Journal of Health, Medicine and Nursing
ISSN 2422-8419 An International Peer-reviewed Journal
Vol.26, 2016

Risk Factors for Congenital Heart Diseases in a Group of Children in Holy Karbala Governorate/IRAQ

* Mohammed Khawwam Abdulwahid FICMS [1]
Zuhair Omran Easa FICMS [2]
Abdulabbas Abduon Hadi FICMS [3]
Nabil Fahim Abdulrazzaq FICMS [4]

1,3 ,4 department of pediatrics in Al-Hindyia general hospital
2 department of Pediatrics in Karbala teaching hospital
* E-mail: khawwam@yahoo.com

ABSTRACT

Background: Prevention of congenital cardiovascular defects has been hampered by a lack of information about modifiable risk factors for abnormalities in cardiac development. Over the past decade, there have been major breakthroughs in the understanding of inherited causes of congenital heart disease (CHD), including the identification of specific genetic abnormalities for some types of malformations.

Aim of study: To investigate some of the risk factors and their significance in the development of congenital heart diseases among children in Holy Karbala governorate.

Methods: A case control study was done on pediatric patients with a confirmed diagnosis of congenital heart disease from January 2012 to January 2013 in Karbala Pediatric Teaching Hospital. A total of 212 patients, 106 cases and 106 controls were included in this study.

Results: maternal age<20 years represent 4.7 % of cases, while those above 30 years of age represent 37.7 % of cases. Paternal age >40 years found in 37 cases (34.9 %) and 24 control (22.6 %). full term gestation found in 91 cases and 101 controls. Residency in urban area found in 84 % of cases and 75.5 % of controls. Consanguinity was positive in 37 cases (34.9 %) and 18 controls (17 %). Second birth order and more found in 81 % of cases. Family history of congenital heart disease was positive in 11(10.4%) cases and 2 control (1.9%). Winter months' conception found in 44 cases (41.5%) and 21 control (19. 8%).low social class found in39 cases (36.8%) and 17 control (16%).isolated VSD found in 29 % of cases for whom consanguinity was positive in 9 cases and negative in 21 cases.

Conclusion: Analysis of our results showed that paternal and maternal age, urban residency, winter month's conception, low socioeconomic status, being 2nd borne or more and positive consanguinity are independent risk factors for CHD.

KEY WORDS: CHD, pediatric, risk factors, Karbala.

INTRODUCTION

Congenital heart disease occurs in approximately 0.8% of live births. The incidence is higher in stillborn (3-4%), spontaneous abortuses (10-25%), and premature infants (about 2% excluding patent ductus arteriosus [PDA]). This overall incidence does not include mitral valve prolapse, PDA of preterm infants, and bicuspid aortic valves (present in 1-2% of adults). [(1)]

Only a small percentage of cases have identifiable causes:
1- Genetic-environmental interactions (i.e., multifactorial): 85%.

2- Primary genetic factors (chromosomal abnormalities, single gene abnormalities): 10%
2- Environmental factors (e.g., chemicals; drugs such as isotretinoin or Accutane; viruses such as rubella; maternal disease): 3% to 5 %. [2]
Disease prevention has been hampered by a lack of information about modifiable risk factors for abnormalities in cardiac development. Over the past decade, there have been major breakthroughs in the understanding of inherited causes of CCVDs, including the identification of specific genetic abnormalities for some types of malformations. [3] Although relatively less information has been available on non -inherited modifiable factors that may have an adverse effect on the fetal heart, there is a growing body of epidemiological literature on this topic. The proportion of cases of CCVDs that are potentially preventable through changes in the fetal environment is currently unknown. [4] The lack of reliable information on modifiable risk factors has made it difficult to create population-based strategies to reduce the burden of illness from CCVDs and for couples to make lifestyle choices to reduce the likelihood of having a child with a major cardiac malformation. [5] Some studies show that periconceptional intake of multivitamin supplements containing folic acid may reduce the risk of CCVDs in offspring, similar to the known risk reduction for neural tube defects seen with folic acid. This finding was first identified after analysis of data from a Hungarian randomized trial on birth defects. [6] Findings from subsequent case-control studies have been generally supportive but not conclusive. [6-7] Many syndromes are commonly associated with cardiovascular anomalies; however, the frequency of CHD differs among these syndromes. [8]

Maternal hyperpyrexia
Maternal hyperpyrexia is not commonly thought of as a fetal teratogen but there are a number of experimental and observational studies suggesting otherwise. In laboratory guinea pigs, Edward et al has shown that heat exposure to fetal pup at a critical stage in development has induced a number of neurologic developmental anomalies and vascular disruption defects such as bowel atresias. In human, maternal exposure to hot tubs significantly increased the incidence of neural tube defects. [9]

Maternal diabetes mellitus
Pregestational diabetes is a known risk factor for congenital CHD as well as abnormal development of many other organ systems. Heart defects most commonly associated with diabetes include conotruncal defects and less commonly left ventricular obstructive defects. Identification of this risk factor is crucial so that control of blood sugar during pregestation and gestation can decrease the risk of such defects. [10] In a study performed by Hanson et al, hemoglobin A1c levels for those women seeking prenatal care were linearly correlated with the rate of miscarriage and anomalies. [11] Moreover, in a summary of 11 studies by Gabbe, the incidence of birth defects is 2.5% in those women seeking glucose control pre-conceptually versus 7.8% in those women presenting after conception. The HbA1c level at 14 weeks' gestation is predictive of the rate of fetal anomalies. A HbA1c level of >8.5% confers a risk of birth defects of about 20% versus 3.4% in women with HbA1c <8.5. [12]

Maternal age
There is mounting evidence indicates that advanced maternal age has significant effect on the risk of CHD, [13] though there are reports showing that young maternal age below 20 years is also associated with increased risk of CHD. [14]

Consanguineous marriages
This type of marriage is known to be one of the main causes for an increase of recessively transmitted diseases. [15] Overall the results suggest that the risk for congenital heart disease is increased in consanguineous unions in the studied populations, principally at first-cousin level and closer, a factor that should be considered in empiric risk estimates in genetic counseling. [16]

