

Risk Factors for Congenital Heart Disease (CHD) in Vellore, India

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Abstract: The aim of this study was to investigate the probable risk factors implicated in the aetiology of Congenital Heart Disease (CHD) in Vellore population, India. CHD is now a most common cause of birth defects. The burden of CHD in India is enormous due to very high birth rate. This emphasizes the importance of this group of heart diseases. The cause of 90% of the CHDs is multifactorial, but little is known about the environmental risk factors. Thus a matched case control study was conducted in Vellore, India, aiming at investigating the risk factors responsible for the causation of CHDs. Descriptive statistics was reported as mean value and 95% Confidence Interval (CI). Chi-square (χ^2) test was used for testing the association between two variables. Univariate analysis was performed followed by multivariate logistic regression analysis to provide the estimated effect of each risk factor. Thus Chi-square (χ^2) test showed that significant risk factors that are associated with CHDs were maternal and paternal age at pregnancy, rural residence, birth order, birth weight of the individual, consanguineous marriages, family history of inherited disorder, maternal drug exposure, maternal illness, maternal infection, socio-economic status of the family. Logistic regression analysis revealed that only maternal and paternal age at pregnancy, rural residence, birth order and birth weight of the individual were only found significantly associated in the development of CHDs. This study emphasizes on the augmenting pre-marital counselling and regular health counselling during pregnancy, extending health education to women of childbearing age and need of occupational health system to monitor the residential areas for risk of any environmental teratogen.

Key words: Chi-square (χ^2), Congenital Heart Disease (CHD), multivariate logistic regression, risk factors, univariate analysis

INTRODUCTION

Congenital Heart Disease (CHD) refers to a problem with the heart's structure and function due to abnormal heart development before birth. Congenital malformations are the most common of all birth defects. CHD affects about 8-10 per 1000 live births and is a leading cause of infant mortality. The burden of CHD in India is enormous due to very high birth rate. This emphasizes the importance of this group of heart diseases. It is known that 180,000 children are born with CHD each year in India. Approximately 10% of present infant mortality in India may be accounted for the CHD alone (Saxena, 2005). Rapid advances have taken place in the diagnosis and treatment of CHD in last six decades. Due to the currently available sophisticated diagnostic tools, accurate diagnosis of CHD can be made even before birth. But, unfortunately this privilege of early diagnosis and timely management is restricted to children in developed countries only. There are still majority of CHD cases in a

developing country like India due to lack of necessary care leading to mortality and morbidity (Saxena, 2008). It has been estimated that some types of CHD can be related to the defects in the chromosome, gene or environmental factors (Nora and Nora, 1976). There is relative importance of both genetic and environmental risk factors in the causation of CHD. However, the specific role played by each of the factors is still contradictory. Environment plays a significant role and constitutes about 1% in the causation of CHDs. It was hypothesized that environmental agents act on the individuals predisposed to the malformation and to the agent, and the exposure must occur at the vulnerable period of cardiac development (Nora and Nora, 1978). Several risk factors like demographic, reproductive and factors in lifestyle or environment have been proposed for CHD. There is mounting evidence that indicates that advanced maternal age has significant effect on the risk of CHD (Tikkanen and Heinonen, 1990), though there are reports showing that young maternal age (<20 years) is also associated

with a increased risk of CHD (Ferencz *et al.*, 1997). Many studies have centred on paternal age as a risk factor for congenital cardiac defects in offspring and have showed varied results (Olshan *et al.*, 1994; Stoll *et al.*, 1989; Yang *et al.*, 2007; Zhan *et al.*, 1991). Consanguineous marriages are known to be one of the main causes for an increase of recessively transmitted diseases (Faeser and Biddle, 1976). Several investigations report the increased risk of CHD in case of birth order more than second (Nora and Nora, 1984; Rothman and Fyler, 1976; Tay *et al.*, 1982). There are reports showing maternal rubella infection as the only well documented infectious teratogen (Jackson, 1968), however maternal upper respiratory tract infection and Cytomegalovirus have also proven as the risk factor for CHD (Feingold and Payshan, 1983). Maternal diseases like type I diabetes, influenza, febrile illness, Phenylketonuria (PKU) are considered as definite risk factors for CHD. There is evidence showing certain drugs as potential teratogen when ingested by the mother like lithium, retinoid, thalidomide, insulin, antihypertensive, anti-convulsants (Mone *et al.*, 2004). There have been conflicting results between associations of maternal alcohol consumption; maternal smoking and risk of CHD (Ferencz *et al.*, 1997; Tikkanen and Heinonen, 1990, 1991, 1992b; Kallen, 1999). Maternal exposure to certain chemicals like dyes, lacquers, paints and organic solvents during the first trimester of pregnancy was found to be associated with slightly higher incidence of CHD than the unexposed control group (Tikkanen and Heinonen, 1992a).

