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Risk Factors of Congenital Heart Diseases in Children: A Hospital-Based Case-Control Study

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Abstract

Background: Survival and quality of life for children with congenital heart diseases (CHDs) have improved over the last few decades due to different interventional strategies. However, primary prevention is the next barrier to be surmounted. **Objectives:** The present study is aimed at determining the risk factors of CHDs, their associations and comparison with those without CHD. **Methods:** The case-control study was conducted over a period of 12 months on 208 children aged 1 month to 60 months (case and control =1:1). Children diagnosed with CHDs by echocardiography were included in the study as cases. Controls (age and gender matched) were selected from the well-baby and immunization clinic. A univariate and multivariate logistic regression analysis was done to find out the necessary associations. A P-value of <0.05 was set asstatistically significant. **Results:** 85.58% of the cases were acyanotic CHDs, and the rest were cyanotic CHDs. Multivariate logistic regression analysis showed **that** advanced paternal age (≥30 yrs.) (OR: 2.52, 95% CL: 1.155–5.510), no intake of iron folic acid (IFA) antenatally (OR: 2.78, 95% CI: 1.112–6.155), and higher birth order (>2) (OR: 3.09, 95% CI: 1.176–8.132) were independently associated with increased risk of CHDs and was statistically significant. **Conclusion:** The present research concludes that a higher birth order, advanced paternal age, and no IFA intake have been independently associated to an increased risk of CHDs.There is a dearth of information in the present area of study regarding the risk factors of CHDs. This study may serve as a baseline data to compare and follow for further research. A better glimpse on the associations of possible risk factors with CHDs will lead to better primary prevention and reduction in the burden of the disease.

Keywords: children, case-control, congenital heart disease, risk factors

Introduction

The most prevalent congenital disease in children is CHDs, which is also the most prevalent of all cardiac disorders.[1] "A gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance" is what Mitchel et al. defined as CHDs.[2] Based on multiple studies, the incidence of CHDs is 8–10 per 1000 live births globally, with a higher incidence in preterm, stillbirth, and spontaneous abortion.[3]

The causes of CHDs are multifaceted.[4-7] The commonly studied ones are alcohol consumption, smoking, genetics, high blood pressure, diabetes, taking medication during pregnancy, connective tissue disorder, epilepsy, mood disorder, obesity, contracting German measles while pregnant, consanguineous marriage, advanced maternal age, and no intake of iron folic acid tablets during pregnancy.[4, 5, 7]Incidence of CHDs ranges from 0.8 to 4.2 per 1000 live births in India, and the condition accounts for 10% of infant mortality.[8-10] The burden of CHDs in India is likely to be the largest simply because of more child-births in India than anywhere else.[11, 12] Most children with CHDs in our region escape detection, the reasons being lack of awareness, poor socioeconomic status, and poor availability of echocardiography. As the infant mortality rate(IMR) from readily preventable causes declines, the contribution of CHD to IMR is likely to increase.[13] Evaluation of risk variables of CHD and addressing them in the right way is essential to bringing down IMR further. Lack of previously conducted studies on risk factor evaluation in the eastern part of the country necessitates carrying out the present study.

Aims and Objectives

This study was undertaken to determine the risk factors of CHDs and to study the profile of the patients with it.

Methodology

Study area: Department of Pediatrics in a tertiary teaching hospital in India.

Study design: Hospital based case-control study.

Study period: 1stOctober, 2022 to 31st August 2023.

Ethical clearance: Ethical clearance (vide memo no: BSMC/IEC/3341, dated – 29.09.2022) has been taken from Institutional Ethics Committee before the initiation of this research work.

Study subjects:

Inclusion criteria –

Cases: 1 month to 60 months aged children of either gender, either attending the pediatrics outpatient department (POPD) or admitted in the pediatric ward with suspicion of having CHDs and subsequently subjected to relevant investigations including echocardiography and finally diagnosed to having structural abnormalities of heart.

Controls: Age and gender matched children clinically having no CHD, were selected from both well baby and immunization clinic.