Birth order
Several studies report the increased risk of CHD in case of birth order more than second. [17,18]

Risk of medications
The US Food and Drug Administration (FDA) have classified a number of medications according to risk for

birth defects if ingested during pregnancy, although this classification relates to birth defects in general and not specifically to congenital cardiac defects. [19]

Maternal environmental exposure

Organic solvents: studies of this topic can be difficult because organic solvents often comprise a mixture of chemicals, because the composition varies between different commercial preparations, and because of limitations in the way that exposure was defined in retrospective case-control studies. a few have reported associations of cardiac defects with reported maternal exposure to solvents and paints. Reports of exposure to degreasing ether solvents have been associated with an increased risk of hypoplastic left heart syndrome, coarctation of the aorta, pulmonic stenosis, Transposition of the great arteries with intact ventricular septum, tetralogy of Fallot, total anomalous pulmonary venous return, nonchromosomal atrioventricular septal defects and Ebstein's anomaly. Maternal reports of occupational exposure to organic solvents have been associated with an increased risk of VSDs, dyes, lacquers, and paints with conotruncal malformations; and mineral oil products with coarctation of the aorta. [19]

Herbicides, pesticides, and rodenticides: a study suggesting an association of maternal employment in the agricultural industry with an increased risk of conotruncal defects suggested a possible association with chemicals used in agriculture. In the Baltimore-Washington infant study (BWIS), maternal reports of potential exposure to herbicides and rodenticides were associated with an increased risk of transposition of the great arteries and of potential exposure to pesticides with total anomalous pulmonary venous return and membranous VSDs. [20] a case-control study of various potential sources and numerous measures of maternal exposure to pesticides and congenital anomalies found mixed results for conotruncal defects. A more recent case-control study of various end-product uses reported an increased risk of conotruncal defects with maternal reports of exposure to insecticides. [19]

Air quality: two recent studies have examined possible associations of ambient air pollutants with CCVDs. One study conducted in southern California reported possible increased risks of any heart defects and of VSDs with increased ambient levels of carbon monoxide of aortic artery and valve anomalies with increased levels of ambient air levels of ozone during the second month of pregnancy and possible decreased risks of these defects with increased air levels of these pollutants during the 3rd month of pregnancy. [19] Groundwater contamination: the risk of congenital cardiac defects was reported to be greater among children of parents who had contact with areas that had groundwater contaminated with trichloroethylene than among children of parents who had no such contact. [19]

Water chlorination byproducts: a possible association between maternal exposure to chlorination byproducts that result from the interaction of residual chlorine and organic matter in tap water and cardiac defects in offspring has been the subject of several investigations. [35-39] These studies evaluated information on the type of chlorination treatment at the water plant or on levels of trihalomethanes measured at sampling points in the water distribution but not on actual levels of contaminants in water consumed or used for showering. Other studies found no associations with cardiac defects. [19]

Maternal stress

Maternal stress as measured by maternal reports of job loss, divorce, separation, or death of a close relative or friend was found to be associated with an increased risk of conotruncal heart defects (OR, 2.4; 95% CI, 1.42 to 4.2) in a case-control study in Atlanta. A more recent case-control study in California obtained a similar result (OR, 1.4; 95% CI, 1.0 to 2.1) with a stronger effect among offspring of mothers who had not completed high school (OR, 2.4; 95% CI, 1.3 to 4.8%). [21]

Paternal exposures: there is growing concern that paternal factors may play a role in the origin of congenital defects in general and of CCVDs in particular. New dominant mutations are more common in older fathers, and paternal age has been shown to be associated with birth defects such as Achondroplasia and in genetic conditions known to affect the cardiovascular system such as Marfan syndrome. [22,23]

Paternal age: Several studies have focused on paternal age as a risk factor for congenital cardiac defects in

offspring. Olshan et al evaluated the effect of paternal age on the risk of congenital heart defects in 4110 cases of congenital heart defects from the British Columbia Health Surveillance registry; matched controls were obtained from the birth files of British Columbia. The association of paternal age with 8 cardiac defects was examined after controlling for maternal age and other risk factors. A general pattern of increasing risk with increasing paternal age was found for ASDs, VSDs and PDA. (24)

Assisted reproductive technology (ART): ART increases the risk for congenital heart disease, particularly for malformations of the outflow tracts and ventriculoatrial connections. It is unclear if this risk is related to the underlying etiology of infertility in the couple or the ART per se. (25)

Demographic variation in incidence: certain population based studies show significant variation in incidence among different regions of the world. (26)

AIM OF STUDY: the aim of this study was to investigate the effects of certain risk factors implicated in the etiology of CHD in a group of pediatric patients in Holy Karbala governorate, Iraq.

PATIENTS AND METHODS: the present study was conducted from January 2012 to January 2013 in Karbala pediatric teaching hospital.

CHD cases: Karbala pediatric teaching hospital is the main pediatric hospital in the city with an influx of majority of patients from in and around Holy Karbala. The subjects for the study consisted of inpatients and outpatients that were examined for various illnesses in the hospital. CHD cases were confirmed by Echocardiography done by experienced general pediatricians.

Control population: Hospital-based and outpatient controls, equal in number as the subjects with CHD (cases) and suffering from conditions unrelated to cardiac disease and within the same age category and sex of cases were randomly collected. No familial relationship exists between cases and control.

Data collection and management: the participant asked to reply to a questionnaire which consisted of the following details:

Demographic characteristics: This included name of the child, sex, exact date of birth, taken from the identity card of the child, and full residential address.

Patients birth details:

1-Gestational age: preterm (<37 weeks), term (37-42 weeks) or post term (>42 weeks).

2-Birth order: this involved the exact birth order of the child including previous abortions and stillborn.

3-season conception: this factor estimated retrograde the 1st 12 weeks of conception from date of birth after considering the child gestational age for statistical purposes we divided the months of conception into 4 seasonal categories; winter (12-2), spring (3-5), summer (6-8) and autumn (9-11).