Keeping in mind the multitude of health problems a developing nation like India faces, like inadequate health education and weak legislation for the control of environmental pollution that may influence the aetiology of this disease, this study was designed with an intent to investigate the probable risk factors implicated in the aetiology of CHD in Vellore population, India, as the role played by these risk factors in the causation of the defect is not well documented in this region.

MATERIALS AND METHODS

The present investigation was conducted from the year 2006 to 2008 in Christian Medical College (CMC) and Hospital, Vellore.

CHD cases: This study was carried out in Vellore, which is a city in southern India situated 135 km from Chennai and 220 Km from east of Bangalore. Being an administrative centre it is located on the plains surrounded by low, rocky hills. The geographical area of the district is 6077 Km² and the total population as per 2001 census is 900,000. The present investigation was conducted from the year 2006 to 2008 in Christian Medical College, Vellore. This is one of the major hospitals in Vellore with

an influx of majority of patients from in and around Vellore region due to the low-cost but effective diagnosis and treatment. The subjects for the study consisted of paediatric live births and inpatients that were examined for various illnesses in the hospitals.

Control population: Hospital-based controls, equal in number as the subjects from different ethnic background and suffering from condition unrelated to cardiac disease and within the same age category and sex of cases were randomly collected.

Clinical evaluation: The suspected CHD patients with symptoms such as rapid breathing, fatigue, cyanosis, heart murmur, failure to thrive, abnormal chest X-ray or family history were referred to the clinicians for further clinical diagnosis, X-ray analysis, EEG and echocardiographic examination to confirm the defect. A total of 110 confirmed CHD patients were selected for this study with age range from 5 to 47 years. Equal number of age and sex matched control samples were also collected.

Data collection and management: All the participants' birth parents were retrospectively interviewed using a standardized questionnaire. A written informed consent was taken from each patient and control individuals and their family members. The questionnaire consisted of the following details:

Demographic characteristics: This included name of the child, sex, exact date of birth, full residential address, nationality.

Patients birth details: Gestational age, birth weight, birth order

Birth parent details: parental age at pregnancy, parental consanguinity, familial incidence of the disease, congenital anomalies of the sibs of the proband, other associated disorders of the proband, occupational exposure history, or change in lifestyle, reproductive history of the mother and environmental exposures (infection, exposure to drugs, maternal illness like cold and fever, irradiation), socio-economic status of the family, paternal occupation.

The above-mentioned information was carefully recorded and maintained in a register.

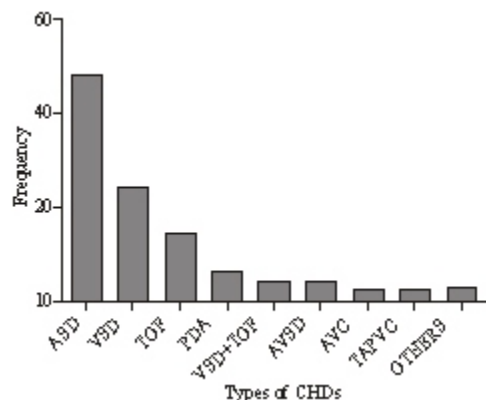
Statistical analysis: Statistical analysis was done using Sigma Plot statistical software 11.0. Descriptive statistics was reported as mean value and 95% Confidence Interval (CI). Chi-square (χ^2) test was used for testing the association between two variables. Univariate analysis was performed followed by multivariate logistic regression analysis to provide the estimated effect of each

risk factor. Case-control status was used as dependent variable and maternal and paternal age at pregnancy, gender, birth weight, birth order of child, consanguineous marriages, family history of the disease, maternal therapeutic drug exposure, maternal illness, maternal infection, socio-economic status of the family and paternal residence as co-variates.

