers, specially cesarean deliveries and induced abortion, the possibility of CHD incidence increases.[18-20] Thererfore, proper controlling programs should be implemented in order to prevent and reduce pregnancies leading to cesarean delivery and induced abortion.

In the present study, among investigated diseases, the rate of diabetes mellitus and hypertension in the case group was significantly much more than that of the control group. In the studies conducted in some regions of the world such as China[18,21], South America[22] and Peru[23], it has been showed that living in high altitude is a convincing factor in developing CHD and its reason is related to low oxygen level in height and raising of blood pressure as a consequence. Considering the fact that Azerbaijan province is a mountainous region, this factor could contribute to the increase in the prevalence of this disease. In this study, diabetes mellitus also runs in CHD group three times more than that of the healthy infants' group. A study conducted on 470 infants in Boston (USA), showed that prevalence of CHD among infants with diabetic mothers was about 5 times more than that of infants with healthy mothers[24] which was similar to the results of this study. Hence, more attention should be paid to the control of diabetes in pregnant mothers. In this study, no smoker was present in the case group and there was only one smoker in the control group. This hampered us to study the effect of smoking in developing CHD. The reason could be cultural as in Iran, especially Azerbaijan most women are not accustomed to smoking; however, in most of the previously conducted studies in other parts of the world, where smoking is common among women, there is a significant relationship between smoking and developing CHD. In a case-control study conducted in Lithuania, mothers' smoking was reported as one of the main hazardous risk factors of developing CHD in newborn infants.[25] Also in another case-control study conducted in that country, it has been shown that possibility for CHD risk in infants whose mothers had smoking habit during pregnancy is two times more than

that of infants whose mothers do not smoke.[26] Kallen et al. described in their study that there is a significant statistical relationship between the smoking habit of mothers and developing CHD in infants.[27] Although smoking habit among women is too low in Iran especially in Azerbaijan, mothers must be aware of its dangers on their infants' health.

Cardiac system evolution defect results in diminished perfusion in different organs, thus birth weight decreases. Also decreased perfusion results in defective cerebral structure evolution and low head circumference at birth. With regard to hypoxic condition of neonates suffering CHD, it is postulated that they have respiratory problems. Therefore, sympathetic system stimulation, diastolic blood pressure, PR HB and HCT increase, seems to be of great assistance in order to overcome this condition.

Result of multi-variate regression analysis showed that consanguinity marriage had a significant relationship with CHD (OR=0.45 95%, CI=0.26 – 079, P=0.005). Studies conducted in Alexandria of Egypt[28], Saudi Arabia[29], and Lebanon[30] showed that consanguinity marriage had a promoting effect on CHD risk. So, there should be plans to reduce consanguinity marriages along with providing more and better pre-marriage counseling services. This problem is a matter of concern in Iran, especially in rural areas where consanguinity marriages are more prevalent.

Analyzing the birth age of infants showed that there was a significant relationship between infants' age at birth and risk of CHD in two groups. In some other conducted studies it has been shown that the risk of developing CHD could increase in preterm birth infants which is due to incomplete development of cardiac tissues and structures and specially interatrial and interventricular shunts remaining open.[31] Consequently, the preterm birth of infants should be prevented by improving the quality of pregnancy cares.

Low number of variables that limits the possibility of more investigations and comparison with other studies is the notable weak point of this study. So it is suggested to survey diverse variables in future studies. Variables such as mothers' educational background, mothers' occupational status, abortion history, mental-psychological status of mothers, patients' social and economic status, could be mentioned. The incomplete data is due to undependable hospital records in terms of recording and filing. More attention must be paid to the hospital records. It's advised to conduct a general study with high number of patients in different centers of Iran at the same time.

Conclusion

Although the pattern and etiology of diseases in various parts of the world and even inside a country are different from one region to another, and due to scant studies conducted in our country in the field of CHD, the results of this study could provide authorities, policy makers, and health care providers with useful information about

regional reasons of developing CHD for the purpose of further decision makings and planning in health sectors. Based on the results of this study, the most important and significant effective factors in developing CHD are repeated cesareans, family history, general health status of infant including birth age, weight at birth, heartbeat and etc. So, in order to improve general health of newborn infant, control and reduce of CHD cases, it seems necessary to plan and make policy for decreasing cesarean cases, decreasing consanguinity marriages, providing a proper counseling, recognizing dangerous pregnancies, prompt managing of mothers' diseases, and improving pregnancy care and mothers' health status.

Acknowledgments

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