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RISK FACTORS FOR CONGENITAL HEART DISEASE AMONG PEDIATRIC AGE GROUPS FROM BIRTH UNTIL 5YEARS OLD IN MOSUL CITY

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ABSTRACT

Background: Congenital Heart Disease (CHD) is the most prevalent congenital defect, affecting the anatomy and function of the heart from birth. Congenital cardiac disorders frequently have unknown etiologies. On the other hand, chromosomal anomalies, environmental stressors, and genetic variables may all have a role in a large number of CHD instances. **Aim of the study:** To determine the extent to which suggested risk variables are linked to the development of congenital heart disease in neonates receiving care at Mosul city's pediatric teaching institutions. **Patients and methods:** A case-control prospective study was conducted at a pediatric cardiology center in Mosul city, involving 100 cases with congenital heart diseases and 100 controls aged less than 5 years. Data was collected through a questionnaire formula, which included information about gender, age at diagnosis, family history of CHD, consanguinity, type of CHD, maternal age at conception, paternal age, chronic drug use, smoking, x-ray exposure, and full term or preterm gestation. The cases involved confirmed CHD by echocardiography, while the controls included patients with no CHD. **Results:** The study found that the median age of patients with CHD was 6 months, significantly higher than that of controls (8.5 months). Maternal age was significantly higher in cases (30 years) than in controls (25 years). Male-gender and prematurity were significant risk factors for CHD. Family history of CHD, consanguinity, maternal history of Diabetes Mellitus and Hypertension were also associated with increased risk. **Conclusion:** Congenital heart diseases has many associated risk factors which are consanguineous marriage, prematurity, advanced maternal and paternal age, family history of CHD, male gender of the baby and age < 1year, maternal history of Diabetes Mellitus and Hypertension.

KEYWORDS: Congenital Heart Disease, Pediatric Age, Risk Factors.

INTRODUCTION

Congenital heart disease (CHD) is a heart defect that affects the heart's structure and function at birth, affecting nearby blood vessels. It's the most common congenital disorder in newborns, occurring in 8 per 1,000 births. 25% of newborns have critical CHD, requiring surgery or catheter-based intervention. CHD cases are multifactorial, with some linked to chromosomal disorders, single gene defects, teratogens, or maternal metabolic disease.[1]

PGDM and GDM are strongly linked to CHD risk and several of its manifestations. Compared to GDM, the PGDM appears to be more likely to result in CHDs in offspring, although Pregnancy induced hypertension is associated with an increased risk of CHDs morbidity.[2]

Risk factors for preterm birth include low birth weight, family history of congenital cardiac abnormalities, first-born child, prolonged exposure to environmental contaminants, and maternal age-associated risk factors.[3]

Many studies show a higher prevalence of congenital heart disease (CHD) in mothers aged 35 and above, with a 12%-36% increased risk. Maternal lifestyle behaviors such as smoking, using tobacco, and drinking alcohol are linked to increased risk. Maternal caffeine consumption, maternal TORCH infection, and certain drugs during pregnancy are also risk factors. CHD may lead to increased morbidity and mortality rates in infancy and long-term consequences in adolescents and adults. A public health approach is necessary to address these frequent, important, and expensive occurrences.[4,5]

There are numerous approaches to prevention, including lowering the incidence of congenital infections and altering risk factors by changing one's lifestyle.[7] Additionally, by initially recognizing the social and economic risk factors and providing educational health services, as well as by implementing a screening program for the social factors linked to CHD, it is possible to prevent and promote cardiac health[8], despite the fact that prenatal screening for CHD could largely control the burden disease, the increased rates of pregnancy termination had an adverse effect on the physical and mental health of mothers.[9]

The prognosis for infants born with severe congenital heart disease (CHD) has improved in industrialized nations due to advancements in medical and surgical care; nevertheless, in many underdeveloped nations, access to treatment for more severe diseases is still limited. In fact, it is currently unknown with accuracy how common CHD is at birth worldwide, which may mask regional variations in environmental and/or genetic risk factors for the disease that could have an impact on public health.[9] Medical conservative treatments, surgery, or catheterization are possible forms of treatment.[10] There are eight common congenital heart lesions (VSD, ASD, PDA, coarctation of aorta, TOF, TGA, PS and AS), which together make up to 90% of all cases. The VSD considered the commonest lesion and constitute about 25-30% of all CHD while ASD, PDA and coarctation of aorta are considered the next most common congenital heart diseases and each lesion forms about 8-10% of all congenital heart diseases (CHD). Tetralogy of fallot, which is the most common cyanotic congenital heart disease accounts for 6-8% of the whole CHD and the TGA for 5-6% of these diseases.[11]

AIM OF THE STUDY

To determine the extent to which suggested risk variables are linked to the development of congenital heart disease in neonates receiving care at Mosul city's pediatric teaching institutions.