The caregivers of enrolled cases and control gave consent after proper explanation of the research work.

Exclusion criteria:

(i) Children aged less than 1 month and more than 60 months age,

(ii) Children having acquired heart diseases such as rheumatic heart disease, and

(iii)Children with caregivers who did not consent.

A semi -structured questionnaire was prepared after pilot testing for the interview of caregiver of both cases and control. The questionnaire contained basic demography of enrolled children and medical records. Cases were selected consecutively from POPD and pediatrics ward till we got the required number of samples.

Sample size: 208 (case and control = 1:1, 104 each).

Sample size calculation is done by software (Epiinfo3.5.1) based formula designated for case control study. Taking the ratio of case and control 1:1, power - 80%, two-sided confidence interval - 95%, and putting the odds ratio of the event of interest is consanguinity among parents that is 2.34, percent of controls exposed – 28.9 and percent of cases exposed – 48.8 as per previous study.[14]If the odds ratio for disease in exposed subjects relative to unexposed subjects is 2.34, we will need to study 104 cases with 104 matched controls to be able to reject the null hypothesis that this odds ratio equals 1 with power of 80%, assuming that the Type I error probability associated with this test of this null hypothesis is 5%. Thus, the total calculated sample size is 208.

Statistical analysis: Various risk factors for the development of heart diseases have been compared between cases and controls. The risk factors analyzed were age of the parents, history of consanguinity, any febrile illness during 1st trimester of pregnancy, iron and folic acid (IFA)intake, bad obstetrics history, and higher birth order (>2). Collected data was put into Microsoft Excel Spread Sheet and analyzed by EpiInfo (version 3.5.1) software. Continuous variables were expressed as mean and standard deviation and categorical was as percentages and ratio. A univariate and multivariate logistic regression analysis was run to find out the association between risk factors and CHD. Odds ratio (OR) was calculated for risk factors. A P-value =<0.05 was set as statistically significant.

Case definition: Any child showing visible cyanosis or SpO_2 (saturation) < 93% in room air, frequent chest infections in the past, inexplicable failure to thrive, difficulty feeding or effort intolerance, inexplicable congestive heart failure, murmur, abnormal electrocardiography (ECG), abnormal heart sounds, abnormal blood pressure, differential peripheral pulses, and an abnormal chest x-ray were taken as suspected cases.[15]

Results:

During the span of the study period, 104 children with CHDs were included in this research study. Male children exceeded female children in the research cohort; the male-to-female child ratio was 1.08:1, and first and second birth orders together outnumber third or higher birth orders. 82.69% of the babies were delivered vaginally, while the majority of the babies (91.35%) were delivered in healthcare facilities. Between the ages of one and six months, 52.88% of babies were diagnosed. The majority of the children's clinical presentations (56.73%) which brought them to the hospital were lower respiratory tract infections

(LRTIs). The basic demography and clinical presentation of cases of CHD are represented in Table 1.

Spectrum of congenital heart diseases with age at presentation

Acyanotic CHD was the most common condition seen in 85.58% of the children in the present research. Of which the ventricular septal defect alone accounted for 45.19% of all cases. ASD and PDA came in second and third, respectively, with 13.46% and 9.62% of the total cases of CHD. Tetralogy of Fallot (TOF), which accounts for 7.69% of all CHD cases, was the most common cyanotic CHD. Table 2 shows the age at presentation along with different types of CHD.

Analysis of risk factors by univariate logistic regression model

Table 3 compares the different risk variables for the development of CHD between the cases and controls. A statistically significant (P-value = <0.5) association was found between the presence of consanguinity among parents (OR:5.14, 95% CI:1.082-24.380), presence of bad obstetric history (OR:4.24, 95% CI:1.146-15.663), advanced paternal age (≥30 years) (OR:2.69), no IFA intake (OR:2.87, 95% CI:1.194-6.888), and higher birth order (>2) (OR:3.10, 95% CI:1.234-7.776) and the development of CHD. On the other hand, febrile illness during the first trimester of pregnancy (OR: 2.58, 95% CI: 0.649–10.271) and advanced maternal age (≥30 yrs.) (OR: 1.93, 95% CI: 0.687–5.435) were statistically insignificant (P-value = >0.5).