4- Other gross congenital malformation.

Parent details:

Maternal age; divided into 4 age groups; <20, 20-29, 30-39, and 40-49 years old.

Paternal age: divided into 4 age groups; 20-29, 30-39, 40-49, and >50 years old.

Parental consanguinity: weather positive or negative.

Family history of CHD: weather positive or not. Those with positive response divided into 5 categories and weather the affected patient is a sibling, father, mother, paternal or maternal side relative. Socio-economic status: this factor assessed by asking about the occupation of father and mother and weather the house of the family is rented or owned, subsequently divided into low, middle and high social classes.

Level of education of mother divided into Illiterate (not complete the primary school), primary school, secondary school and higher education (college graduate or more).

Systemic illnesses of mother during index pregnancy: this include diabetes mellitus, hypertension, urinary tract infections, asthma, epilepsy or others.

Mother weight during index pregnancy.

The number of patients was 106 for both cases and control, 52 were male and 54 were female. Age ranged from 1 day to 15 years old. Source of information were mainly the mothers and to a lesser extent grandparent, fathers or other relatives.

Statistical Analysis: the following statistical data analysis approaches were used in order to analyze and assess the results under application of the statistical package (SPSS) ver. (10.0): 1. Descriptive data analysis: a-Tables (Frequencies and Percentages). b- Contingency Coefficients for the association tables. c-Graphical presentation by using: Bar Charts and Cluster Bar Charts.

2. Inferential data analysis: These were used to accept or reject the statistical hypotheses, which included the following: a- Contingency Coefficients (C.C.) test for the causes correlation ship of the association tables. b- Odds Ratio coefficient for represents the number of times that the target Related Rates (Control / Study) at the association tables. c- Z - test for testing a single ratio under a null hypothesis which says that: (HØ: $\rho = 0$). d- Z - test for testing a double ratio (a difference between two ratios) under a null hypothesis which says that: (HØ: $\rho 1 = \rho 2$).

RESULTS

Maternal age: the result had indicated that there was a significant difference at $P<0.05$ for the distribution of maternal age groups between the two samples. The result shows that the study group shows more elderly mothers than control group, figure (II).

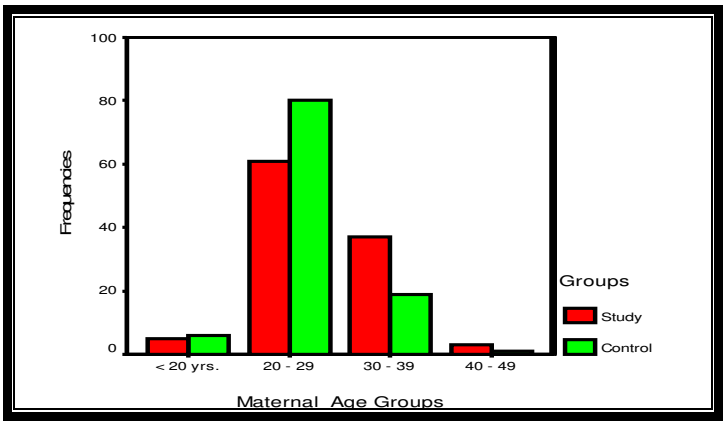

Figure (II): Cluster Bar Charts for the distribution of the studied samples according to maternal age.

Paternal age

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, figure (III).

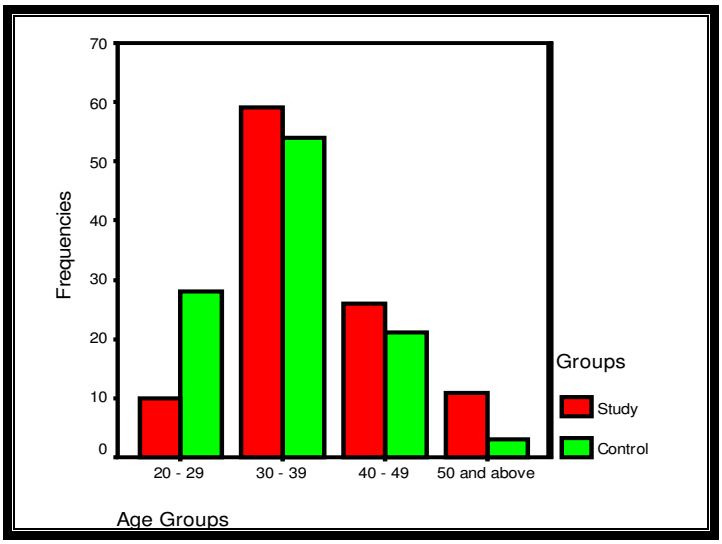

Figure (III): Cluster Bar Charts for the distribution of the studied samples according to paternal age.

Gestational age: The result had indicated that there was a non-significant differences at P>0.05 for the distribution of gestational age (per months) groups between the two samples, figure (IV).

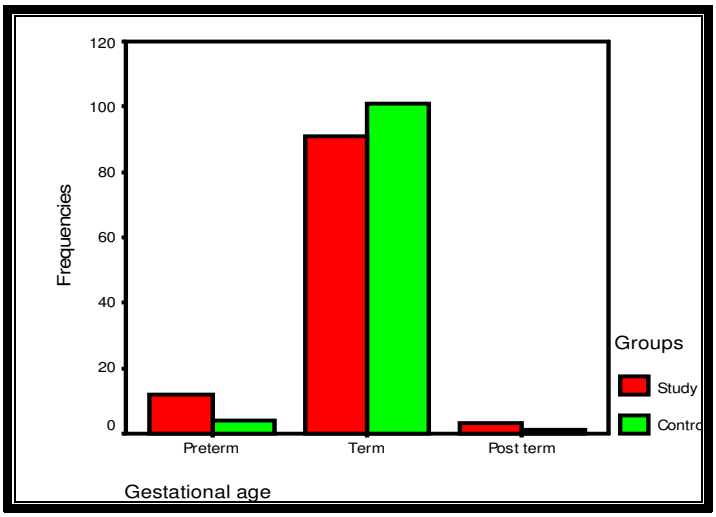

Figure (IV). Cluster Bar Charts for the distribution of the studied samples according to gestational age (per months).