PATIENTS AND METHODS

A case-control prospective study was carried out at pediatric cardiology center in Mosul city on infant 1day to 5years old age with congenital heart diseases, who attended the pediatric cardiology center during 6 months from 1st June 2022 to 1st November 2023. To collect the data, a questionnaire formula containing inquiries about gender, age at diagnosis, family history of CHD in the 1st degree and 2nd degree, consanguinity of the parents whether it was 1st degree cousins or 2nd degree, type of CHD and whether it was solitary or associated with extra cardiac malformations, maternal age at conception, paternal age, maternal history of chronic drug use whether it was before or during current pregnancy which included (Antiepileptics, Isotrenitoin, Indomethacin, ACE inhibitors, Antidepressants, lithium, Cytotoxic drugs and birth control pills), maternal history of smoking, maternal history of x-ray exposure during gestation, and whether the product of gestation were full term or preterm baby and this questionnaire data were collected through interviews with parents of enrolled infant.

The inclusion criteria included (age less than 5yrs, patients with confirmed CHD from Mosul city) while the exclusion criteria where (age more than 5 years, not from Mosul city). The total number of the study sample were 200 divided into 100 cases and 100 controls less than 5 years old. The cases involved patients with confirmed CHD by 2 dimensional colored Doppler echocardiography, while the controls involved patient chosen randomly with no CHD who attended pediatric consultation departments at Al-khansaa teaching hospital during the same period of time and of the same age groups.

Statistical analysis: The data collected during the study were summarized in sheets of Microsoft Excel 2010. The statistical analysis performed by using Statistical Package for Social Science (IBM-SPSS 20). The normality of these data was tested by Shapiro-Wilk test. The numerical data were expressed in median, range, minimum, and maximum values while the categorical data were expressed in frequencies and percentages. Mann-Whitney U test has been used to find the association between the numerical data while Chi square test was performed for comparison between categorical variables and if any cell had an expected value below 5, the fissure exact teas has been used instead of Chi square test. Odd's ratio (OR)(>1,1,<1) and 95% confidence interval (95% CI) was used as a measure of association between risk factors and development of disease. The p-value ≤ 0.05 considered as significant.

RESULTS

Comparison of age parameters between cases and controls was demonstrated in table (1) and revealed that the median age of the patients among the cases was 6 months and 8.5 months among the controls and the difference was statistically significant (p=0.037). The maternal age among the cases (30 years) was significantly higher (p=0.000) than that among the controls (25 years). Moreover, the paternal age among the cases (32 years) was significantly higher (p=0.001) than that among the controls (28.5 years). Among cases; 68.0% were under one year and 32.0% from one year up to 5 years while among the controls, 62.0% were under one year of age and 38.0% from 1-5 years old.

Table 1: Comparison of age parameters between cases and controls.

Age parameters	Cases (n=100) Median (Range) 25^{th}, 75^{th} Quartiles	Controls (n=100) Median (Range) 25^{th}, 75^{th} Quartiles	p-value *
Age in patients/months	6.0(60.0) 2.0, 14.4	8.5(59.4) 3.1, 18.0	**0.037**
Maternal age/ years	30.0(36.0) 25.0, 35.0	25.0(19.0) 23.2, 29.0	**0.000**
Paternal age/years	32.0(32.0) 27.0, 37.7	28.5(27.0) 25.0, 35.0	**0.001**
Age groups	**No. (%)**	**No. (%)**	**p-value ****
< 12 months	68(68.0%)	62(62.0%)	0.374
12-60 months	32(32.0%)	38(38.0%)	

**Mann-Whitney U test has been used; **Chi square test.*

Comparison of study variables between cases and controls were demonstrated in table (2) and revealed that males account for 61.0% of cases and 41.0% of the controls while the females found in 39.0% of cases and 59.0% of the controls; the difference was statistically significant (p=0.005). Concerning the gestational age, the 27.0% of cases and only 2.0% of the controls were premature while 73.0% of cases and 98.0% of the controls were full term; the risk of prematurity was 21 times with statistically significant difference (p=0.000). The positive family history of CHD was associated with development of the disease (OR=21.73) with statistically significant difference (p=0.000) between the cases 18.0% and controls 1.0%. The positive consanguinity was found among 52.0% of cases and among 19.0% of controls with 4 times risk (OR= 4.61) and the difference was statistically significant (p=0.000). The +ve maternal history of smoking and the use of COCP showed no significant difference.