Analysis of risk factors by multivariate logistic regression model

Multivariate logistic regression analysis was then performed on all the risk factors that the univariate analysis had determined to be significant. The results showed (Table 4) that having a higher birth order (OR: 3.09, 95% CI: 1.176–8.132), no IFA intake (OR: 2.78, 95% CI: 1.112–6.155), and advanced paternal age (≥30 years) were associated with a statistically significant (P-value =<0.05) increased risk of developing CHD. Conversely, consanguinity among parents (OR: 2.40, 95% CI: 0.448–12.953) and the presence of a bad obstetric history (OR: 3.54, 95% CI: 0.902–13.880) lost significance (P-value = >0.5).

Discussion

This hospital-based case-control study was conducted to determine the risk factors for CHD, as well as to look into the characteristics of patients who have the disease in the area being studied, West Bengal, India. Consistently with previous investigators, 89 cases (85.58%) of the 104 total CHD cases in the current study were acyanotic CHDs.[16-19] Like other researchers from different study areas, VSD constituted 45.19% of all cases of acyanotic CHD. [18, 20] The present research showed that cyanotic CHDs comprised 14.42% of all CHDs, with TOF accounting

for 53.32% of all cyanotic CHDs. The results obtained are consistent with a study carried out in Odisha, India, by Patra U et al.[21]
In accordance with most studies that reported a male preponderance, our study also found a M:F ratio of 1.08:1, which was comparable to the results published by Patra et al., Thomford et al., and Amro K., who reported ratios of 1.06:1, 1:1, and 1.12:1, respectively.[21, 22, 18] The ratio was higher than in the current study, according to Khan et al.and Hussain et al., who found it to be 1.40:1 and 1.52:1, respectively.[19, 17] This discrepancy could be brought about by the varying degrees of gender inequality in society and more attention of care givers on male children in these studies. According to the current study, 85.58% of all cases of CHD first appeared in infants. Of which, 61.8% had a diagnosis made between the ages of one and six months, which is consistent with findings from other published studies.[17, 19]

The results of the present research showed a statistically significant association (OR: 2.52, 95% CL: 1.155–5.510) between advanced paternal age and CHDs. The conclusions of Olshan et al., Lian et al., and Abqari S et al., who discovered a similar association, which is compatible with this.[23, 24, 15] However, advancing paternal age was not associated to CHDs, in accordance with a Chinese study.[25] This is an interesting observation because, while maternal age has received a lot of attention, advanced paternal age may also be an indicator of risk for the development of heart defects. Which may be brought on by an increase in germ cell line mutations due to cumulative cell replications with the advancement of paternal age.[26]

It is also well known that an advanced maternal age has been associated to a high incidence of CHDS. This study is consistent with the studies done by Shiwei Liu et al. and Chaudhuary R et al. since it did not find a significant association between CHDs and advanced maternal age (OR: 1.93, 95% CI: 0.687–5.435).[27, 28] In contrast to the present research, a significant association was observed by Reefhuis et al. and Miller et al. between advanced maternal age and CHDs.[29, 30]

According to the present study, there was statistically significant association between the absence of IFA intake during pregnancy and a higher risk of CHDs (OR: 2.78, 95% CI: 1.12–6.955). Ionescu-Ittu R et al.from Canada and Van Beynum IM et al. from the Northern Netherlands noted what the present research explored. China's Jin X et al. found no correlation between IFA intake and the risk of CHDs, which is the opposite of the present research.[31-33] These differences may be linked to the quality of the pregnant woman's diet, but there are other possible reasons as well, such as a different study area or study design.

The current study provided insight into the relationship between birth order and a higher risk of CHDs. It was found that having a higher birth order (>2) was

associated to a statistically significant increased risk of CHDs (OR: 3.09, 95% CI: 1.176–8.132), which is comparable with research from China conducted by Zhan SY et al.[25] More thorough research is necessary to determine whether this association is related to higher birth orders with older parents.