RESULTS

A total of 110 CHD cases were taken for this study. Among the CHD cases analyzed 59 (53.63%) were females and 51 (46.36%) were males. The age range was 5 to 47 years and the mean age was 19.08 years. Among the CHD cases 49 (44.54%) had atrial septal defect, 25 (22.72%) had ventricular septal defect, 15 (13.63%) had tetralogy of fallot, 6 (5.45%) had patent ductus arteriosus, and 15 (13.63%) had other types of CHDs (Fig. 1). The assignment and proportion of potential risk factors for CHDs in Vellore population are listed in Table 1. The mean maternal age at pregnancy was 23.07 years (standard deviation [SD] ± 5.52) and mean paternal age at pregnancy was 27.51 years (standard deviation [SD] ± 6.52). There were 29.09% CHD cases with birth weight < 2.5 kg with mean birth weight of the subjects being 1.29 kg (standard deviation [SD] ± 0.457). The percentage of cases with 1st, 2nd, +3rd birth order were 38.18, 23.63, 38.18% respectively. Consanguineous marriages were prevalent in 26.36% of our study subjects. Socio-economic status of the family was also taken into account and was categorized as low (56.36%), middle (43.63%), and high (0%). There were 19.09% cases in which history of inherited disorders was reported in the family. Our study consisted of cases of teratogenic exposure also among which 11.81% cases were of maternal exposure to therapeutic drugs, 7.27% cases of maternal illness (fever and cold) and 20% cases of maternal infection (upper respiratory tract infection).

Risk factor analysis: As shown in Table 2, with respect to demographic factors maternal age ($p < 0.001$) and paternal age at pregnancy (0.001), birth weight of the individual ($p < 0.001$) and birth order ($p < 0.001$) were found significantly associated with CHD. Though gender of the individuals was not found associated with the risk for CHD as there was no significant difference ($\chi^2 = 0.0183$, $p = 0.892$) in the number of males and females that participated for the study, both in cases and controls. CHD cases had an almost even distribution as regards their residences, while controls showed a predominance of urban residence over the rural one. Socio-economic status of the family was found to be significantly associated with the causation of CHDs ($\chi^2 = 96.568$, $p < 0.001$). The average inbreeding coefficient was higher in families of cases (0.33) compared to the families of



Atrial Septal Defect (ASD) is the most frequent defect of all the recorded defects, followed by Ventricular Septal Defect (VSD), Tetralogy of Fallot (TOF), Patent Ductus Arteriosus (PDA), Ventricular Septal Defect with TOF (VSD+TOF), Atrioventricular Septal Defect (AVSD), Atrioventricular Canal Defect (AVC), Total Anomalous Pulmonary Venous Connection (TAPVC)

Fig. 1: The various major types of CHDs recorded during the study period from 2006-2008

controls (0.018), there was significant difference between the cases and controls as regards the proportion of consanguineous marriages ($\chi^2 = 33.403$, $p < 0.001$). Thus, risk factors for CHDs, such as maternal age ($p < 0.001$) and paternal age (0.002) at pregnancy, birth weight ($p < 0.001$), birth order ($p < 0.001$), consanguineous marriages ($p < 0.001$), family history of inherited disorders ($p < 0.001$), paternal residence ($p < 0.001$), socio-economic status of the family ($p < 0.001$), maternal therapeutic drug exposure ($p < 0.001$), maternal illness ($p < 0.001$), maternal infection ($p < 0.001$) were found significantly associated with CHDs while gender ($p = 0.892$) was not significantly associated with CHD, were identified by univariate analysis.

Multivariate logistic regression analysis followed the univariate analysis to assess the significant risk factors for developing any type of CHD in our study population. Case-control status was used as the dependent variable and maternal and paternal age at pregnancy, gender, birth weight, birth order of child, consanguineous marriages, family history of the disease, maternal therapeutic drug exposure, maternal illness, maternal infection, socio-economic status of the family and paternal residence as co-variates. Estimates of logistic regression co-efficient, significance probability and relative odds ratio were calculated for each variable in the analysis as shown in Table 3.