Residency: the result had indicated that there was a highly significant differences at P<0.01 for the distribution of residency groups between the two samples. In addition to that, an odds ratio represented that rural individuals were reported more than twice and a half times at the control sample than the study sample i.e. (1: 2.581), figure (V).

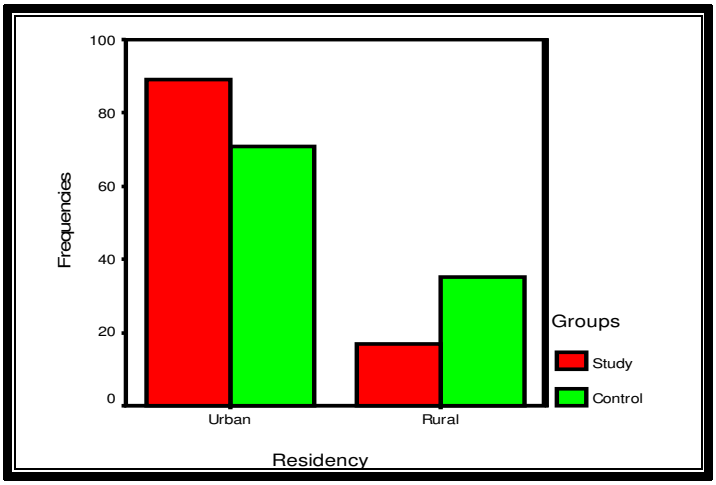

Figure (V): Cluster Bar Charts for the distribution of the studied samples according to residency.

Consanguinity: the result had indicated that there was a highly significant differences at P<0.01 for the distribution of consanguinity groups between the two samples. In addition to that, an odd ratio represented that whom had yes responding at the study sample were reported more than twice and a half times than the control sample i.e. (1: 2.622), figure (VI).

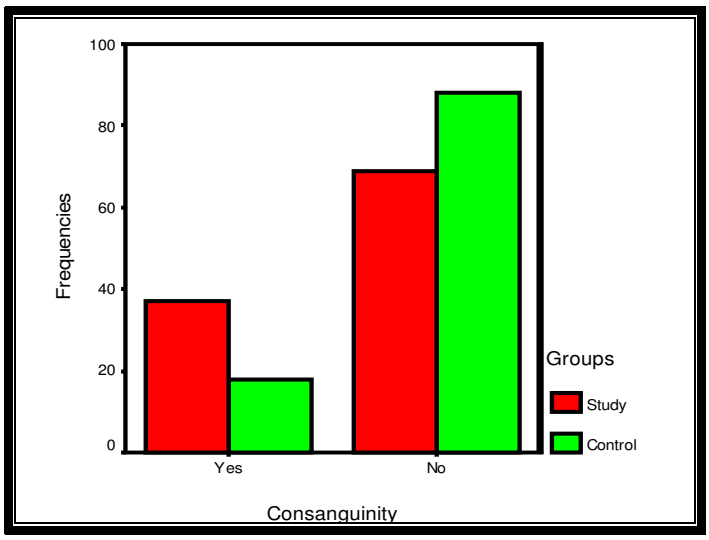

Figure (VI): Cluster Bar Charts for the distribution of the studied samples according to consanguinity.

Birth order: The result had indicated that there was a highly significant difference at P<0.01 for the distribution of birth order groups between the two samples, figure (VII).

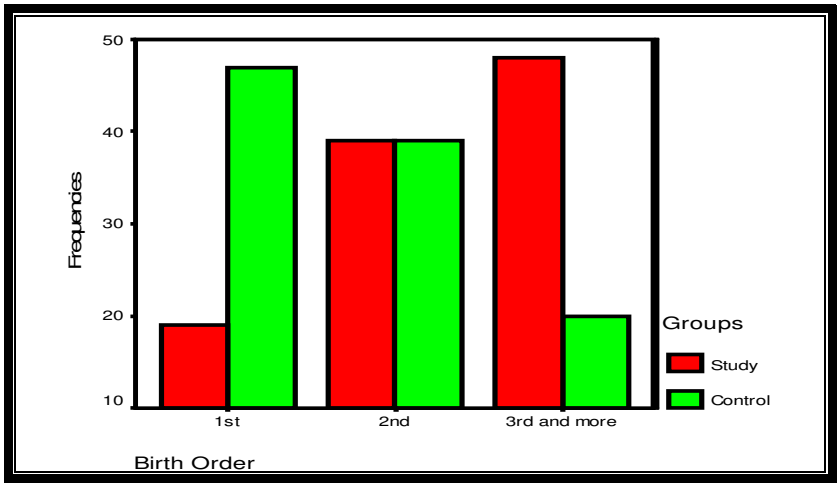

Figure (VII): Cluster Bar Charts for the distribution of the studied samples according to the birth order.

Diseases during index pregnancy: the result had indicated that there was a non-significant differences at P>0.05 for the distribution of diseases during index pregnancy groups between the 2 samples, Table (VII).

Parameter	Groups	Freq. & Percent	Samples		Total	C.S. [P-value]
			Study	Control		
Diseases during index pregnancy (% D. D.I.P.)	UTI	Freq.	28	19	47	C.C.=0.235 P=0.503 NS
		% D. D.I.P.	59.6%	40.4%	100%	
		% Groups	77.8%	90.5%	82.5%	
	DM	Freq.	4	0	4	
		% D. D.I.P.	100%	0.0%	100%	
		% Groups	11.1%	0.0%	7.0%	
	H.T.	Freq.	2	1	3	
		% D. D.I.P.	66.7%	33.3%	100%	
		% Groups	5.6%	4.8%	5.3%	
	More than one disease	Freq.	1	0	1	
		% D. D.I.P.	100%	0.0%	100%	
		% Groups	2.8%	0.0%	1.8%	
	others	Freq.	1	1	2	
		% D. D.I.P.	50%	50%	100%	
		% Groups	2.8%	4.8%	3.5%	

Family history of CHD: the result had indicated that there was a highly significant difference at P<0.01 for the distribution of family history of CHD groups between the two samples. In addition to that, an odd ratio represented that whom had yes responding at the study sample were reported more than sixth times than the control sample i.e. (1: 6.021), figure (VIII).