Consanguinity among parents and having a bad obstetric history were associated, according to univariate logistic regression analysis, to statistically significant increases in the risk of CHDs (P-value = 0.039, OR: 5.14, 95% CI: 1.082-24.380 and P-value = <0.03, OR: 4.24, 95% CI: 1.146-15.663, respectively). However, on multivariate logistic regression analysis, they lost significance (P-value = 0.306, OR: 2.40, 95%CL:0.448-12.953 and P-value = 0.070, OR:3.54, 95%CI:0.902-13.880, respectively). Unlike the present research, Nabulsi et al. and Becker SM et al. found a significant association between first cousin consanguinity between parents and CHDs.[34, 35] In accordance with a study by Hasan I et al., the present research did not find a significant correlation between a bad obstetric history and CHDs.[36] Bad obstetric histories, such as abortion and stillbirth, are associated to an increased risk of CHD, as reported by Abqari S et al., which contrasts with the present research and Hassan I et al.'s findings.[15]

Univariate logistic regression analysis in the present research showed that a history of febrile illness during the first trimester of pregnancy was not associated with an increased risk of CHD (P-value =0.18, OR: 2.58, 95% CI: 0.649–10.271). Contrasting the present research, febrile illness during pregnancy was associated with a higher risk of CHD in research conducted by Abqari S et al., Jin X et al., and Shi QY et al.[15, 33, 37] This discrepancy could be a consequence of participants forgetting their prior health status, particularly in the first trimester of pregnancy.

Limitations of the study:

Some limitations of the present study are:

- The data was obtained from a tertiary care hospital, so they may not be truly representative of the profile of CHD in the community.
- Many children with CHD with no symptoms usually don't come to a healthcare facility and remain undetected forever until they encounter a healthcare professional for other reasons.
- The study may have recall bias as risk factors were evaluated using a questionnaire rather than resting on validated evidence.
- Chances of forgetting some significant events like exanthematous febrile illness during pregnancy and history about unwanted outcomes of previous pregnancy.
- Most of the neonates born with complex cardiac defects may die within the neonatal period either due to a lack of facilities or being born with so critical clinical conditions which do not allow time for diagnosis. PDA in preterm may close spontaneously or require medicine to close. This study

did not include neonates who had CHD and died within the neonatal period or children older than 5 years with CHD.

- Willful denial to share any kind of information about intake of any habit-forming substances by both parents.

Conclusion

In the present research area, there is an association between a greater risk of CHD and advanced paternal age, higher birth orders (>2), and no IFA intake. To prevent babies from being born with congenital heart disease (CHD), it is indispensable that IFA supplementation be addressed, especially during the first trimester of pregnancy, and that the prevailing family planning program be modified. Furthermore, since there is a dearth of information in the present area of being studied regarding the risk factors of CHD, this study may serve as baseline data to compare and follow for further research. This study also sought additional knowledge regarding whether to agree or disagree with the previously known risk variables or find any new risk variables. Though it is not a novel one, the advanced paternal age associated with a statistically significant risk of CHD in offspring was documented in a few studies worldwide. On the other hand, consanguinity among parents and bad obstetric history were associated with a statistically significant risk of CHD documented in innumerable literature around the globe. However, in the present study, these two variables lost significance in multivariate logistic regression analysis. It signifies the importance of geographical influence on the occurrence of CHD.

Author contribution:

All authors contributed to the conceptualisation anddesign of the study. They were actively involved in data collection and analysis, and critically and intellectually reviewed the manuscript and edited and approved the final version. All of them have agreed tobe accountable for ensuring the integrity and accuracy of the final manuscript.

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Tables:

Table 1: Basic demography and clinical presentation of cases of CHD.