The regression coefficients (β) for maternal age and paternal age at pregnancy was 1.447 and 2.484 respectively, which implies that age of the mother and

Table 1: Risk Factor exposures among cases and controls

Risk factor	CHDs	Controls	Risk factor	CHDs	Controls
Maternal age range at pregnancy (years)			Paternal age range at pregnancy (years)		
<20 years	25.45*	4.54	<20 years	0	0
20-29	57.27	89.09	20-29	69.09	87.27
30-39	15.45	5.45	30-39	23.63	10.90
>39 years	1.81	0.90	>39 years	7.27	1.8
Socio-economic status			Birth Order		
Low	56.36	0	1	38.18	74.54
Middle	43.63	83.63	2	23.63	23.63
High	0	16.36	3+	38.18	2.72
Family inherited disease history			Maternal drug exposure		
Yes	19.09	0	Yes	11.81	0.9
No	80.90	100	No	88.18	99.09
Consanguinity			Maternal illness		
Yes	26.36	1.81	Yes	7.27	1.81
No	73.63	98.18	No	92.72	98.18
Gender			Maternal infection		
Male	46.36	46.36	Yes	20	0
Female	53.63	53.63	No	70.90	100
Birth weight			Paternal residence		
<2,500 g	29.09	3.63	Urban	59.09	80.90
≥2,500 g	70.90	96.36	Rural	40.90	19.09

*: Proportion (%)

Table 2: Details of contingency analysis of various risk factors in CHD in Vellore population

Variables	Cal. χ^2 Value	df	Significance
Maternal age at pregnancy [§]	25.143	1	p<0.001*
Paternal age at pregnancy [§]	10.168	1	0.001*
Birth weight	25.473	1	p<0.001
Birth order	25.191	1	p<0.001
Consanguinity	33.403	2	p<0.001
Family history	21.058	1	p<0.001
Maternal drug exposure	11.773	1	p<0.001
Maternal illness	6.356	1	0.012*
Maternal infection	22.273	1	p<0.001
Socio-economic status	95.568	2	p<0.001
Gender	0.0183	1	0.892**
Paternal residence	11.450	1	p<0.001

*: Significant at p<0.001, **: Non-Significant

§: Factors reassigned after function transform of the discrete ranked variables, 0: <20 or ≥35 years, 1: 20-35 years of maternal and paternal age at pregnancy

father at the time of pregnancy had a positive impact on the occurrence of CHD in our study and was significant at $p = 0.05$. The odds ratio for maternal and paternal age (i.e., <20 and ≥35 years) at pregnancy were 4.251 and 11.994, respectively that indicates that both maternal age and paternal age at pregnancy increases the risk for CHD in the Vellore population by 4.251 and 11.994 times the maternal and paternal age between 20-35 years. The regression coefficient (β) and odds ratio for birth weight were -2.478 and 0.0839 respectively, which has significantly (at $p = 0.05$) negative impact on CHD. The regression coefficient (β) and odds ratio for birth order (birth orders > 1) of cases was 1.367 and 3.925 respectively, which significantly increases the risk of CHD by 3.925 times the normal birth order (birth order 1). Paternal residence (rural) had a regression coefficient (β) of 1.685, which implies that it strongly influences the occurrence of CHD in our study and was significant at $p = 0.05$. It had an odds ratio of 5.392 that indicates that there is 5.392 times more risk of occurrence of CHD in the case of rural residents than the urban. Thus in multivariate analysis, paternal residence, maternal and

paternal age at pregnancy, birth weight and birth order of the individual was only statistically significant risk factors for CHD.