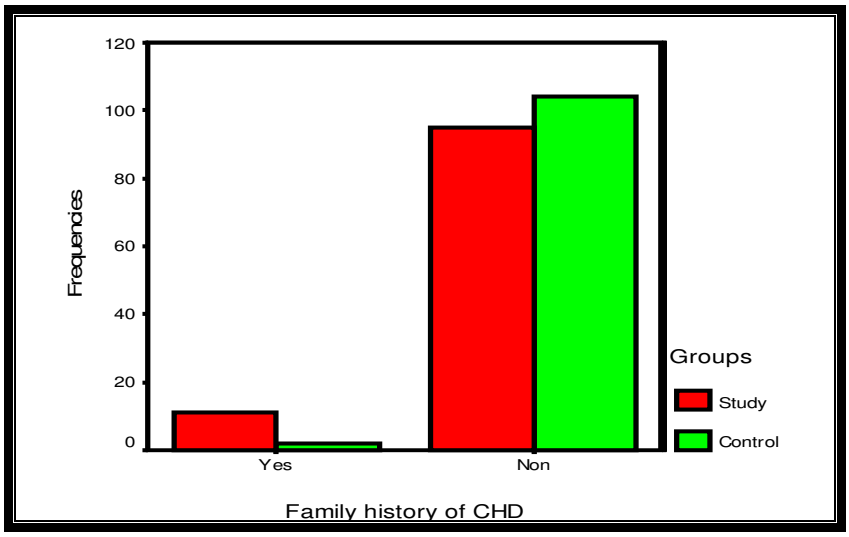

Figure (VIII): Cluster Bar Charts for the distribution of the studied samples according to family history of CHD.

Level of education of mother: the result had indicated that there was a non-significant difference at P>0.05 for the distribution of level of education of mother groups between the two samples, figure (IX).

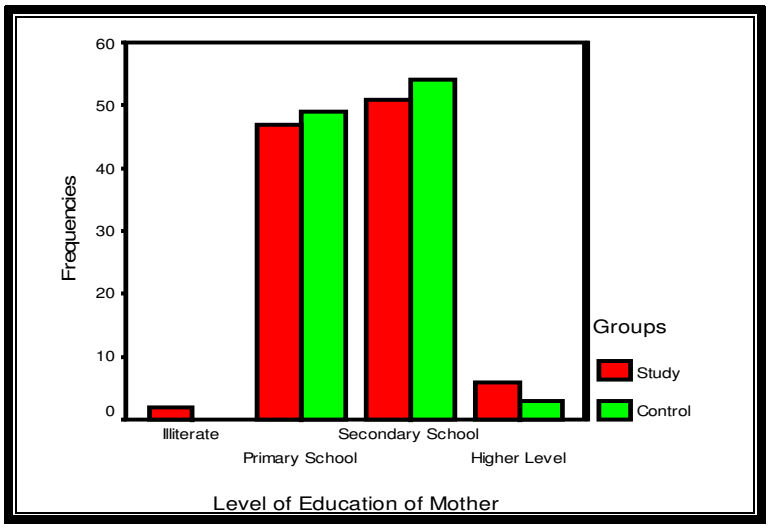

Figure (IX): Cluster Bar Charts for the distribution of the studied samples according to level of education of mother.

Socioeconomic status: the result had indicated that there was a highly significant difference at P<0.01 for the distribution of socioeconomic groups between the two samples, figure(X).

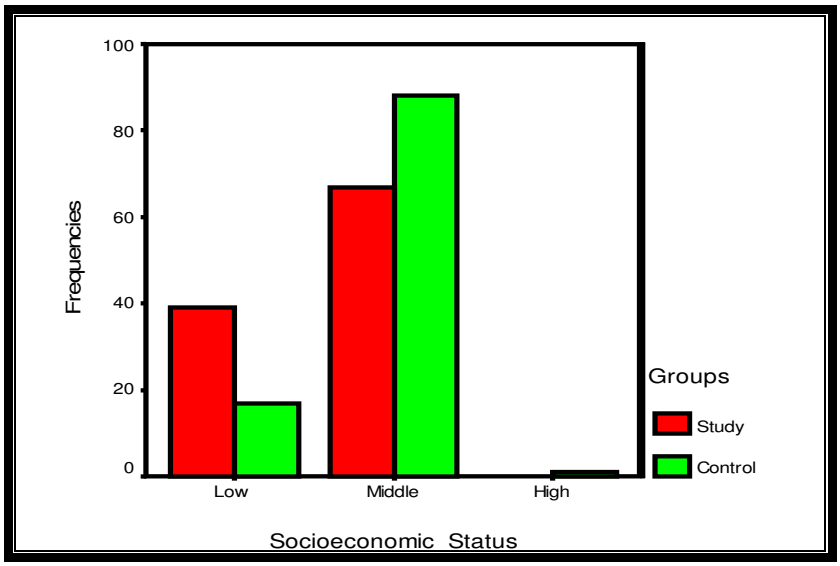

Figure (X): Cluster Bar Charts for the distribution of the studied samples according to socioeconomic status.

Season of conception: the result had been indicated that there was a highly significant difference at P<0.01 for the distribution of season of conception groups between the two samples, figure (XI).