Variables	***Subgroup***	***Number of Cases***	***Percentages***
Gender	Male Female	54 50	51.92 48.08
Birth order	≤2 >2	86 18	82.69 17.31
Place of delivery	Home Institutional	9 95	8.65 91.35

Mode of delivery	NVD LUCS	86 18	82.69 17.31
Age (month)	1-6 7-12 13-60	55 34 15	52.88 32.69 14.42
Body weight (kg)	1-5 6-10 11-15	67 25 12	64.42 24.04 11.54
Clinical presentation	LRTI CCF LRTI + CCF Cyanotic Spell Sepsis Poor weight gain Fever	59 18 6 7 4 6 4	56.73 17.31 5.77 6.73 3.85 5.77 3.85

Table 2: Spectrum of CHDs with age at presentation.

Types of CHD	***1 -6 months***	***7 - 12 months***	***13 – 60 months***	***Total (%)***
Acyanotic CHD				**89 (85.58)**
**VSD*	24	13	10	47 (45.19)
***ASD*	4	8	2	14 (13.46)
$PDA	7	2	1	10 (9.62)
$$ECD	1	0	0	1(0.96)
VSD +ASD	2	1	0	3 (2.88)
VSD + PDA	2	0	0	2 (1.92)
ASD + PDA	1	1	0	2(1.92)
VSD +ASD + PDA	1	0	0	1(0.96)
VSD + ^TR	0	1	0	1(0.96)
ASD + TR	0	1	0	1(0.96)
VSD +ASD + Situs inversus	1	0	0	1(0.96)
TR	0	1	0	1(0.96)
^^MR	0	2	0	2(1.92)
#AS	0	0	1	1(0.96)
##PS	0	1	0	1(0.96)
Cor triatinum	1	0	0	1(0.96)
Cyanotic CHD				**15 (14.42)**
▽TOF	4	3	1	8 (7.69)
Pentalogy of	1	0	0	1(0.96)

Fallot				
VSD + PS	1	0	0	1(0.96)
ASD + PS	1		0	1(0.96)
TGA	1	0	0	1(0.96)
TGA + VSD	2	0	0	2(1.92)
TGA + ASD	1	0	0	1(0.96)
Total	55	34	15	104 (100%)

*VSD- Ventricular septal defect, **ASD- Atrial septal defect, $PDA- Patent ductus arteriosus, $$ECD- Endocardial cushion defects, ^TR- Tricuspid regurgitation, ^^MR- Mitral regurgitation, #AS- Aortic stenosis, ##PS- Pulmonary stenosis, ▽TOF- Tetralogy of Fallot

Table 3: Risk factors of CHDs on univariate logistic regression model

Risk factors	***Sub groups***	***Cases (N=104)***	***Control (N=104)***	***P-value***	***OR***	***CI(95%)***	
						Lower	***Upper***
Paternal age	<30 yrs. ≥30 yrs.	77 27	90 14	0.009	2.69	1.277	5.659
Maternal age	<30 yrs. ≥30 yrs.	93 11	98 6	0.212	1.93	0.687	5.435
Bad obstetric History	Absent Present	93 11	102 3	0.03	4.24	1.146	15.663
History of febrile illness	Absent Present	94 10	102 2	0.18	2.58	0.649	10.271
History of Consanguinity	Absent Present	95 9	100 2	0.039	5.14	1.082	24.380
History of IFA intake	Absent Present	19 85	8 96	0.018	2.87	1.194	6.888
Birth order	≤ 2 >2	86 18	97 7	0.016	3.10	1.234	7.776

Table 4: Risk factors for congenital heart disease by multivariate logistic regression analysis

Risk factors	****S.E***	***P-value***	*****O R***	***Lower 95%***	***Upper 95%***
Paternal age > 30 years	0.398	0.020	2.52	1.155	5.510
History of consanguinity	0.858	0.306	2.40	0.448	12.953
Bad obstetric history	0.697	0.070	3.54	0.902	13.880
No intake of IFA	0.468	0.029	2.78	1.112	6.955
Birth order >2	0.493	0.022	3.09	1.176	8.132

Chi square value of this logistic regression analysis: 25.440.

*S.E: Standard Error, **OR: Odds Ratio