Table 2: Comparison of study variables between cases and controls.

Study variables		Cases (n=100) No. (%)	Controls (n=100) No. (%)	OR	95% CI	p-value*
Gender	**Males**	61(61.0)	41(41.0)	2.25	1.27, 3.96	**0.005***
	Females	39(39.0)	59(59.0)			
Gestational age	**Premature**	27(27.0)	2(2.0)	21.34	4.82,94.3	**0.000***
	Full-term	73(73.0)	98(98.0)			
Family history of CHD	**Positive**	18(18.0)	1(1.0)	21.73	2.84,166.2	**0.000***
	Negative	82(82.0)	99(99.0)			
Consanguinity	**Positive**	52(52.0)	19(19.0)	4.61	2.44,8.71	**0.000***
	Negative	48(48.0)	81(81.0)			
History of smoking	**Positive**	1(1.0)	2(2.0)	0.49	0.04,5.54	1.000**
	Negative	99(99.0)	98(98.0)			
History of using chronic drugs	**COCP**	6(6.0)	4(4.0)	1.53	0.41,5.60	0.516*
	Negative	94(94.0)	96(96.0)			

**Chi square test; **Fisher Exact test.*

Comparison of maternal history of chronic diseases between cases and controls was showed in table (3). It was found that the DM was found among 9.0% and 2.0% of cases and controls respectively; the association was risky (OR=4.846, 95% CI=1.019, 23.027) and the difference was statistically significant (p=0.030). Moreover, HT was found among 8.0% of cases and 1.0% among the controls, the association was significant risky (OR=8.608, p=0.035). While asthma showed no significant difference.

Table 3: Comparison of maternal history of chronic diseases between cases and controls.

Maternal history of chronic diseases		Cases (n=100) No. (%)	Controls (n=100) No. (%)	OR	95% CI	p-value
DM	**Positive**	9(9.0)	2(2.0)	4.846	1.019, 23.027	**0.030***
	Negative	91(91.0)	98(98.0)			
HT	**Positive**	8(8.0)	1(1.0)	8.608	1.056, 70.169	**0.035****
	Negative	92(92.0)	99(99.0)			

Asthma	**Positive**	2(2.0)	1(1.0)	2.020	0.180, 22.645	1.000
	Negative	98(98.0)	99(99.0)			

**Chi square test has been used; ** Fisher Exact test.*

Comparison of maternal history of x-ray exposure during 1st trimester between cases and controls was demonstrated in table (4) and revealed that positive x-ray exposure found in 4.0% of cases and in only 1.0% of controls which although appeared to have a risky role in the development of the disease but statistically the difference was not significant.

Table (4): Comparison of maternal history of x-ray exposure between cases and controls.

Maternal history of x-ray exposure	Cases (n=100) No. (%)	Controls (n=100) No. (%)	OR	95% CI	p-value *
Positive	4(4.0)	1(1.0)	4.125	0.452, 7.572	0.469
Negative	96(96.0)	99(99.0)			

**Fisher Exact test has been used.*

DISCUSSION

Comparison of age's parameters between cases and controls revealed that the median age of the patients among the cases was 6 months and 8.5 months among the controls and the difference was statistically significant (p=0.037) and this is compatible to the study conducted in Iraq/Al-Anbar governorate by Al-Dalla *et al.,* (2019).[12] where the range of age was from 1 day to 14 years and the mean age was (16.6 ± 30.3 months). Most of the patients presented in infancy 188 (71.76%), 52 (19.85%) of them were neonates and 136 (51.91%) beyond the neonatal period up to 1year. And also to the study conducted in Egypt by Al-Fahham *et al.,* (2021)[13] were most of patients (86.8%) were diagnosed below the age of 1 year (37.8% in the neonatal period, and 49% within the first year of life).

In this study the results showed that strong association between maternal age more than 30 years and the development of CHD with a p value (0.000) and this is consisted with the study conducted in Iraq/ Basra by Abood *et al.,* (2014)[14] were p value was (0.01) for women aged 30-35 years and also similar to a study conducted by Ou *et al.,* (2016).[15]

In this study there was association between median paternal age greater than 32 years in comparison with the controls which was 28.5 years with p-value (<0.001) which is considered significant and this is almost the same result conducted in Iraq/Holly Karblaa by Abdulwahid *et al.,* (2016).[16] The result had indicated that there was a significant difference at P<0.01 for the distribution of paternal age groups between the two samples. The result shows that the study group shows more elderly fathers than control group and almost the same results conducted by Joinau-Zoulovits *et al.,* (2020)[17], in this meta-analysis, it is found that advanced paternal age (>30 years) was significantly associated with a 16% increase in the odds of CHD and the dose–response meta-analysis shows a linear association between paternal age and CHD.