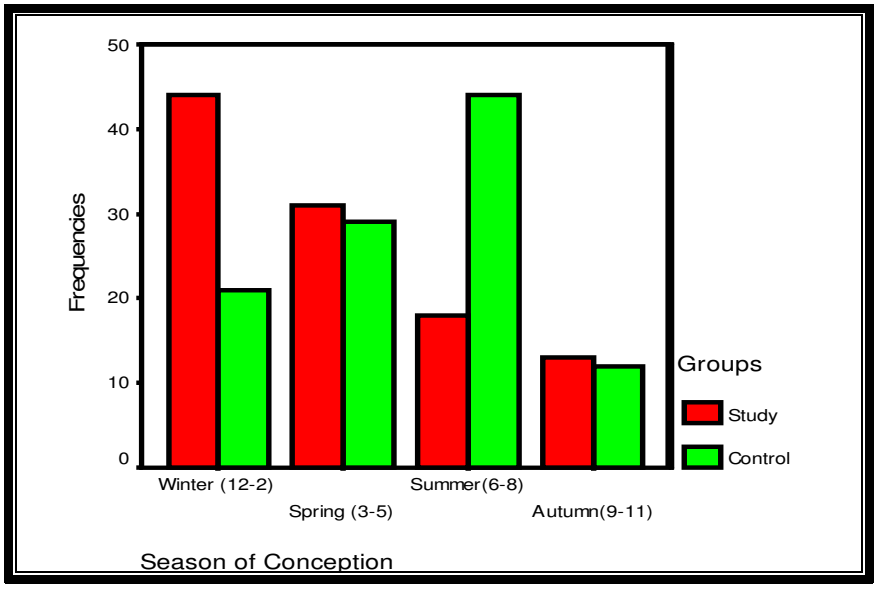

Figure (XI): Cluster Bar Charts for the distribution of the studied samples according to season of conception.

Association of CHD with other congenital malformations or syndromes. Table (VIII).

Table (VIII): Distribution of the study sample according to types of CHD and Other associated non-cardiac congenital malformations.

Type of Malformation	Numbers	Type of CHD
Cleft palate	1	VSD
Hydrocephaly	1	ASD (Seccundum)
Down syndrome	2	AV canal, VSD
Patau syndrome	1	VSD

Distribution of the study sample according to types of CHD with comparisons significance. Table (IX).

Table (IX). Distribution of the study sample according to Types of CHD and other non-cardiac congenital malformations.

Types of CHD	Number	Percent	Z-test	C.S. [P-value]
Isolated VSD	31	29.2	6.612	HS
ASD (Seccundum)	11	10.4	3.508	HS
PDA	7	6.6	2.737	HS
TOF	9	8.5	3.138	HS
AV canal	5	4.7	2.286	S
TGA	7	6.6	2.737	HS
MVP + regurgitation	3	2.8	1.747	NS
Single ventricle	2	1.9	1.433	NS
Hypo plastic left heart	1	0.9	3.238	HS
Hypo plastic right ventricle	1	0.9	3.238	HS
Pulmonary stenosis	4	3.8	2.046	S
Coarctation of aorta	3	2.8	1.747	NS
Aortic Stenosis	2	1.9	1.433	NS
VSD+PS	2	1.9	1.433	NS
VSD+PDA	3	2.8	1.747	NS
TOF+ASD	1	0.9	3.238	HS
ASD+PS	1	0.9	3.238	HS
Others	11	10.4	3.508	HS
TOF + Pulmonary atresia	1	0.9	3.238	HS
ASD+VSD+PDA	1	0.9	3.238	HS
Total	106	100	-	-

Statistical Hypothesis ($H_{Ø}$: $\rho = 0$)

Relationship between consanguinity and types of CHD: The study indicated that there is significant correlation between consanguinity and isolated VSD at $p<0.05$. Table (X). Table (X). Distribution of the studied samples according to types of CHD and relationship with consanguinity, with comparisons significance.

Types of CHD	Consanguineous	Percent ρ_1	Non-consanguineous	Percent ρ_2	Z-test	C.S. [P-value]
Isolated VSD	10	24.3	21	30.9	2.365	S
ASD	4	10.8	7	10.3	0.929	NS
PDA	3	8.1	4	5.9	0.384	NS
TOF	6	16.2	3	4.4	1.022	NS
TGA	3	8.1	4	5.9	0.384	NS
Coarctation of Aorta	1	2.7	2	2.9	0.581	NS
AV Canal	1	2.7	4	5.9	1.358	NS
MVP + Regurgitation	0	0.0	3	4.4	2.252	S
Single Ventricle	1	2.7	1	1.5	0.00	NS
Hypo Plastic Left Heart	0	0.0	1	1.5	1.002	NS
Pulmonary Stenosis	1	2.7	3	4.4	1.010	NS
Aortic Stenosis	0	0.0	2	2.9	1.421	NS
VSD + PS	1	2.7	1	1.5	0.00	NS
VSD + PDA	2	5.4	1	1.5	0.581	NS
TOF + ASD	0	0.0	1	1.5	1.002	NS
ASD + PS	1	2.7	0	0.0	1.002	NS
Others	3	8.1	8	11.8	1.548	NS
TOF + Pulmonary Atresia	0	0.0	1	1.5	1.002	NS
ASD + VSD + PDA	1	2.7	0	0.0	1.002	NS
Hypo Plastic Right Ventricle	0	0.0	1	1.5	1.002	NS
Total	38	100.0	68	100.0	4.258	HS

Statistical Hypothesis ($H_\emptyset$: $\rho_1 = \rho_2$).

DISCUSSION

This study has been conducted to screen some of the possible risk factors for CHD in Karbala.