DISCUSSION

This study has been conducted to screen the possible risk factors for CHD in the Vellore region, Tamil Nadu, India. Paternal residence is observed to be the most important factor ($\beta = 1.685$, $p = 0.008$) in the occurrence of CHD. This might be as results of large number of parents belonging to rural areas of Vellore are factory workers (leather, tannery, chemical, heavy metal and explosive industries). The mainstay of people in rural areas is industries like weaving, beedi and matchstick rolling. There are reports showing use of organic solvents in weaving operations, which are considered to be significantly associated in the causation of CHD (Tikkanen and Heinonen, 1990; Zhu, 1993; Hook, 1992; Belletti *et al.*, 1993). Though, relatively few studies have evaluated the effects of paternal age on the risk of CHDs and those that did found negligible, if any, effect. In this

Table 3: Logistic Regression analyses of case-control study of CHD patients

Multivariate analysis			
Variable	Coefficient (β)	p-value	odds ratio (95% CI)
Maternal Age at pregnancy	1.447	0.068*	4.251 (0.899; 20.105)
Paternal Age at pregnancy	2.484	0.008	11.994 (1.921;74.873)
Birth Weight	- 2.478	0.003	0.0839 (0.0159;0.443)
Birth Order	1.367	0.028	3.925 (1.158;13.309)
Consanguinity	- 21.626	0.997	----
Family History**	- 19.761	0.997	----
Maternal Drug Exposure	- 20.795	0.999	0.0264 (0.00161;0.431)
Maternal Illness	- 0.705	0.666	0.494 (0.0201;12.116)
Maternal Infection**	- 19.986	0.997	----
Gender	- 0.0201	0.973	0.980 (0.307; 3.131)
Socio-economic Status**	21.101	0.995	----
Paternal Residence	1.685	0.008	5.392 (1.565;18.572)

*: p<0.05; CI, Confidence Interval, **: Odds ratio are not shown if the 95% CI are extremely wide

study, older paternal age is found to be significantly associated with CHD and this association could be explained by dominant mutations (Olshan *et al.*, 1994). Most recently a large study reported a significant trend of increasing risk for CHDs with increasing paternal age (Yang *et al.*, 2007). Our study also reports the risk of CHD in younger mothers below 20 years of age and older mothers above 35 years of age at the time of pregnancy. There are reports that show increased maternal age at conception is associated with increased risk of CHD (Tikkanen and Heinonen, 1990). It is reported from some high- prevalence areas of China that teenage and older mothers are found to be at higher risk of having a child with CHDs and the prevalence rates less than 20 years maternal age group is 188.7 per 10,000 live births whereas corresponding rate for groups over 30 years of maternal age is 91 per 10,000 live births (Zheng *et al.*, 2007). A study on Polish population had also reported parental age as a risk factor for isolated congenital malformations (Kirylyuk *et al.*, 2008). Birth order of infant more than one is another important risk factor that our study reports, which has been found, associated with the occurrence of CHD. Several investigations have also found that birth order more than the second consistently increases the risk of CHDs (Nora and Nora, 1984; Rothman and Fyler, 1976; Tay *et al.*, 1982). We observed that the occurrence of CHD was inversely associated with the birth weight of the individual. We also suspect that individuals with lower birth weight (<2,500 g) were at a higher risk for the development of CHD than those with birth weight ≥ 2,500 g. There are evidences reporting that certain CHDs are associated with low birth weight (Ferencz *et al.*, 1997).

CONCLUSION

This study is one of the few studies undertaken in the developing world that throws light on the types of risk factors for CHD in the Vellore region inspite of multitude of health threats in the environment and inadequate health care system. Nevertheless, this study offers the information to assist in suggesting following recommendations for local CHD prevention.

- The government should promote health education and communication strategies for women of childbearing age. Pre-marital counselling should be emphasized to avoid teenage marriages and in case if married, it should be strongly urged that they delay childbearing as teenage mothers are at a greater risk than women over 20 for pregnancy complications and risk of CHDs.
- Married couple should seek advice of their genetic counsellor to know about the risks of old age pregnancy.
- Teenage mothers are more likely to have a low birth weight baby with risk of CHDs. Thus early and regular prenatal care should be recommended to all women who could become pregnant, that they should eat a healthy balanced diet and achieve a healthy weight to reduce the risk of having a baby with low birth weight defects.
- Need of occupational health system to monitor residential areas for risk of any environmental teratogen should be emphasized.

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