In this study we found significant male predominance (61.0%) among cases with CHD in comparison to the controls (41%) and the difference was statistically significant with (p-value=0.005) and this is almost compatible with the study conducted in Iraq/Hilla and Baghdad city by Alghanimi *et al.,* (2018)[18] which shows that predominant were male (60%) and majority their age below one year (54.5%).

Comparison of gestational age between cases and controls revealed that 27.0% of cases and only 2.0% of the controls were premature while 73.0% of cases and 98.0% of the controls were full term; the risk of prematurity was 21 times and the difference was statistically significant (p=0.000) and these results are almost compatible with the study conducted in Iraq/ Mosul by Attia *et al.,* (2020)[19] which revealed that 68.4% of patient were premature and to the study conducted in Egypt by Al-Fahham *et al.*,(2021)[13] which detect prematurity in 19.3% of studied patients similar results are observed in a study conducted in keynyata national hospital by Aiko study (2022)[20] which implied that prematurity was significantly associated with the development of CHD.

In this study positive family history was found in 18% of cases with odd ratio (21.731) and p-value (0.000) which is considered significant risk factor and this result is compatible with the study conducted in Iraq/ holly karbala governorate by Easa study (2016)[21] which reported more than six times the control sample.

In this study revealed positive result with 4 fold increase risk with consanguineous marriage(1st and 2nd degree) and this is almost compatible with the study conducted in Iraq/Baghdad/ Ibn-Al-Nafees hospital by Batool *et al.,* (2015)[22] which revealed higher risk inside inter family marriage and to the study conducted in Pakistan by Mughal *et al.,* (2022).[23] showed that occurrence of congenital heart disease in children with consanguineous parents was 5.84 times higher as compared to those with non-consanguineous parents and to study conducted in

Bangladesh by Al Mamun *et al.*, (2021)[24] were parental consanguinity is significantly associated with CHDs.

In this study there was no significant role of smoking in the development of CHD ant this is compatible with the study conducted in Iraq/Mosul governorate by Attia *et al.*,(2020)[19] and to study conducted at Kenyatta National Hospital in Nairobi by Aiko study (2022)[20] while another study published by Correa *et al.*, (2015)[25] observed associations between maternal cigarette smoking during the first trimester of pregnancy and 3 phenotypes: pulmonary valve anomalies, pulmonary artery anomalies, and isolated secundum type of atrial septal defects and this difference could be explained by low prevalence of smoking in our community in comparison to the western countries judged by ethical and social habits.

In this study among the cases, 6.0% were used COCP while among the controls, the use of COCP was found in 4.0%; although the association was risky (OR=1.531), the difference was statistically not significant (p=0.516) but in comparison to study conducted in Iraq/Mosul by Attia *et al.*, (2020)[19] noticed that the frequency of CHD was increased among mothers who used contraception before the pregnancy of the affected gestation and this is may be explained by smaller sample size taken in our study.

In this study there was significant association between maternal hypertension, and diabetes with CHD while there was no significant difference with Asthma. The hypertension was found among 8.0% of cases and 1.0% among the controls, the association was highly significant risk factor (OR=8.608, p=0.035) and this is almost compatible with study conducted by Boyd *et al.*, (2017)[26] in which strong association between maternal hypertension and development of CHD was observed. In this study it was found that the DM was found among 9.0% and 2.0% of cases and controls respectively; the association was highly significant (OR=4.846) and the difference was statistically significant (p=0.030) and this is almost compatible with the study conducted in Iraq/Mosul by Hyali *et al.*,(2015)[27] were 6.5%of cases has maternal diabetes mellitus with p value (<0.05) and to the study conducted by Poly *et al.*, (2018).[28]

In this study we found there is no significant association between maternal asthma and development of CHD and this is similar the study conducted by Zutphen *et al.*,(2015)[29] which did not observe statistically significant associations between the reported use of asthma medications during pregnancy and most specific types of CHDs. The current study showed that although x-ray exposure have risky role in the development of disease but statistically the difference was not significant and this is almost compatible with the study conducted in Iraq/Mosul by Al-Hyali *et al.*, (2015).[27] The study showed that 2.2% of mother's patients with CHD had exposed to irradiation (x – ray) during first trimester of pregnancy in corresponding to 1.3% to mother's patients without CHD with non-significant p value (>0.05).

CONCLUSION

Congenital heart diseases has many associated risk factors which are consanguineous marriage, prematurity, advanced maternal and paternal age, family history of CHD, male gender of the baby and age < 1year, maternal history of Diabetes Mellitus and Hypertension.

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