1- **Maternal age:** The study shows significant correlation between maternal age and CHD in offspring. In the BWIS, maternal age was not associated with CHD as a group but analysis by specific defects found that maternal age of >30 years was associated with an increased risk of transposition of the great arteries and Ebstein's anomaly and that more advanced maternal age (>34 years) was associated with an increased risk of bicuspid aortic valve and ASDs. [20] An analysis of non-chromosomal birth defects of the Metropolitan Atlanta Congenital Defects Program from 1968 to 2000 found associations of advanced maternal age (35 to 40 years) with an increased risk of all heart defects. [27]

2-**Paternal age**: Relatively few studies had evaluated the effect of the paternal age on the risk of CHD. [28] This study shows significant increase in CHD in the older age groups of fathers in comparison to control. Similar

results found in Olshan et al study. [24] Lian et al also found an increased risk for ASDs and VSDs with increasing paternal age after adjustment for maternal age and race. This association could be explained by dominant mutations. [22]

3- **Residency**: According to this study, residency in an urban area is a highly significant risk factor of CHD. This may be explained by the high exposure to air pollutants such as carbon monoxide. A study conducted in 7 Texas counties evaluating potential exposures during weeks 3-8 of pregnancy reported possible increased risks of tetralogy of Fallot with carbon monoxide, isolated ASDs with particulate matter < 10 micron in aerodynamic diameter, and isolated VSDs with similar dioxide, as well as a possible risk of isolated ASD with carbon monoxide and isolated VSD with ozone.[19] In the BWIS, maternal reports of potential exposure to herbicides and rodenticides were associated with an increased risk of TGA and of potential exposure to pesticides with TAPVR and membranous VSDs. [20] Another case-control study by Shaw et al reported an increased risk of conotruncal defects with maternal reports of exposure to insecticides. [29]

4-**Consanguanity**: This study indicates consanguinity as a highly significant risk factor of CHD as a group. In a study from India by Anshula showed similar result with significant difference between the cases and controls as regards the proportion of consanguineous marriages. [30] A study from Lebanon by Nabulsi et al, showed that consanguinity as a risk factor for CHD is highly significant. [31] Another study from Saudi Arabia indicated that the proportion of first cousins in the CHD sample is higher than the proportion in the general population, supporting a hypothesis of autosomal recessive gene involvement in congenital heart disease. [32] When studying the relation between consanguinity and type of CHD, only VSD is a significant risk factor with a $p<0.05$.A study from Lebanon by Yunis et al showed that first-cousin marriage was a significant risk factor for VSD, ASD, HLH, and SV. [33] Our study showed consanguinity is not significant risk factor for ASD and PDA. This may be explained by the small size of our study (106 cases) compared with Yunis et al study (173 cases).

5-**level of education of mother**: This study showed that level of education of mother had no significant correlation with CHD in offspring.

6-**Birth order**: 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. Other two studies one by Rothman and Fyler, [18] and the other by Tay et al [34] had also found that birth order more than the second consistently increases the risk of CHD.

7-**Diseases during index pregnancy:** this factor did not significantly increase the risk of developing CHD according to our study. Study from Pakistan by Faheem et al show similar results. [35]

8- **Family history of CHD**: The study showed that the presence of a family history of CHD is a highly significant risk factor for the occurrence of CHD which is similar to Faheem et al study [35].

9-**Socioeconomic status:** this is another highly significant risk factor according to our study with those of low social class had showed more cases than control.

10-**Season of conception**: Another risk factor that had been studied is the season of conception. Our study shows that winter month's conception associated with the greatest risk of CHD while Liverpool study (1960- 69) showed no consistent seasonal variation in the incidence of any of the main congenital heart lesions. [36] This may be attributed to the fact that embryonic stage of development is the period during which congenital malformation occur. During winter months the prevalence of viral infections is high which in a way or another may produce deleterious effects on organs development including the heart.

11-**Gestational age**: The study found that the gestational age is not a significant risk factor for the development of CHD. A study by Gunatilake et al show a 3 times increased risk of CHD in preterm infants. [37] A study from United Kingdom (UK) showed that preterm infants have more than twice as many cardiovascular malformations as do infants born at term. [38] This may be explained by the small size of our study in which the majority of cases were term infant and the preterm represent 11%; while in the UK study the premature infants represent 16% of cases.

CONCLUSIONS

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 Holy Karbala/ IRAQ. The study indicated that the following factors significantly increase the risk of developing CHD:

1- Advanced maternal age.
2- Advanced paternal age.
3- Increasing birth order.
4- Residency in urban area.
5- Low socioeconomic status.
6- Positive family of CHD.
7- Winter month's conception.
8- Consanguineous marriage.

Other factors had no significant role such as systemic diseases during index pregnancy, gestational age and level of education of mother. The study showed that positive consanguinity is more evident in isolated VSD as compared to other CHD.

RECOMMENDATIONS

- For parents who had a child with CHD, counseling about birth control is recommended, to decrease the number of children in the family, thereby decreasing the risk of developing CHD
- Families with positive history of CHD need prompt prenatal and natal care to detect CHD early.
- For family planning, early paternal and maternal age of conception is recommended.
- Prompt measures should be taken by governmental and non-governmental organizations to decrease air pollution.
- Promotion of the standards of living for families with limited financial resources.

ACKNOWLEDGEMENT

We are very grateful to Professor Dr. Abdulkhaliq Al-Naqeeb, College of Health and Medical Technology, Baghdad, for his assistance in the statistical data of the study.
Our great thanks and appreciation is to Dr. Eman Al hemiary and Dr. Ahmed Tawfiq, from echocardiography department and to all the parents and caregivers who participate in this study.

REFERENCES

1-Daniel Bernstein: Epidemiology and Genetic Basis of Congenital Heart Disease. In: Robert M. Kliegman, Bonita F. Stanton, Joseph W. St. Geme III, et al. Nelson text of pediatrics 2011; 418.
2- Thomas J. Starc, Constance J. Hayes, Allan J. Hordof: Etiology of Cong heart diseases. In: Richard A. Polin, Mark F. Ditmar. Pediatric Secrets 2010; 3:87.
3- Kathy J. Jenkins, Adolfo Correa, Jeffrey A. Feinstein. Non- inherited Risk Factors and Congenital Cardiovascular Defects: Current Knowledge. Circulation, 2007; 115:2995-3014.
4- Pierpont ME, Basson CT, Benson DW, et al: Genetic basis for congenital heart defects: current knowledge: a scientific statement from the American Heart Association Congenital Cardiac Defects Committee, Council on Cardiovascular Disease in the Young. Circulation 2007; 115:3015–3038.
5- Wilson PD, Loffredo CA, Correa-Villasenor A, et al: Attributable fraction for cardiac malformations. Am J Epidemiology 1998: 148:414–423.
6- Czeizel AE: Periconceptional folic acid containing multivitamin supplementation, Eur J Obstet Gynecol Reprod Biol 1998; 78:151–161.

7- Scanlon KS, Ferencz C, Loffredo CA, et al: The Baltimore Washington Infant Study Group Pre conceptional and folate intake and malformations of the cardiac outflow tract. Epidemiology1998; 9:95–98. 8- Carmen M Coombs, Arhusa Stevens Kirk: Oski pediatric certification and recertification board review 2010; 4: 75.
9-Mills JL, Troendle J, Conley MR, et al: Maternal obesity and congenital heart defects: a population-based study. Am J Clin Nutr 2010.
10- Marie. M. Gleason, Robert shaddy, Jack Rychicet: Pediatric Practice Cardiology 2012; 3: 74.
11- Renata Kucien, Virginija Dulskiene: Selected environmental risk factors and congenital heart defects in Lithuanians. Medicina 2008; 44 (11).
12-Watkins M.L, Rasmusen S.A et al: Pediatrics 2003:111:1152-8.
13-Reller MD, Strickland MJ, Riehle Colarusso T, et al: Prevalence of congenital heart defects in metropolitan Atlanta, 1998-2005. J Pediatrics 2008; 153(6):807.
14- Oyen N, Poulsen G, Boyd HA, et al: Recurrence of congenital heart defects in families. Circulation 2009; 120(4):295.
15-Khoshnood B, Lelong N, Houyel L, et al: Prevalence, timing of diagnosis and mortality of newborns with congenital heart defects: a population-based study. Heart 2012 Nov; 98(22):1667-1673.
16- Wu MH, Chen HC, Lu CW, et al: Prevalence of congenital heart disease at live birth in Taiwan. Journal of Pediatrics 2010; 156(5):782.
17- Tanner K, Sabrine N, Wren C: Cardiovascular malformations among preterm infants. Pediatrics 2005; 116(6): e833.
18-Rothman KJ, D C Fyler: Sex, birth order and maternal age characteristics of infants with CHD. Am J Epidemiol1976; 104: 527-534.
19- Kathy J. Jenkins, Adolfo Correa, Jeffrey A. Feinstein, et al: Noninherited Risk Factors and Congenital Cardiovascular Defects: Current Knowledge. A Scientific Statement from the American Heart Association Council on Cardiovascular Disease in the Young, endorsed by the American Academy of Pediatrics. Circulation 2007; 115:2995-3014.
20- Ferencz C, Correa-Villasenor A, Loffredo CA, et al: Genetic and Environmental Risk Factors of Major Cardiovascular Malformations: The Baltimore-Washington Infant Study: 1981–1989. Armonk, NY: Futura Publishing Co; 1997.
21- Carmichael SL, Shaw GM: Maternal life event stress and congenital anomalies. Epidemiology 2000; 11: 30 –35.
22- Lian ZH, Zack MM, Erickson JD: Paternal age and the occurrence of Birth defects. Am J Hum Genet1986; 39:648–660.
23- Murdoch JL, Walker BA, McKusick VA: Parental age effects on the occurrence of new mutations for the Marfan syndrome. Ann Hum Genet.1972; 35:331–336.
24-Olshan AF, Schnitzer PG, Baird PA: Paternal age and the risk of congenital heart defects. Teratology1994; 50:80–84.
25-Tararbit K, Houyel L, Bonnet D, et al: Risk of congenital heart defects associated with assisted reproductive technologies: a population-based evaluation. Euro Heart J 2011; 32(4):500.
26- Carolyn A Altman: Congenital heart disease (CHD) in the newborn: Presentation and screening for critical CHD .Up to date pediatric. Dec, 2012.
27- Reefhuis J, Honein MA: Maternal age and non-chromosomal birth defects. Atlanta–1968 –2000: teenager or thirty-something, who is at risk? Birth Defects Res. A Clinical Mol Teratol 2004: 70:572–579. 28- Zhan SY, Lian ZH, Zheng DZ, et al: Effect of fathers' age and birth order on occurrence of congenital heart disease. J Epidemiology Community Health 1991; 45:299 –301.
29- Shaw GM, Nelson V, Iovannisci DM, et al: Maternal occupational chemical exposures and biotransformation genotypes as risk factors for selected congenital anomalies. Am J Epidemiology 2003; 157:475– 484.
30-Anshula Tandon, Sonali Sengupta, Vinayak Shukla, et al: Risk Factors for Congenital Heart Disease in Vellore, India; Current Research Journal of Biological Sciences 2(4): 253-258, 2010.
31-Nabulsi MM, Tamim H, Sabbagh M, et al: Parental consanguinity and congenital heart malformations in a developing country. Am J Med Genet A 2003 Feb 1; 116A (4):342-7.
32- Becker SM, Al Halees Z, Molina C, et al: Consanguinity and congenital heart disease in Saudi Arabia. Am J Med Genet 2001 Feb 15; 99(1):8-13.
33-Yunis K, Mumtaz G, Bitar F, et al: Consanguineous marriage and congenital heart defects: a case-control study in the neonatal period. Am j Med Genet A 2006 Jul 15; 140(14):1524-30.

34- Tay S H, W CL Yip, R Joseph: Parental age and birth order in Chinese children with CHD. J Med Genet1982; 19: 441-443.
35-Faheem UL Haq, Fatima Jalil, Saman Hashmi, et al: Risk factors predisposing to congenital heart defects. Ann Pediatr Cardiol 2011 Jul-Dec; 4(2): 117–121.
36- A P Kenna, RW Smithells, DW Fielding: Congenital Heart Disease in Liverpool: 1960–69. QJM (1975) 44 (1): 17-44.
37-Gunatilake RP, Perlow JH, Obesity and pregnancy: clinical management of the obese gravida. Am J Obstet Gynecol 2011 Feb; 204 (2):106-19.
38- Tanner K, Sabrine N, Wren C: Cardiovascular malformations among preterm infants. Pediatrics 2005 Dec; 116(6): e833-8.